

Review of Dietary Reference Intakes for Selected Nutrients

Challenges and Implications for Federal Food and Nutrition Policy

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Abstract

Dietary Reference Intakes (DRIs) are the most recent set of nutrient-based reference values, which, together with recommended dietary assessment methods, are being used to update estimates of nutrient adequacy of population subgroups. Recent estimates suggest both dramatic dietary deficiencies and excesses for selected nutrients among some subgroups. This report takes a critical look at the studies and methods used to set DRIs. The findings show that errors in dietary recall data—either underreporting or overreporting of intakes—may partially explain the inadequacies and excessive intakes. In addition, the lack of sensitive, specific biochemical markers has resulted in DRIs for selected nutrients to be based on less than optimal data. Because the DRIs are used by food and nutrition assistance programs to set nutritional objectives, establish program benefits, and evaluate program outcomes, it is important to understand the issues involved in deriving the DRIs and how to interpret the results of dietary assessments.

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CHAPTER I

INTRODUCTION

Food and nutrition assistance programs use nutrient reference standards to establish nutritional objectives, set benefit levels, and evaluate program outcomes and effectiveness. Nutrient reference standards are critical to the Food Stamp Program—the largest of all food and nutrition assistance programs, at an annual cost of \$27 billion in 2005—through their role in the Thrifty Food Plan, a food plan designed to meet nutrient standards at a minimal cost and used to set program benefits. The National School Lunch Program underwent a major nutritional overhaul under the Healthy Meals for Healthy Americans Act of 1994 based on dietary assessments that showed that American children were consuming excessive amounts of fat, saturated fat, cholesterol, and sodium relative to dietary standards. The Special Supplemental Nutrition Program for Women, Infants and Children (WIC) designs its food packages to provide nutrients found to be lacking in the diets of low-income populations. More recently, the Institute of Medicine report on revising the WIC food packages used results from dietary assessment studies in proposing revisions to existing food packages (Institute of Medicine (IOM) 2006).

This report examines a set of nutrient reference standards, called the Dietary Reference Intakes, for selected nutrients—food energy, zinc, preformed vitamin A, magnesium, vitamin E, fiber, and potassium. These nutrients are those that have been highlighted in recent dietary assessment studies indicating potential concern about either inadequate or excessive intakes.

BACKGROUND

Over the past decade, our knowledge about human nutrient requirements has increased significantly, resulting in a set of new nutrient reference standards called the Dietary Reference Intakes (DRIs) (Institute of Medicine 1997, 1998, 2000b, 2001, 2002/2005, 2005). The DRIs cover more nutrients and dietary constituents than did the previous Recommended Dietary Allowances. In addition, where data are available, the DRIs are based on a reduction in the risk of chronic disease rather than merely the absence of signs of deficiency.

The development of the DRIs was accompanied by two additional IOM reports that provide guidance on methods for using the DRIs for dietary assessment and planning (Institute of Medicine 2000a, 2003). In recent years, several studies using the recommended dietary assessment methods have become available, allowing researchers and policy makers to take a new look at which nutrients may be of concern—or potential concern—because of either inadequate or excessive intake levels. Many of these studies consistently point to several nutrients of potential concern:

- ***Estimated energy intakes exceed energy requirements for infants and children.*** In several studies of the nutrient intakes of young children, mean energy intakes exceed mean estimated energy requirements. This finding is observed for infants and toddlers in the Feeding Infants and Toddlers Study; for infants and toddlers participating in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) from the Continuing Survey of Food Intakes by Individuals (CSFII); and for other subgroups of children 4 to 8 years of age in the CSFII.
- ***High proportions of infants and children have usual intakes above Tolerable Upper Intake Levels for zinc and vitamin A.*** Data from the CSFII show that almost 90 percent of non-breastfeeding WIC infants and more than half of WIC children have usual intakes of zinc above the Tolerable Upper Intake Level. For vitamin A, the proportion with usual intakes above the Tolerable Upper Intake Level is between 38 and 56 percent for non-breastfeeding WIC infants and about 25 percent for WIC children.
- ***All subgroups of the population have a high prevalence of inadequacy of magnesium and vitamin E.*** Estimates of the prevalence of inadequate intakes of magnesium and vitamin E range from about 50 percent for young children to almost 100 percent for some subgroups of adult women.
- ***Fiber and potassium intakes are very low relative to DRI standards.*** For children 2 years of age and over and for all adult subgroups, mean usual intakes of fiber and potassium are far below the Adequate Intakes defined in the DRIs. For most groups, even the 90th percentile of usual intake is less than the Adequate Intake level.

These empirical findings are striking. They imply either dramatic dietary deficiencies among some population subgroups, excessive intakes of some nutrients, limitations of dietary assessment studies, or shortcomings with the DRIs for some nutrients. It is important to understand which interpretation is most valid. If nutrient deficiencies and/or excesses do exist, these findings have important implications for food assistance and nutrition programs—from designing programs that achieve nutrient and food objectives to assessing program benefits and costs. If limitations of dietary assessment studies—such as over- or under-reporting of dietary intakes—explain the results, then concerns about inadequate or excessive nutrient intakes are allayed but important questions could be raised about the validity and usefulness of dietary recall data. Or if shortcomings in the DRIs,

rather than real dietary inadequacies or excesses, contribute to the study findings, then efforts could be directed to addressing the issues associated with the DRIs.

One important issue associated with these dietary assessment results concerns the nature of the DRIs. As described above, the DRIs were established with the goal of reducing the risk of chronic disease, not simply eliminating signs of deficiency. As such, it may be difficult to observe or measure any adverse health impact in the short term (particularly among certain age groups), even if the long-term health impact is important.

A second possible methodological problem associated with the recent set of dietary assessment studies includes misreporting of intakes from 24-hour dietary recalls. A fairly extensive literature acknowledges possible underreporting of intakes by adults, especially adolescent females and adult women (Mertz et al. 1991; Johansson et al. 1998; Schoeller 2002). For infants and young children, some recent studies suggest that intakes may be overreported (Devaney et al. 2004; Institute of Medicine 2006). While it is likely that underreporting of intakes by adults and overreporting of intakes by young children may explain some of the surprising findings, the magnitude of some of the inadequacies and excesses identified in this report cannot be explained solely by biases in 24-hour dietary recall data collection methods.

A third methodological issue is that many of the recent dietary assessment studies used 24-hour dietary recall data from the CSFII, which did not include intakes from dietary supplements. Thus, findings may overestimate the prevalence of inadequate intakes and underestimate the prevalence of excessive intakes. However, other data sets do include the nutrient contribution of dietary supplements, and many of the surprising results are also found in these studies.

A final methodological issue, and the one considered in the following chapters, is whether the methods used to set some of the DRIs need to be examined more closely. Since the publication of the new DRIs and the methods for their use in dietary assessment, researchers have tended to take the DRIs as given and to interpret the results of dietary assessment studies in a straightforward manner. That is, a high prevalence of inadequacy implies nutrient deficiencies and a high prevalence of excessive intakes implies risk of nutrient toxicity.

OVERVIEW OF REPORT

This report reviews and discusses the methods and studies used to set relevant DRIs for food energy, zinc, vitamin A, magnesium, vitamin E, fiber, and potassium. It presents findings from two basic analytic tasks:

1. An in-depth analysis of the underlying models used to calculate the EERs for infants and young children
2. A review and discussion of the literature and methods used to set the DRIs for zinc, preformed vitamin A, magnesium, vitamin E, fiber, and potassium

This review of models and methods used to set the DRIs is not intended to identify errors or problems with the DRIs. Rather, it is intended to add to our understanding of which nutrients are of concern and why, and to help policy makers and the public health community determine whether there are dietary concerns that need to be incorporated into the design of food and nutrition assistance programs and the provision of dietary guidance.

The organization of this report is as follows: Chapter II provides additional background information on nutrient requirements and dietary assessment methods; Chapter III examines estimates of energy requirements for infants and toddlers; Chapter IV describes and discusses the methods and studies used to set the DRIs for the other nutrients; and the final chapter summarizes the main findings and discusses research needs.

CHAPTER II

NUTRIENT REQUIREMENTS AND DIETARY ASSESSMENT METHODS

As knowledge of the relationship between diet and long-term health status has increased over the past several decades, so has our understanding of the nutrients required for optimal growth and development, as well as for reduced risk of chronic health conditions. Building on this improved knowledge base, the recently developed dietary reference intakes (DRIs) represent our best understanding of the nutrient *requirements* of individuals. In turn, dietary assessment studies use data on nutrient *intakes* to determine whether diets provide enough nutrients to meet the requirements without being excessive.

During the development of the new DRIs, it became clear that guidance on how to interpret and use them would be important for researchers, policy makers, and dietary professionals. As a result, the Institute of Medicine (IOM) established a Subcommittee on the Interpretation and Uses of the DRIs, which produced two volumes on how to use the DRIs in dietary assessment and planning (Institute of Medicine 2000a, 2003). Several recent studies have used methods recommended by the IOM to assess the adequacy of diets consumed by specific population subgroups using the DRIs. Overall, this emerging literature has been extremely useful for producing more reliable and precise estimates of the prevalence of inadequacy and for identifying nutrients and dietary components where there are concerns about excessive intakes. Previous dietary assessment studies, based on the old RDAs and inappropriate assessment methods, had findings that were either incorrect or misinterpreted.

This chapter provides background information on the DRIs and dietary assessment methods. It focuses first on nutrient requirements, as summarized by the DRIs, and then discusses the dietary assessment methods used to determine nutrient adequacy.

NUTRIENT REQUIREMENTS

The IOM Committee on the Scientific Evaluation of Dietary Reference Intakes defined nutrient requirements as “the lowest continuing intake level of a nutrient that will maintain a defined level of nutriture in an individual.” To develop the DRIs, the committee used data from observational studies (case reports, cross-sectional, cohort, and case-control studies) and experimental studies (randomized and nonrandomized treatment or prevention trials

and controlled dose-response, balance, turnover, and depletion-repletion studies). In the absence of human studies, selected animal studies were also considered. The primary sources of data were studies published in the peer-reviewed literature. The quality of the studies was evaluated on the basis of study design and power; methods of measuring intake and indicators of adequacy; and potential biases, nutrient interactions, and confounding factors. Data were often sparse or came from studies that were limited in their ability to provide the information needed by the committee. For example, the existing data on many nutrients did not provide a basis for setting specific requirements for different age and gender subgroups. In general, there was a lack of information relating the effects of inadequate intake to indicators of health status (Institute of Medicine 2001).

The DRIs for vitamins and minerals include four reference standards—the Estimated Average Requirement, the Recommended Dietary Allowance, the Adequate Intake, and the Tolerable Upper Intake Level, as defined in Table II.1. All DRIs pertain to *usual intake*—an individual’s average daily nutrient intake over time. In general, the DRIs are intended to apply to healthy individuals with diets similar to those consumed in the United States and Canada (Institute of Medicine 2001).

Table II.1. Dietary Reference Intakes

Estimated Average Requirement	The usual intake level estimated to meet the requirements of half the healthy individuals in a life stage and gender group. At this level of intake, the other half of the healthy individuals in the specified group would not have their needs met.
Recommended Dietary Allowance	Usual intake level that is sufficient to meet the nutrient requirements of nearly all healthy individuals in a particular life stage and gender group (97.5 percent of the individuals in a group).
Adequate Intake	Usual intake level based on experimentally derived intake levels or approximations of observed mean nutrient intakes by a group (or groups) of apparently healthy people who are maintaining a defined nutritional state or criterion of adequacy—used when an EAR and RDA cannot be determined.
Tolerable Upper Intake Level	Highest level of usual nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the specified life stage group. As intake increases above the UL, the risk of adverse effects increases.

Source: Institute of Medicine 2000a.

Estimated Average Requirement (EAR). The general method for developing the EARs was to review the scientific evidence available on nutrient function, absorption, and metabolism; the clinical effects of inadequate nutrient intake; potential functional, biochemical, or other indicators of nutrient status; and factors affecting the nutrient requirement (such as nutrient-nutrient interactions). A criterion of nutritional adequacy was then chosen for each nutrient and, in some cases, for individual life-stage groups. Because

of a paucity of data on children's requirements, EARs for children were often extrapolated from adult EARs.

Recommended Dietary Allowance (RDA). If nutrient requirements were determined to be normally distributed, the RDA was defined as the EAR plus two standard deviations of the EAR. When data on the variability in requirements were not available, a coefficient of variation of 10 percent was assumed. The RDA was then calculated as 120 percent of the EAR ($EAR + 2(0.10 \cdot EAR)$).

Adequate Intake (AI). If the information available to the committee was not sufficient to determine an EAR (and thus an RDA), an AI was set for the nutrient. AIs were based on experimentally derived or observed levels of intake by groups of healthy people. For young infants, the AI equals the average amount of the nutrient in human milk for exclusively breastfed, full-term infants. Various data sources were used to determine the AIs for adults—intake data from a single experiment, estimated dietary intakes in a healthy population, or data from several sources, each of which alone did not provide a reliable estimate of an EAR.

Tolerable Upper Intake Level (UL). The need for establishing ULs arose primarily in response to the increased use of dietary supplements and fortified foods. For most nutrients, ULs apply to total intake from food, water, and supplements. If adverse health effects have only been associated with intake from supplements or forms of the nutrient used in food fortification, the UL may apply to only those sources. Adverse effects were defined as “any significant alteration in the structure or function of the human organism, or impairment of a physiologically important function that could lead to a health effect that is adverse” (World Health Organization 1996). Adverse nutrient-nutrient interactions were also considered in setting the UL.

A risk assessment model was developed and used to establish the ULs.^{1,2} This model involves four steps. The first is hazard identification, which is a comprehensive review of data on adverse health effects caused by excessive intake of the nutrient. Step two is dose-response assessment. Dose-response assessment involves selecting a data set, identifying a critical endpoint with its associated level(s) of nutrient intake, and assessing the extent of uncertainty, resulting in an estimate of the UL for each life stage group. Steps three and four are intake assessment and risk characterization, respectively. These steps entail estimating distributions of usual total daily intake (or intake from supplements only) of the nutrient and estimating the proportion of the population with nutrient intakes that exceed the UL.

¹The subcommittee considered the possibility of developing a mathematical model to determine the ULs for each nutrient. Because of the paucity of data on levels of intake associated with adverse effects, uncertainties associated with extrapolating from clinical studies to the healthy population, and scientific judgments that would be required, they concluded that this approach would not be consistent with acceptable risk assessment practices.

²A comparable international model for establishing ULs was recently developed by participants in a workshop convened jointly by the Food and Agriculture Organization and World Health Organization (2006).

The dose-response assessment, which results in an estimate of the UL, depends on toxicological concepts often used in assessing the risk of exposures to chemicals:

- No-observed-adverse-effect level (NOAEL) is the highest usual intake of a nutrient at which no adverse effects have been observed in individuals or groups.
- Lowest-observed-adverse-effect level (LOAEL) is the lowest usual intake level of a nutrient at which an adverse effect has been identified. When the data are not available to reveal the NOAEL, the LOAEL is used to set the UL.
- An uncertainty factor (UF) is applied to the NOAEL and LOAEL to account for inter-individual variation in sensitivity, extrapolation from animal studies, or lack of data on the consequences of long-term excessive intake.

The UL is calculated by dividing the NOAEL or LOAEL by the final uncertainty factor, which combines all potential sources of uncertainty for the nutrient. For some nutrients, data were not sufficient to estimate a UL reliably. The absence of a UL does not imply that the nutrient does not have a tolerable upper intake level. Rather, it indicates available evidence is not sufficient to permit estimation of a UL. When no data were available to determine the NOAEL or LOAEL for a particular life stage group, the UL was usually extrapolated from data for other age groups, based on known differences in body weight.

ENERGY REQUIREMENTS

In the case of food energy, nutrient requirements are expressed in terms of estimated energy requirements (EERs) (Institute of Medicine 2002/2005). An adult EER is the usual intake level needed to balance energy expenditures in a healthy adult of a given age, gender, weight, height, and level of physical activity. In children, the EER is defined as the sum of the dietary energy intake predicted to maintain energy balance for an individual's age, weight, height, and physical activity level, plus an allowance for normal growth and development, called Energy Deposition.

Data on total energy expenditures were used to estimate EERs for age and gender subgroups. For most age and gender subgroups, estimated EERs for individuals within the group depend on weight, height, and physical activity level. For infants and young children up to age 3, however, the total energy expenditure equations, and thus the EERs, depend only on weight in kilograms.

DIETARY ASSESSMENT METHODS

To assess the nutrient adequacy of population subgroups, dietary assessment studies generally address two main questions:

1. What proportion of a population subgroup has nutrient intakes that do not meet nutrient requirements?

2. What proportion is at risk of excessive intake levels?

For both questions, the usual intake of a nutrient—as opposed to intake on a given day—is the relevant construct, since an individual’s health depends on long-run or usual dietary patterns. Usual intake seldom, if ever, can be observed. Rather, dietary recalls provide data on observed nutrient intakes over some specified period of time. Observed daily intake measures individual usual intake with error. That is, nutrient intake varies from individual to individual in the group, but it also varies from day to day for a given individual. This day-to-day variability is “noise,” as what is of most interest is the individual-to-individual variability in usual nutrient intake. Because for most nutrients, the day-to-day variability in intakes can be larger than the individual-to-individual variability, it is very important to “remove” the effect of this additional variability when estimating the distribution of usual intakes.

In recent years, most dietary assessment studies have used a method developed by researchers at Iowa State University (ISU) to produce estimates of usual intake distributions. The method is based on a simple additive measurement error model that permits adjusting the data for the presence of day-to-day variability (Nusser et al. 1996). It is known as the ISU method for estimating usual nutrient intake distributions, and has been widely adopted by the nutrition community (see, for example, Beaton 1994; Carriquiry 1999; Institute of Medicine 2000a).

What Proportion of a Population Subgroup has Nutrient Intakes that Do Not Meet Nutrient Requirements?

An exact estimate of the prevalence of nutrient inadequacy is impractical because the requirement for a nutrient is seldom observed. Typically the only information available is summary measures of the distribution of nutrient requirements—the EAR, RDA, and measures of variation in nutrient requirements.

It is possible to show, however, that the proportion of individuals in a group whose nutrient intakes do not meet requirements can be approximated, if both the specific EAR for the appropriate age-gender subgroup and a reliable estimate of the distribution of nutrient intakes are available. It has been shown that, under certain assumptions, the proportion with intakes less than the EAR is an estimate of the proportion of a group whose intakes do not meet requirements (Beaton 1994; Carriquiry 1999; Institute of Medicine 2000a). The approach, known as the EAR cut-point method, produces a reliable estimate of the prevalence of nutrient inadequacy in a group.

For nutrients with an AI, only limited inferences can be made regarding the prevalence of inadequacy. If mean intake levels are equal to or exceed the AI, it is likely that the prevalence of inadequacy is low; but if mean intakes are less than the AI, no conclusions can be drawn about the prevalence of inadequacy (Institute of Medicine 2000a). In practice, for nutrients with an AI, dietary assessment studies present estimates of mean intakes and various percentiles of the intake distributions and make qualitative conclusions about adequacy.

In the case of energy, requirements are expressed in terms of EERs. Since populations maintaining their body weight should have intake and EER distributions with roughly equal mean values, dietary assessment studies often compare the mean intake of food energy with the mean EER for each subgroup to assess reported energy adequacy from dietary recall data.

What Proportion of a Population Subgroup is at Risk of Excessive Intake Levels?

To estimate the proportion of each subgroup at risk of excessive intake levels, dietary assessment studies calculate the percentage with intakes exceeding the UL. Because ULs have not been established for all nutrients, this research question can be addressed only for those nutrients with ULs. Some ULs refer to intakes from supplements and fortified foods, and others to intakes from foods, beverages, and supplements.

SUMMARY

Recent dietary assessment studies have used the methods described above to determine the proportion of individuals with inadequate or excessive usual nutrient intake. As discussed in Chapter I, many of these studies have found several subgroups with unexpectedly high proportions with intakes of certain nutrients that exceed or fall below the established DRIs. The following chapters examine the development of the estimated energy requirements for children and youth, as well as the methods used to set the DRIs for a selected group of nutrients, in an effort to better understand these findings and to determine whether they signal important public health concerns.

CHAPTER III

ESTIMATED ENERGY REQUIREMENTS FOR INFANTS AND YOUNG CHILDREN

Dietary assessment studies use data on energy intakes and compare usual intakes with energy requirements to assess whether diets provide enough energy without being excessive. For infants and young children, the results of recent analyses of dietary intakes show that mean usual energy intakes exceed mean Estimated Energy Requirements (EERs). This finding is observed for infants and toddlers in the Feeding Infants and Toddlers Study, for infants and toddlers participating in the Continuing Survey of Food Intakes by Individuals (CSFII), and for other subgroups of children 4 to 8 years of age in the CSFII (Institute of Medicine 2006, 2004; Devaney et al. 2005, 2004).

Four possible explanations could potentially account for the excess of reported energy intakes over requirements:

- 1. *Infants and young children consume more energy than required.*** Although overconsumption of food energy is consistent with the increasing prevalence of overweight and obesity among children, the discrepancy between mean usual intake and mean EER is too large to account for increases in the rate of overweight children.
- 2. *Parents and caregivers overreport the amount of foods and beverages that infants and young children consume.*** If this is true, dietary assessment studies would lead to an overestimate of energy intakes.
- 3. *Parents underreport children's body weight.*** As children's weights are the key determinant of their EERs, underreporting body weights will also understate their EERs.
- 4. *EERs for young children are too low.*** The EERs presented in the macronutrient report for children 0 through 36 months of age are about 20 percent lower than the 1985 World Health Organization (WHO) estimates of energy requirements of young children.

This chapter examines the fourth possibility. Specifically, for young children 0 through 36 months of age, this chapter examines the sensitivity of the EERs to alternative specifications of the total energy expenditure equation presented in the macronutrient report (Institute of Medicine 2002/2005). The chapter first presents background information on energy requirements and recent estimates of EERs developed by the macronutrient panel. Next, it briefly summarizes studies of energy intake, documenting the energy imbalance reported in these studies. Estimates of alternative specifications for total energy expenditures are then presented. Finally, a concluding section summarizes the results.

The results of this re-analysis suggest that the EERs for young children do not appear to be too low. In fact, many of the alternative specifications produced estimates of total energy expenditure, and EERs, that were lower than those reported in the macronutrient report.

BACKGROUND

People need energy to live. Energy is necessary for the functions of the human body—respiration, circulation, physical work, and maintenance of body temperature (Institute of Medicine 2002/2005). People consume energy through intakes of food and beverages, and they expend energy through the activities of daily living. Energy balance occurs when energy intakes equal energy expenditures. Imbalances between energy intakes and energy expenditures lead to body weight gains or losses.

A person's energy requirement is the usual intake level necessary to achieve energy balance in a healthy adult of a given age, gender, weight, height, and physical activity level (Institute of Medicine 2002/2005). For adults who are not pregnant or lactating, energy requirements equal total energy expenditures. For infants and young children and for pregnant or lactating adults, energy requirements equal total energy expenditures plus the energy needed for growth, called energy deposition.

Total energy expenditure (TEE) has several components (Institute of Medicine 2002/2005; Food and Agriculture Organization 2004):

- ***Basal Energy Expenditure (BEE).*** Derived from extrapolating the basal metabolic rate (BMR) to a 24-hour period. The BMR is defined as the rate of energy expenditure that occurs in the postabsorptive state, which occurs after an overnight fast of 12 to 14 hours and when a person is resting comfortably, supine, awake, and motionless in a thermoneutral environment.
- ***Thermic Effect of Food (TEF).*** The increase in energy expenditure above the BMR to eat and process (that is, digest, transport, metabolize, and store) food.
- ***Physical Activity.*** Every bodily movement that requires energy expenditure. Physical activity is usually the second-largest component of daily energy expenditure (after BEE), and the most variable across individuals.

- **Thermoregulation.** The ability of an individual to keep his or her body temperature within certain limits, even when the surrounding temperature differs.

TEE is the sum of BEE, TEF, physical activity, and thermoregulation (Institute of Medicine 2002/2005). The macronutrient panel measured TEE using the doubly labeled water method, which measures the average daily energy expenditure of free-living people over a period of days (typically, 10 to 14 days). The technique involves a subject's ingestion of a dose of water enriched with an isotope of hydrogen and an isotope of oxygen; then researchers determine the disappearance of both isotopes as their concentrations decline (Schoeller et al. 1986). The doubly labeled water method is generally considered the "gold standard" for measuring energy expenditures and is the basis for the most recent energy requirements set by the IOM macronutrient panel and the WHO. Direct measurement of TEE through the doubly labeled water method accounts for the difference between recent estimates of estimated energy requirements and previous estimates (such as the 1985 WHO estimates), which generally relied on either dietary intake data or a factorial approach (Food and Agricultural Organization and WHO 2006).

Using doubly labeled water method data, the macronutrient panel estimated regression equations of TEE for age and gender subgroups. For most adult subgroups, energy requirement is equivalent to TEE. For infants, young children, and adolescents, energy requirements include TEE plus energy deposition (ED). The energy needed for growth is estimated to decline from more than a quarter of total energy requirements at three months of age to less than five percent at 12 months of age and older (Food and Agriculture Organization 2004). Based on the TEE equations and estimates of ED, Table III.1 presents estimates of EERs for infants and young children at selected ages.

Table III.1. Estimated Energy Requirement (EER) for Boys and Girls

Age (mos.)	Boys			Girls		
	TEE (kcal/d)	ED (kcal/d)	EER (TEE+ED)	TEE (kcal/d)	ED (kcal/d)	EER (TEE+ED)
3	434	138	572	389	132	521
6	603	42	645	541	52	593
12	817	27	844	745	23	768
18	941	20	961	879	20	899
24	1,030	20	1,050	977	20	997
30	1,101	20	1,121	1,057	20	1,077

Source: Institute of Medicine 2002/2005, Tables 5-16 and 5-17.

REVIEW OF STUDIES ASSESSING USUAL ENERGY INTAKES

One underlying principle of assessing energy intakes and expenditures is energy balance. Over a period of time, energy intakes equal energy expenditures to maintain stable body weight. If a person's energy balance is negative over time—intakes lower than expenditures—then that person will take energy from his or her reserves and lose body

weight. Conversely, if the energy balance is positive over a period of time—intakes higher than expenditures—then excess energy intakes are added to reserves and the person gains body weight.

Since the macronutrient panel published its report on energy requirements, several studies have used 24-hour dietary recall data to compare reported energy intakes with EERs. These studies found that, for most adolescent and adult subgroups, mean usual energy intake was less than the mean EER (Devaney et al. 2005; Institute of Medicine 2006). This result is generally considered implausible, because such a negative energy balance would imply weight loss in these subgroups and the exact opposite pattern of weight gain has been observed. In light of the substantial difference between EER and intake—coupled with the fact that adults and adolescents are not losing weight but actually gaining weight—a likely explanation is that adults and adolescents underreport their food and beverage intakes (Schoeller 2002; Johansson et al. 1998; Mertz et al. 1991).

For young children, however, the findings of studies assessing energy intakes indicate a positive energy balance. As Table III.2 shows, several studies using replicate observations from 24-hour dietary recall data have found that mean usual energy intakes of infants and young children exceeded the mean EER. In the Feeding Infants and Toddlers Study, the positive energy balance increased with the age of the study respondents. Mean usual energy intake was 10 percent higher than the mean EER for infants 4 to 6 months of age, 23 percent higher for infants 7 to 12 months of age, and 31 percent higher for toddlers 12 to 24 months of age (Devaney et al. 2004). Mean usual energy intake was also higher than mean EER for subgroups of young children, including Hispanic and non-Hispanic infants and toddlers and WIC participants (Briefel et al. 2006b; Ponza et al. 2004; Institute of Medicine 2006, 2004; Devaney et al. 2005).

As mentioned earlier, four possible explanations could account for the positive energy balance reported in analyses of usual energy intakes of infants and young children. First, infants and young children could be consuming more energy than they need. This possibility is consistent with empirical evidence showing the increasing prevalence of overweight among children. However, the discrepancy between mean usual intake and mean EER is too large to be consistent with increases in the prevalence of overweight. For example, the mean energy intake for toddlers 1 to 2 years of age in the Feeding Infants and Toddlers Study was 1,220 kcal/d, compared with a mean EER of only 931 kcal/d (Devaney et al. 2004). This imbalance of almost 300 kcal/d would be projected to lead to an excess weight gain of at least 1 lb. every two weeks, or at least 25 lbs. over a year. Such excessive weight gain is far greater than the weight gain observed for toddlers over time.

Second, parents may be overreporting the intakes of infants and young children. Although most dietary recall studies provide visual aids to help parents or caregivers accurately report the quantities of foods and beverages consumed, respondents may underestimate the amounts spilled, spit up, or otherwise left uneaten. In addition, parents may have an unconscious desire to describe their child as a “good eater,” which could also

Table III.2. Studies Assessing Usual Energy Intake of Infants and Young Children

Reference	Data Set	Key Results for Energy Intake
Briefel et al. 2006	FITS 2002	<i>Infants 4 - 5 months:</i> mean usual energy intake was 9% higher than the mean EER for Hispanic (H) and non-Hispanic (NH) infants. <i>Infants 6 - 11 months:</i> mean usual energy intake was 17% higher than the mean EER for H, 22% higher for NH. <i>Toddlers 12 - 24 months:</i> mean usual energy intake was 36% higher than the mean EER for H, 31% higher for NH.
Institute of Medicine 2006	CSFII 1994 - 1996, 1998	<i>Non-breastfed WIC infants and children:</i> <i>0 - 3 months:</i> mean usual energy intake was 21% higher than the mean EER. <i>4 - 5 months:</i> mean usual energy intake was 29% higher than the mean EER. <i>6 - 11 months:</i> mean usual energy intake was 32% higher than the mean EER. <i>12 - 23 months:</i> mean usual energy intake was 37% higher than the mean EER. <i>2 through 4 years:</i> mean usual energy intake was 24% higher than the mean EER for low-active children and 14% higher than the mean EER for active children.
Devaney et al. 2005	CSFII 1994 - 1996, 1998	<i>WIC infants < 1 year:</i> mean usual energy intake was 22% higher than the mean EER. <i>WIC toddlers 1-3 years:</i> mean usual energy intake was 27% higher than the mean EER.
Devaney et al. 2004	FITS 2002	<i>Infants 4 - 6 months:</i> mean usual energy intake was 10% higher than the mean EER. <i>Infants 7 - 12 months:</i> mean usual energy intake was 23% higher than the mean EER. <i>Toddlers 12 - 24 months:</i> mean usual energy intake was 31% higher than the mean EER.
Institute of Medicine 2004	CSFII 1994 - 1996, 1998	<i>Non-breastfed WIC-income-eligible infants and children:</i> <i>< 1 year:</i> mean usual energy intake was 30% higher than the mean EER. <i>1 through 4 years:</i> mean usual energy intake was 25% higher than the mean EER for low-active children and 17% higher than the mean EER for active children.
Ponza et al. 2004	FITS 2002	<i>Infants 7 - 12 months who participated in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC):</i> mean usual energy intake was 32% higher than the mean EER. <i>WIC toddlers 12 - 24 months:</i> mean usual energy intake was 40% higher than the mean EER.

CSFII = Continuing Survey of Food Intake by Individuals

FITS = Feeding Infants and Toddlers Study

NHANES = National Health and Nutrition Examination Survey

lead to overreporting of intakes. (This is in stark contrast to the general finding of underreporting of intakes among adults.)

Third, parents may be underreporting children's weights. Such mistakes could be prevalent if, for example, many parents do not know their child's exact current weight but instead report their weight based on past measurements. This would be especially likely if parents rely on measurements during doctor visits and check-ups. As a consequence, EERs, which increase linearly with body weight, will also be understated. The understatement may not be trivial, either: if body weight is underreported by 1 kg (about 2.2 pounds), EER will be underestimated by approximately 70 kcal/d.

Fourth, energy requirements may be underestimated. The EERs for energy presented in the macronutrient report are generally lower than previous estimates of energy requirements. The TEE estimates are approximately 80 percent of the 1985 WHO recommendations for energy intake of infants and toddlers. Those estimates, however, were based on energy intakes, not on estimates of TEE from doubly labeled water techniques, and they included an extra five percent allowance for presumed underreporting of intakes (Institute of Medicine 2002/2005). Recent WHO estimates of energy requirements, which use doubly labeled water methods, are similar in magnitude to those developed by the IOM macronutrient panel (Food and Agriculture Organization 2004).

RE-ESTIMATION OF THE TOTAL ENERGY EXPENDITURE EQUATIONS

Given the discrepancy observed between reported energy intakes and mean EERs of infants and young children, it is useful to examine in more detail the estimates of TEE to determine how sensitive the requirement estimates are to model specification. The macronutrient report summarizes the vast literature that examines the factors associated with total energy requirements of young children and concludes that energy requirements of children 0 through 2 years vary by age, gender, and feeding mode. The final specification of the TEE equation, however, uses only weight as the predictor of energy expenditures for young children. The panel finds that adding additional covariates beyond weight—covariates such as gender, age, height, and squares of age, weight, and height—does not improve the predictive power of the TEE equation (Institute of Medicine 2002/2005). The TEE equation for young children 0 through 2 years of age is

$$(IOM) \text{ TEE (kcal/d)} = -100 + 89 * \text{weight of the child (kg)} .$$

The doubly labeled water data set for infants and young children used to estimate the TEE equation reported in the macronutrient report is included in Appendix Table I-1 of the macronutrient report (Institute of Medicine 2002/2005). This data set includes doubly labeled water data for 71 individuals 0 through 2 years of age, with repeated measurements on each child as he or she ages (for a total of 320 observations). In addition to TEE calculations, the data set includes information on each individual's age, height, weight, body mass index, gender, and feeding type.

Methods

The doubly labeled water data set is used to estimate regression equations for TEE with additional covariates included in the regression. The additional covariates include a set of covariates C_i that do not vary over time (such as gender) and covariates X_{it} that do vary with time (such as age, age-square, and height):

$$(3.1) \quad TEE_{it} = \beta_0 + \beta'_X X_{it} + \beta'_C C_i + \eta_i + \varepsilon_{it}.$$

Note that, because characteristics such as an infant's gender do not change over time, C is not indexed by t . The error term has two components, each of which has a mean of 0: an individual component that varies across infants but not over time (η_i) and an error term that varies both over time and across infants (ε_{it}). The individual-specific component captures any characteristics that are correlated with TEE but unobservable. If these unobservable characteristics are also correlated with the covariates, accounting for them can potentially improve the accuracy of our estimates.

As in the macronutrient report, the initial analysis estimates fixed effects models that use the repeated observations on individual TEEs. Such models help isolate the effect of observable characteristics that vary over time, including height, weight, and age. The fixed effects model also accounts for unobservable individual characteristics by focusing on how the dependent and independent variables change over time. Taking the mean of equation (3.1) for each individual gives

$$(3.2) \quad \overline{TEE}_i = \beta_0 + \beta'_X \bar{X}_i + \beta'_C C_i + \eta_i + \bar{\varepsilon}_i.$$

Subtracting (3.2) from (3.1) yields

$$(3.3) \quad (TEE_{it} - \overline{TEE}_i) = \beta'_X (X_{it} - \bar{X}_i) + (\varepsilon_{it} - \bar{\varepsilon}_i),$$

where the time-invariant terms C_i and η_i difference out of the equation. Because fixed individual variables difference out of equation (3.3), it is not possible to determine the effects that characteristics such as gender have on energy expenditures. To estimate the effects of time-invariant factors such as gender, the analysis also estimates Ordinary Least Squares (OLS) regression equations, as depicted by equation (3.1).

To assess the predictive power of the alternative model specifications, the root mean square error of the model, the F-statistic for adding covariates beyond weight, and the R-square are reported. TEE is then estimated for boys and girls of selected ages using the coefficients of the regression equations together with median weight and height for boys and girls at each age according to published data. Adding an allowance for ED yields the EERs.

Results

Table III.3 presents the results of estimating alternative fixed effects model specifications of the TEE equations. The first column of the table shows the estimates presented in the macronutrient report. Alternative specification (1) is the attempted replication of the IOM results, and the remaining columns show estimates that include additional covariates in the TEE equations. Overall, the fixed effects results are consistent with the findings of the TEE equation presented in the macronutrient report, which indicates that body weight alone is the best predictor of energy expenditures and energy requirements. Although specification (4) in Table III.3 has a slightly lower mean square error than the specification in the macronutrient report (108 versus 109), the difference is small, and the F-statistic for the addition of covariates beyond age is not statistically significant.

The bottom panel of Table III.3 presents EERs based on the alternative model specifications for TEE, published data on standard reference heights and weights, and estimates of energy deposition. Regardless of the model specification, EERs for infants and boys and girls up to 18 months of age are similar. However, for older children, especially at 30 months of age, EERs based on the more inclusive specifications—with age and age-square as covariates—are lower than EERs from the simpler specifications.

A drawback to fixed effects models is that they do not separately identify the importance of time-invariant individual characteristics (such as gender); individual characteristics are collectively represented by the fixed effect for that person. Such characteristics may be important predictors in the model and would help in determining whether, for example, boys and girls have different energy requirements. Further, unobservable individual characteristics do not appear to be important determinants of TEE.¹

In this context, OLS models are a more appropriate specification. Not surprisingly, the OLS model of TEE as a function of infants' weight alone, reported in column (1) of Table III.4, is very similar to the macronutrient report.² Height also does not provide additional explanatory power (column 2) nor does a linear term for age (column 3). However, this latter result may be a misspecification: when a quadratic function of age is included in column (4), both age and its square are highly significant at the one percent level. A female indicator variable is marginally significant in columns (5) – (8).

¹Estimates of the fixed effects model indicate that the variance of the individual effects (η_i) is very small relative to the variance of ε_{it} ; that is, TEE does not vary much across individuals beyond what is explained with observable characteristics. This suggests that treating $(\eta_i + \varepsilon_{it})$ as the error term in (3.1) rather than ε_{it} alone has little effect on the parameter estimates in an OLS regression. In addition, since η_i does not vary over individuals, there is less concern that these combined error terms will be correlated for repeated observations of the same infant. Thus, a random effects estimation approach is not necessary.

²The estimates reported in Table III.4 are clustered by infant to account for the fact that most individuals show up in the data multiple times, but as there is no evidence of individual-specific effects, this makes little difference.

Table III.3. Total Energy Expenditures and Estimated Energy Requirements—Fixed Effects Models

	(IOM)	(1)	(2)	(3)	(4)	(5)
<i>TEE Regression Results</i>						
Intercept	-100 (56)	-101** (35)	-116 (155)	-66 (302)	505 (401)	-8 (89)
Weight (kilograms)	89** (3)	89** (4)	87** (20)	87** (20)	77** (21)	64** (18)
Height (meters)			46 (449)	-47 (653)	-1037 (802)	
Age (months)				1.0 (5.8)	32* (16.0)	18.1 (11)
Age squared					-0.6* (0.3)	-.42 (.25)
F-test: Covariates beyond kg			.92	.98	.26	.25
Root MSE	109	109	109	109	108	108
R-squared	.74	.74	.74	.74	.74	.75
<i>Estimated Energy Requirements</i>						
6-month girl	593	589	589	590	605	596
12-month girl	768	764	763	763	793	777
18-month girl	899	894	893	894	924	903
24-month girl	997	991	991	994	994	976
30-month girl	1,077	1,071	1,071	1,076	1,012	1,006
6-month boy	645	641	640	640	631	631
12-month boy	844	839	837	836	841	832
18-month boy	961	956	954	955	961	948
24-month boy	1,050	1,044	1,043	1,045	1,026	1,015
30-month boy	1,121	1,115	1,115	1,119	1,040	1,038

Notes: Doubly labeled water data used to predict energy expenditure include 320 total observations of 71 infants (Institute of Medicine (IOM), 2002/2005). TEE and EER measured in kcal/d. Standard errors in parentheses, clustered by individual. Reported F-test p-value tests the inclusion of the covariates for that specification excepting weight and an intercept term. Estimated energy requirements are based on associated total energy expenditure model plus published energy deposition allowance (IOM 2002/2005, pp. 169-170) using median weight and height for girls and boys at each age (IOM 2002/2005, pp. 132-135).

* indicates statistically significant at the five percent level.

** indicates statistically significant at the one percent level.

Table III.4. Total Energy Expenditures and Estimated Energy Requirements—OLS Models

	(1OM)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
<i>TEE Regression Results</i>										
Intercept	-100** (56)	-92** (27)	-209* (90)	-38 (175)	110 (192)	-78** (29)	-202* (91)	6 (169)	160 (180)	-12 (39)
Weight (kilograms)	89** (3)	88** (3)	74** (11)	76** (11)	74** (11)	88** (3)	73** (11)	76** (11)	73** (10)	67** (7)
Height (meters)			325 (245)	8 (377)	-308 (406)		344 (241)	-37 (364)	-365 (387)	
Age (months)				3.6 (3.5)	19.9** (7.5)			4.4 (3.4)	21.2** (7.0)	17.1** (5.5)
Age squared				-0.4* (0.2)					-0.5* (0.2)	-0.4* (0.2)
Female						-21 (14)	-22 (13)	-24 (13)	-25* (12)	-24 (13)
F-test: Covariates beyond kg			.19	.27	.03	.13	.09	.08	.00	.00
Root MSE	109	110	110	110	109	110	109	109	108	108
R-squared	.74	.74	.74	.74	.75	.74	.74	.74	.75	.75
<i>Estimated Energy Requirements</i>										
6-month girl	593	591	589	591	596	583	581	583	587	585
12-month girl	768	763	758	760	782	755	750	751	774	769
18-month girl	809	802	888	894	910	884	879	886	903	896
24-month girl	997	988	987	1000	984	980	979	994	976	970
30-month girl	1,077	1,067	1,070	1,091	1,012	1,059	1,062	1,086	1,005	1,002
6-month boy	645	642	637	635	632	655	650	649	647	646
12-month boy	844	837	827	825	840	850	841	839	855	851
18-month boy	961	953	945	947	957	966	958	962	973	967
24-month boy	1,050	1,040	1,036	1,046	1,024	1,054	1,050	1,063	1,041	1,035
30-month boy	1,121	1,110	1,111	1,129	1,046	1,124	1,124	1,148	1,063	1,060

Notes: Doubly labeled water data used to predict energy expenditure include 320 total observations of 71 infants (Institute of Medicine (IOM), 2002/2005). TEE and EER measured in kcal/d. Standard errors in parentheses, clustered by individual. Reported F-test p-value tests the inclusion of the covariates for that specification excepting weight and an intercept term. Estimated energy requirements are based on associated total energy expenditure model plus published energy deposition allowance (IOM 2002/2005, pp. 169-170) using median weight and height for girls and boys at each age (IOM 2002/2005, pp. 132-135).

* indicates statistically significant at the five percent level.

** indicates statistically significant at the one percent level.

The preferred TEE specification includes weight, age, age squared, and gender (column 9) but excludes height. This specification has the minimum root mean square error of the nine models. An F-test strongly prefers this model to the specification in column (1) that was used for the macronutrient report. Each of the covariates is individually statistically significant at the five percent level as well, with the lone exception of gender, which nonetheless has a p-value of .055.

Using the same specification as used in the macronutrient report (column 1), the EERs for young children are very similar to the DRI estimates. With the preferred specification in column (9), EERs for girls and boys 6- to 18-months of age are also very similar to DRI estimates. However, the EERs for girls and boys 24 months of age (970 kcal/d and 1035 kcal/d, respectively) are slightly lower than the DRI estimates for this age. Extrapolating to children 30 months of age, as done in the macronutrient report, yields EERs that are 7.0 percent lower for girls and 5.4 percent lower for boys than the published EERs. These predictions, however, extend beyond the age range of the data set, which only includes observations on infants and children 0 through 25 months of age.

DISCUSSION

Although the exact TEE model specifications that perform best here differ from the macronutrient report, the resulting EERs are very similar, and there is no evidence that misspecifying the TEE model has understated energy requirements. The analysis presented in this chapter indicates that other characteristics beyond body weight have explanatory power in the TEE model, including age and gender. Nonetheless, neither the inclusion of these factors nor a different estimation strategy (OLS rather than fixed effects) drastically changes the EER predictions.

The statistical model in this chapter focuses on estimating TEE, and ED is taken as known in order to compute EER. As ED contributes to growth, it is especially important for young children. In fact, estimating ED is itself a very challenging task that has not been conclusively accomplished. The estimates in the macronutrient report are based on the work of Butte et al. (2000), who estimated ED by analyzing healthy infants' growth and changes in body composition. Because their methods require close, intensive study of each individual participant, they are necessarily restricted to a small sample (76 infants). Although there is no specific documented reason to suggest that their study sample is not representative, the small sample size nonetheless raises concerns about how well their results generalize to the national population.

Regardless, ED is a very small fraction of EER, and any errors in estimating ED would not explain the observed gap between infants' energy requirements and their intakes. For children 12 to 24 months of age, for example, true ED would have to be 15 times greater than current estimates to explain the difference between mean energy intake and mean EER. Even if ED estimates are imprecise, the estimation error would have to be implausibly large to affect the EERs.

The finding that the EERs estimated here are similar to those in the macronutrient report suggests that other explanations drive the large difference between energy requirements and intakes. One possibility is that intakes actually do exceed requirements by a substantial margin, but as discussed earlier, infants' observed weight gains over time are not of sufficient magnitude to explain the difference. Instead, either overreporting of children's energy intakes or underreporting of children's weights—or some combination of the two factors—is most likely responsible for the disparity.

CHAPTER IV

REVIEW OF STUDIES USED TO SET THE DIETARY REFERENCE INTAKES FOR SELECTED NUTRIENTS

Nutrients are the components of food that are the building materials for substances essential to growth and health. The ways in which nutrients are integrated into the body and influence its functions depend on a wide variety of physiologic and biochemical processes. Dietary protein, fat, and carbohydrate contribute the necessary energy to grow and maintain the body. Vitamins and minerals are required for efficient utilization and conservation of this energy (Mahan and Escott-Stump 1996).

An imbalance between a person's need for and intake of nutrients can lead to nutrient deficiency or toxicity. These conditions usually develop in stages over a considerable period of time. First, nutrient levels in blood and/or tissues change, followed by changes in cell function and structure. Eventually, symptoms and signs of morbidity appear; ultimately, death can result (Merck & Co. 2006).

As discussed earlier, recent studies assessing nutrient adequacy have reported substantial dietary inadequacies or excesses that appear unaccompanied by adverse health effects. Specifically, several studies found that large proportions of infants and young children are at risk of excessive intakes of zinc and vitamin A. Almost all population subgroups have inadequate intakes of magnesium and vitamin E, and intakes of fiber and potassium are far below recommended levels.

In interpreting the results of these dietary assessment studies, some questions have arisen regarding the DRIs for these nutrients. For both zinc and vitamin A, the methods used to estimate the UL resulted in a narrow margin between the RDA and UL for young children. In addition, the high prevalence of inadequacy for vitamin E is inconsistent with other data that show a low prevalence of low plasma vitamin E levels.

To provide some insight into these important concerns, this chapter reviews and discusses the methods and studies used to set relevant DRIs for zinc, vitamin A, magnesium, vitamin E, fiber, and potassium. For each of the nutrients, the discussion first describes its function in humans and its food sources and then summarizes the results of recent studies assessing the adequacy of dietary intakes. The discussion next describes what is known from

clinical or biochemical data on the prevalence of either deficiency from inadequate intakes or toxicity from excess consumption. Finally, each discussion concludes by reviewing and documenting the methods and studies used to set the DRIs for these nutrients.

ZINC

Zinc is an essential trace element important for normal immune response, wound healing, growth, and reproductive function. Zinc is found in a wide variety of foods, particularly in animal sources such as organ meats, beef, pork, poultry, seafood, and eggs. Nuts, seeds, legumes, and whole grains are relatively good plant sources, although the zinc in these foods is less bioavailable—their relatively high content of phytate inhibits zinc absorption (Higdon 2003). Other important sources of dietary zinc include iron-fortified ready-to-eat cereals, infant cereals, and infant formulas, many of which are also fortified with zinc.

A deficiency of zinc can occur as a result of inadequate zinc in the diet or when zinc absorption is inhibited by low bioavailability, by interactions with other nutrients, or in certain disease states. In addition to phytic acid, daily intake of iron at doses found in dietary supplements can decrease zinc absorption. Symptoms of zinc deficiency include growth retardation and delayed sexual maturity, skin changes, diarrhea, hair loss, and loss of appetite. Zinc deficiency among otherwise healthy individuals is not common in the United States (Institute of Medicine 2001; Brown and Hotz 2004).

Zinc toxicity is usually a consequence of acute or chronic intake of high doses of zinc supplements. Signs of acute zinc toxicity are abdominal pain, diarrhea, nausea, and vomiting. Chronic ingestion of excess zinc may result in reduced absorption of copper and iron, copper deficiency anemia, alterations in immune response, and a decline in high-density lipoprotein (HDL) levels (Institute of Medicine 2001; Brown and Hotz 2004).

Studies Assessing Usual Zinc Intakes

Several recent studies have assessed zinc intakes using 24-hour dietary recall data, the new DRIs for zinc, and the recommended methodology for assessing nutrient adequacy. As shown in Table IV.1, these studies have consistently found that high percentages of non-breastfeeding infants and young children have usual intakes of zinc that exceed the established UL.¹ While the finding is most pronounced among infants up to 12 months of age, substantial proportions of children 1 to 3 years old, and even 1 out of 5 children between the ages of 4 to 8 years, have zinc intakes above the UL (Arsenault and Brown 2003; Devaney et al. 2004; Devaney et al. 2005; Moshfegh et al. 2005; Institute of Medicine 2006; Briefel et al. 2006a, 2006b).

¹In contrast, a large proportion (60 percent) of *breastfed* infants 6 through 11 months of age has been found to have inadequate intakes of zinc (Institute of Medicine 2006). Breast milk at 6 to 11 months postpartum is essentially devoid of zinc, and the amounts of complementary foods consumed by breastfed infants, on average, do not provide sufficient zinc.

Table IV.1. Studies Assessing the Zinc Intake of Non-breastfeeding Infants and Young Children

Reference	Data Set	Supplements Included?	Key Results
Arsenault and Brown 2003	CSFII 1994-1996, 1998	No	<i>Infants age 0 - 6 months:</i> 92% had usual zinc intakes above the UL. <i>Infants age 7 - 12 months:</i> 86% had usual zinc intakes above the UL. <i>Children age 1 - 3 years:</i> 51% had usual zinc intakes above the UL. <i>Children age 4 - 5 years:</i> 3% had usual zinc intakes above the UL.
Devaney et al. 2005	CSFII 1994-1996, 1998	No	<i>WIC children and income-eligible non-participants age 1 - 3 years:</i> 60% had usual zinc intakes above the UL. <i>Children age 4 - 8 years from vulnerable subgroups:</i> More than 10% had usual zinc intakes above the UL.
Institute of Medicine 2006	CSFII 1994-1996, 1998	No	<i>WIC infants and children:</i> <i>0 - 3.9 months:</i> 86% had usual zinc intakes above the UL. <i>4 - 5.9 months:</i> 97% had usual zinc intakes above the UL. <i>6 - 11.9 months:</i> 88% had usual zinc intakes above the UL. <i>1 - 1.9 years:</i> 56% had usual zinc intakes above the UL. <i>2 - 4.9 years:</i> 58% had usual zinc intakes above the UL.
Moshfegh et al. 2005	NHANES 2001-2002	No	<i>Children age 1 - 3 years:</i> 69% had usual zinc intakes above the UL. <i>Children age 4 - 8 years:</i> 22% had usual zinc intakes above the UL.
Devaney et al. 2004	FITS 2002	Yes	<i>Toddlers age 12 - 24 months:</i> 43% had usual zinc intakes above the UL.
Briefel et al. 2006a	FITS 2002 Includes breastfed and non-breastfed infants	Yes	<i>Supplement Users:</i> <i>Infants age 6 - 11 months:</i> 60% had usual zinc intakes above the UL. <i>Toddlers age 12 - 24 months:</i> 68% had usual zinc intakes above the UL. <i>Supplement Non-Users:</i> <i>Infants age 6 - 11 months:</i> 59% had usual zinc intakes above the UL. <i>Infants age 12 - 24 months:</i> 38% had usual zinc intakes above the UL.
Briefel et al. 2006b	FITS 2002	Yes	<i>Hispanic toddlers age 12 - 24 months:</i> 47% had usual zinc intakes above the UL. <i>Non-Hispanic toddlers age 12 - 24 months:</i> 40% had usual zinc intakes above the UL.

One study that analyzed data from the 1994-96, 1998 Continuing Survey of Food Intakes by Individuals (CSFII) found that more than 85 percent of infants 0 to 12 months of age and about one-half of children 1 to 3 years of age had intakes of zinc that exceeded the UL (Arsenault and Brown 2003). Slightly higher estimates have been reported for WIC participants and eligible non-participants using the same data set (Devaney et al. 2005; Institute of Medicine 2006). More recently than the CSFII, data from the National Health and Nutrition Examination Survey (NHANES) 2001-2002 showed that 69 percent of children age 1 to 3 years had usual zinc intakes that exceeded the UL (Moshfegh et al. 2005). Neither the CSFII nor NHANES datasets used in these studies included the zinc contribution from dietary supplements, although Arsenault and Brown (2003) found that 77 percent of the zinc consumed by non-breastfed infants was from zinc-fortified infant formula and 68 percent of children consumed one or more zinc-fortified foods providing more than one-third of mean daily zinc intake.

The 2002 Feeding Infants and Toddlers Study (FITS), which did include the zinc from dietary supplements, revealed that 68 percent of supplement-using toddlers 12 to 24 months of age and 38 percent of non-supplement-using toddlers had usual zinc intakes that exceeded the UL (Briefel et al. 2006a). For infants age 6 to 11 months and for toddlers, both mean and median usual zinc intakes were above the UL. Supplements contributed less than one percent of the total daily zinc intake of infants overall and 8 percent of total zinc intake among toddlers taking supplements (Fox et al. 2006; Briefel et al. 2006a).² FITS data also showed that both Hispanic and non-Hispanic toddlers had usual zinc intakes that exceeded the UL (Briefel et al. 2006b).

These studies indicate that the apparent problem of zinc intakes above the UL among infants and young children involves multiple age, socioeconomic, and racial and ethnic subgroups; is not limited to individuals who use supplements; and may be related to the consumption of zinc-fortified foods. At the same time, there is little evidence of harmful effects of zinc at current levels of consumption. To date, there has only been a single reported case of zinc toxicity in a child associated with long-term intake of zinc supplements (Botash et al. 1992). Biochemical indicators of excess zinc intake, such as plasma or serum zinc or copper, were not measured in NHANES nor were biomarkers causally associated with or diagnostic of adverse effects due to excess zinc. Thus data are lacking to determine whether infants or children with zinc intakes above the UL are at increased risk of experiencing toxic effects.

Method and Data Used to Derive the UL for Zinc

To determine the UL for zinc, the IOM Panel on Micronutrients and Subcommittee on Upper Reference Levels of Nutrients used the risk assessment model described in Chapter I

²An analysis of NHANES III data found that between 1988 and 1994, one-tenth of one percent of infants and 5.3 percent of children age 1 to 10 years were taking a zinc-containing supplement (Briefel et al. 2000).

Table IV.2. Derivation of the Tolerable Upper Limit (UL) for Zinc for Infants and Young Children

Life Stage Group	UL	Method Used to Derive UL
Infants	0-6 mos: 4 mg/day	Risk assessment, based on critical adverse effect of excess zinc on copper status in adults. NOAEL of 5.8 mg/L identified from single study of zinc supplementation in formula-fed infants. Based on estimated average daily intake of human milk of 0.78 L/day, the NOAEL = 4.5 mg/day. UF set at 1.0 due to strength of study design and lack of evidence of zinc toxicity in infants. UL = 4.5/1.0=4.5, rounded down to 4 mg zinc/day.
	7-12 mos: 5 mg/day	No data to identify NOAEL or LOAEL. UL extrapolated from UL for infants 0-6 mos, based on relative body weight. For example, $UL_{7-12\text{ mo}} = UL_{0-6\text{ mo}} \times F$, where $F = (\text{Weight}_{7-12\text{ mo}} / \text{Weight}_{0-6\text{ mo}}) 0.75 = 4\text{ mg/day} \times (9\text{ kg}/7\text{ kg}) 0.75 = 5\text{ mg/day}$ of zinc (rounded down).
Young children	1-3 years: 7 mg/day	No data to identify NOAEL or LOAEL. UL extrapolated from UL for infants 0-6 mos, based on relative body weight, as shown above.
	4-8 years: 12 mg/day	

NOAEL = No-Observed-Adverse-Effect Level

LOAEL = Lowest-Observed-Adverse-Effect Level

UF = Uncertainty factor

(Table IV.2).³ In the process of “hazard identification,” the panel found no evidence of adverse effects from the zinc that occurs naturally in food. Chronic use of zinc supplements, however, was found to suppress immune response, decrease HDL cholesterol, induce copper deficiency anemia, and reduce iron absorption. The zinc ULs apply to total daily intake of zinc from food, water, and supplements.

In order to prevent copper deficiency, the adverse nutrient interaction between supplemental zinc and copper status was selected as the “critical” effect on which to base the UL. The choice to examine reduced copper status was based primarily on the availability of data for adults showing reduced activity of an enzyme highly sensitive to the effects of excess zinc on copper status (erythrocyte superoxide dismutase). Studies of the effects of zinc on iron absorption and HDL cholesterol were also reviewed, but results were not consistent enough to serve as the basis for deriving a UL (Institute of Medicine 2001).

³For ease of reading, the collective members of these two groups are referred to as “the panel” or the “IOM panel.” The same convention is used for the other IOM panels mentioned in this report.

Infants 0 to 6 Months. Data on the effects of zinc on the copper status of infants, children, or adolescents are lacking. The panel found only one case report of copper deficiency anemia in an infant. A 13-month old girl who had received 16 milligrams (mg) per day of supplemental zinc for 6 months and 24 mg/day for 1 month was hospitalized with clinical and laboratory signs of copper deficiency (Botash et al. 1992).⁴ Despite the dearth of dose-response data, a no-observed-adverse-effect level (NOAEL) was identified and a UL set for infants as described below.

Walravens and Hambidge (1976) conducted a double-blind controlled study of 68 healthy, full-term infants to determine the effects of supplementing infant formula with zinc. Infants in the control group were fed a formula containing 1.8 mg of zinc/liter, and the test group received the same formula supplemented with an additional 4 mg zinc/liter (5.8 mg/liter total). There was no evidence of reduced copper status (as measured by serum copper level) or other potential effects of zinc toxicity after 3 or 6 months. Based on this single study, a NOAEL of 5.8 mg/liter was identified. To derive the UL, the NOAEL was multiplied by an estimate of the average daily intake of human milk (0.78 liters/day). No adjustment was made for uncertainty (that is, the UF was set at 1.0). Thus, the UL for infants 0 to 6 months was estimated at 4.5 mg, and rounded down to 4 mg of zinc/day.

Infants 7 to 12 Months and Children 1 to 3 Years. There were no reports of adverse zinc-copper interactions in older infants or healthy children. Consequently, the UL values for infants 7 to 12 months and children 1 to 3 years of age were extrapolated from the young infant values, using a metabolic-weight-ratio method (see Table IV.2).

Discussion

Diet assessment studies have shown that substantial proportions of infants and young children have usual intakes of zinc that exceed the UL. These studies were conducted using large, nationally representative data sets covering the last 10 to 12 years, and results are consistent across various subgroups that have been studied. Estimates of the prevalence of zinc intakes above the UL from food alone are large, suggesting that dietary supplements are not the main cause of high zinc intakes among these population subgroups. The ULs for zinc for infants and young children were set on the basis of a single study with the objective of avoiding copper deficiency. Currently, no biomarkers of zinc status are used in NHANES or other large U.S. surveys that would help determine whether the large number of infants and children consuming zinc at levels above the UL show any indication of copper deficiency or other adverse effects of excess zinc.

There are several issues to consider when looking at the findings from dietary intake studies and the methods used to set the UL for zinc. Of particular interest are the recommendations for zinc ULs made by other expert groups, including the World Health Organization (WHO) and the International Zinc Nutrition Consultative Group (WHO 1996,

⁴The zinc (gluconate) supplements were prescribed prophylactically because a sibling had been diagnosed with acrodermatitis enteropathica, a genetic disorder that results in zinc malabsorption.

2002; Brown et al. 2004). The zinc ULs set by the WHO are considerably higher than the ULs set by the IOM panel for almost all life stage groups. The WHO values for older infants and children were extrapolated down from the UL for adult males, in contrast to extrapolating up from the younger to older age groups. A UL was not set for infants 0 to 6 months, but the WHO value for infants 7 to 12 months is 13 mg/day—more than twice that of the IOM value yet still below the 16 mg/day that resulted in copper deficiency for the 13-month old girl.

The International Zinc Nutrition Consultative Group concluded that data are insufficient to set a UL for zinc for either infants or young children. The group recommended reporting only NOAELs to indicate this fact. Their proposed NOAELs consider the results of two recently published zinc supplementation studies in India and Indonesia (Bhandari et al. 2002; Lind et al. 2003). In the Indian study, plasma copper levels were reduced after 4 months in infants 6 to 12 months of age given 10 mg of zinc per day and in children 1 to 2.5 years of age given 20 mg/day compared with the group given a placebo. In the second study, Indonesian infants 6 months of age received either 10 mg zinc/day or a placebo. At the end of 6 months, there was no difference in plasma copper levels between the groups. Considering the actual amount of zinc consumed (mean of 8 mg) and possible differences in copper absorption when zinc is consumed with a meal, a NOAEL of 6 mg zinc/day was recommended for infants 6 to 11 months—1 mg/day more than the UL set by the IOM panel for infants 7 to 12 months. The NOAEL for young children was obtained by adjusting up from the infant value based on reference body weights.

Several researchers have noted that the zinc UL for infants and young children is very close to recommended intake levels. The ULs are 1.7 to 2 times the AI or RDA for infants and 2.3 to 2.4 times the RDAs for children. For example, for infants 7 to 12 months, the UL is 5 mg zinc/day, whereas the RDA is 3 mg zinc/day. For most other nutrients, the gap between the RDA the UL is much larger (Institute of Medicine 2006). The International Zinc Nutrition Consultative Group expressed concerns about the implications of this narrow margin between the RDA and the UL for the development of interventions to improve zinc intakes among children under 3 years of age; however, with the exception of older breastfeeding infants, low zinc intakes are not a problem in the U.S. (Brown et al. 2004).

The biochemical indicators of copper status on which the infant zinc NOAELs were based (serum and plasma copper) differ from the enzyme indicator preferred by the panel in determining the UL for adults (erythrocyte superoxide dismutase activity). Some experts have questioned whether changes in any of the indicators of copper status should be used to determine the risk of zinc toxicity (Institute of Medicine 2001; Brown et al. 2004). While these markers may be sensitive to copper status, it is not clear whether they correlate well with the symptoms of copper deficiency anemia. Moreover, they are not specific to the effects of zinc intake, since high iron intake has also been shown to interfere with copper absorption in infants.

It is also important to recognize that, in general, the ULs were set conservatively, and adverse effects would only be expected at intakes well above the UL. For both infants and toddlers in FITS, the 75th and 90th percentiles of usual zinc intake were only about one and a half times the ULs. Similar results were obtained for children 1 to 3 years of age from the 2001-2002 NHANES analyses.

Given that there has been no evidence of adverse effects from the zinc that occurs naturally in food, a logical question is whether the ULs for zinc intake might be applied to only the zinc from dietary supplements and zinc-fortified foods (that is, non-naturally-occurring forms of zinc), as is the case for the vitamin E, niacin, and folate ULs. This possible amendment would have implications for both food labeling and nutrient databases, neither of which currently distinguish between different forms of zinc, but it is worth consideration.

Infant formula is the leading source of zinc in the diets of infants, contributing from 60 to 80 percent of total zinc intake (Fox et al. 2006; Arsenault and Brown 2003). In a study looking at the amounts and forms of iron, zinc, and copper in various foods and supplements, Johnson and colleagues (1998) found that all 12 ready-to-feed, iron-fortified infant formulas examined contained the highly available sulfate forms of added zinc and copper.⁵ The added copper is thought to counter the potential adverse effect of zinc (and iron) on copper absorption.

Young children's intake of zinc from fortified foods has increased over the past few decades. This change is primarily due to an increase in zinc fortification of ready-to-eat cereals (Arsenault and Brown 2003). Ready-to-eat cereals were the top contributor to zinc intakes among children age 4 to 5 years and second only to milk among children 1 to 3 years old. For toddlers 12 to 24 months in FITS, ready-to-eat cereals were also the second most important source of zinc relative to milk (12 percent and 28 percent of total intake, respectively; Fox et al. 2006). In the Johnson study mentioned previously, 80 percent of the iron-fortified ready-to-eat cereals contained added zinc, but none of these 32 cereals included added copper. The authors raise the question of whether reformulation of ready-to-eat cereals to improve their copper bioavailability is warranted.⁶

It is also noteworthy that the typical children's multivitamin and mineral supplement contains zinc in excess of two times the UL for children age 1 to 3 years. Vitamin and mineral supplements and food fortification are based on Reference Daily Intakes (RDIs) which have not yet been updated to reflect the DRIs. For example, the RDI for zinc is 15 mg. While this is equivalent to the 1989 RDA for adolescent and adult males, the 2001 zinc RDA for these life stage groups is only 11 mg. Johnson and colleagues found that most

⁵Infant formula typically contains from 0.75 to 1.0 mg zinc per 100 kilocalories (Johnson et al. 1998).

⁶Zinc-fortified ready-to-eat cereals commonly contain 10, 25, or 100 percent of the Reference Daily Intake (RDI) for zinc of 15 milligrams (Johnson et al. 1998). The RDI is a population-weighted average of the 1989 RDAs for healthy Americans age 4 years and older and is used as the basis for Daily Values listed on food labels.

multiple vitamin and mineral supplements containing zinc also contained copper but usually in the less available oxide form.

This analysis raises a number of research questions concerning the current UL for zinc for infants and young children. Among the issues to be considered are the paucity of data on the adverse effects of excess zinc consumption, the lack of biomarkers of zinc toxicity, differences in the ULs when extrapolating up from the infant value versus extrapolating downward from an adult value, and the narrow margin between recommended zinc intake levels and the ULs. In addition, if parents and other caregivers are overreporting their infants' and young children's energy intake (as discussed in Chapter III), it seems plausible that the proportions of these subgroups with zinc intakes above the UL are overestimated. With infant formula ranking as the most important source of food energy for non-breastfed infants, and ready-to-eat cereals fortified with zinc a commonly reported food among young children, it is likely that zinc intake is also overreported.

This review also suggests possible revisions to the UL for zinc, including dropping the application of the zinc UL to naturally-occurring zinc from food; changing the terminology to reflect the weaker basis for establishing an upper limit for zinc, such as the International Zinc Nutrition Consultative Group did in establishing only a NOAEL; and redefining the zinc UL to take into account copper intakes. Nevertheless, if a re-examination of the ULs for zinc finds that they are correct, it will be important to examine carefully current levels of zinc fortification and the amount of zinc in dietary supplements made for children.

VITAMIN A

Vitamin A is a fat-soluble vitamin necessary for vision, reproduction, normal growth and development, and immune function. The term vitamin A refers to a number of substances that exhibit vitamin A activity. Preformed vitamin A (mainly retinol) is found in animal products, especially liver, dairy products, and fish. Retinol is also the primary source of vitamin A in dietary supplements and fortified foods, including infant formula, ready-to-eat cereals, margarine, butter, and some fruit drinks and snack foods. Provitamin A carotenoids (mainly β -carotene) are found in deep yellow-orange fruits and vegetables and, to a lesser extent, dark green leafy vegetables (Institute of Medicine 2001). For individuals consuming a mixed diet, total vitamin A intake is composed of about 25 percent provitamin A carotenoids and 75 percent preformed vitamin A (Penniston and Tanumihardjo 2006; Olson 1987).

Vitamin A deficiency is uncommon in the United States. In developing countries, however, vitamin A deficiency is a major public health problem, especially among children. Inadequate vitamin A intake leads to impaired dark adaptation or night blindness, xerophthalmia (dry eye), and ultimately blindness. Vitamin A deficiency also increases the risk of respiratory infection, diarrhea, measles, and overall mortality (Institute of Medicine 2001).

Vitamin A toxicity, also referred to as hypervitaminosis A, is relatively rare. Acute toxicity results in nausea, vomiting, headache, increased cerebrospinal fluid pressure, and other effects, such as bulging fontanel in infants. Chronic toxicity is usually associated with

long-term consumption of “megadoses” of preformed vitamin A—provitamin A carotenoids have not been found to be toxic. Symptoms of chronic toxicity include dry itchy skin, loss of appetite, headache, and bone and joint pain. Severe cases of hypervitaminosis A may result in liver damage and even death (Institute of Medicine 2001).

Studies Assessing Usual Preformed Vitamin A Intake

A number of studies of dietary intake have shown that large proportions of both infants and young children consume preformed vitamin A at levels that exceed the UL (Devaney et al. 2004; Ponza et al. 2004; Moshfegh et al. 2005; Institute of Medicine 2006; Briefel et al. 2006a, 2006b). The UL for vitamin A applies only to the preformed vitamin A, or retinol, in food, fortified food, and/or supplements. Therefore, unless otherwise noted, the discussion in the following sections refers to preformed vitamin A. All of the studies summarized in Table IV.3 measured usual intake of preformed vitamin A. When separate values for the retinol content of foods were not available in the nutrient database, the authors calculated preformed vitamin A from values for total vitamin A and carotenoids.

One finding of high preformed vitamin A intakes among infants was discovered as a result of analyses conducted by the IOM Committee to Review the WIC Food Packages, using the 1994-96, 1998 CSFII data set (Institute of Medicine 2006). The committee found that 38 to 56 percent of non-breastfeeding infants 0 through 11 months of age who participated in WIC had intakes of preformed vitamin A above the UL. Because the nutrient contribution of dietary supplements was not measured in the CSFII, the proportions of infants with preformed vitamin A intakes above the UL are likely somewhat underestimated. In FITS, vitamin supplements contributed from 2 to 7 percent of the total vitamin A intake of infants age 4 to 11 months (Fox et al. 2006).

Analyses of the FITS intake data for toddlers 12 to 24 months of age, including the retinol contribution from dietary supplements, showed that 35 percent had intakes of preformed vitamin A that exceeded the UL (Devaney et al. 2004). The estimates were slightly higher for WIC participants and Hispanic children of the same age (Ponza et al. 2004; Briefel et al. 2006b). When supplement users and non-users were examined separately, almost all (97 percent) toddlers who used supplements were found to have intakes of preformed vitamin A that exceeded the UL, compared with 15 percent of toddlers who did not use supplements (Briefel et al. 2006a). Overall, dietary supplements were second only to milk among the most important contributors to total vitamin A intake for this subgroup (15 and 30 percent, respectively; Fox et al. 2006).

The frequency of high vitamin A intakes among young children who were surveyed in the 2001-2002 NHANES was similar to the FITS estimate for supplement non-users. In that study, 12 percent of children 1 to 3 years old had intakes of preformed vitamin A from food alone that exceeded the UL (Moshfegh et al. 2005).

Table IV.3. Studies Assessing the Preformed Vitamin A Intake of Non-breastfeeding Infants and Young Children

Reference	Data Set	Supplements Included?	Key Results
Institute of Medicine 2006	CSFII 1994-1996, 1998	No	<i>WIC infants and children:</i> <i>0 - 3 months:</i> 38% had usual intakes of preformed vitamin A above the UL. <i>4 - 5 months:</i> 56% had usual intakes of preformed vitamin A above the UL. <i>6 - 11 months:</i> 43% had usual intakes of preformed vitamin A above the UL. <i>1 - 1.9 years:</i> 25% had usual intakes of preformed vitamin A above the UL. <i>2 - 4.9 years:</i> 16% had usual intakes of preformed vitamin A above the UL.
Moshfegh et al. 2005	NHANES 2001-2002	No	<i>Children age 1 - 3 years:</i> 12% had usual intakes of preformed vitamin A above the UL.
Devaney et al. 2004	FITS 2002	Yes	<i>Toddlers age 12 to 24 months:</i> 35% had usual intakes of preformed vitamin A above the UL.
Ponza et al. 2004	FITS 2002	Yes	<i>WIC toddlers age 12 - 24 months:</i> 40% had usual intakes of preformed vitamin A above the UL. <i>WIC non-participant toddlers age 12 - 24 months:</i> 34% had usual intakes of preformed vitamin A above the UL.
Briefel et al. 2006a	FITS 2002	Yes	<i>Toddlers age 12 - 24 months (supplement users):</i> 97% had usual intakes of preformed vitamin A above the UL. <i>Toddlers age 12 - 24 months (supplement non-users):</i> 15% had usual intakes of preformed vitamin A above the UL.
Briefel et al. 2006b	FITS 2002	Yes	<i>Hispanic toddlers age 12 - 24 months:</i> 46% had usual intakes of preformed vitamin A above the UL. <i>Non-Hispanic toddlers age 12 - 24 months:</i> 35% had usual intakes of preformed vitamin A above the UL.

CSFII = Continuing Survey of Food Intake by Individuals

FITS = Feeding Infants and Toddlers Study

NHANES = National Health and Nutrition Examination Survey

The high prevalence of usual vitamin A (preformed) intakes above the UL in infants and young children is concerning, particularly among toddlers taking dietary supplements. At the same time, there is little evidence of an increased risk of vitamin A toxicity in infants or children. Biochemical indicators of high vitamin A intake (plasma retinyl esters) were measured in NHANES, but only among individuals 4 years of age and older. Other than some recent reviews of the toxic effects of preformed vitamin A and a handful of case reports, our search of the literature did not find new evidence of hypervitaminosis A in infants or children.

Methods and Data Used to Derive the UL for Vitamin A

The methods used to set the ULs for preformed vitamin A for infants and young children are summarized in Table IV.4. In accordance with the approach described previously, the panel conducted a full risk assessment beginning with a review of the data on adverse effects for each life stage subgroup. Because high intakes of provitamin A carotenoids have not been associated with vitamin A toxicity, only studies of the adverse effects of preformed vitamin A or retinol were reviewed.

The panel identified 10 case reports of toxicity in infants associated with high preformed vitamin A intakes over periods of months to years. All infants had been given supplemental forms of vitamin A (preformed) in doses ranging from 5,500 to 60,000

Table IV.4. Derivation of the Tolerable Upper Limit (UL) for Preformed Vitamin A for Infants and Young Children

Life Stage Group	UL ^a	Method Used to Derive UL
Infants	0-12 mos: 600 mcg/day	Risk assessment, based on critical adverse effects of bulging fontanel and skeletal abnormalities due to excess preformed vitamin A. No data to identify NOAEL. LOAEL calculated by averaging the lowest doses of 5,500-6,750 mcg/day of vitamin A from four case reports of hypervitaminosis A in infants 2.5 to 5.5 months old (LOAEL = 6,460 mcg/day, rounded to 6,000 mcg/day). UF set at 10 considering uncertainty of extrapolating from a LOAEL to NOAEL and interindividual variability. UL = LOAEL/UF = 6,000/10 = 600 mcg/day of preformed vitamin A.
Young children	1-3 years: 600 mcg/day	Limited data to identify NOAEL or LOAEL. UL extrapolated from UL for adults, based on relative body weight: $UL_{\text{child}} = UL_{\text{adult}} \times \text{Weight}_{\text{child}} / \text{Weight}_{\text{adult}}$ $= 3,000 \text{ mcg/day} \times (68.5 \text{ kg} / 13 \text{ kg}) = 600 \text{ mcg/day of preformed vitamin A (rounded).}$

^a As preformed vitamin A.

NOAEL = No-Observed-Adverse-Effect Level

LOAEL = Lowest-Observed-Adverse-Effect Level

UF = Uncertainty factor

micrograms (mcg) per day, although in one case chicken liver was the major source of high preformed vitamin A intake. Based on these reports, the critical adverse effects for infants were determined to be intracranial (bulging fontanel) and skeletal abnormalities. Other commonly reported symptoms of excess preformed vitamin A included anorexia, hyperirritability, edema of the occipital area, bone changes, and skin lesions and desquamation. Comparable data were not found for young children (Institute of Medicine 2001).

Infants 0 to 12 Months. No additional data were available to identify a NOAEL. The lowest observed adverse effect level (LOAEL) was determined by averaging the lowest doses of 5,500-6,750 mcg/day of preformed vitamin A from four of the ten case reports of hypervitaminosis A described by Persson (1965). In each of the four infants, signs of toxicity were observed within three months, at ages ranging from 2.5 to 5.5 months. The UF was set at 10 to balance the need for conservatism due to differences in individual tolerance of excess vitamin A (preformed) and the uncertainty of extrapolating from a LOAEL to NOAEL for a “nonsevere and reversible effect” (bulging fontanel). The LOAEL was divided by the UF to calculate the UL of 600 mcg/day of preformed vitamin A for infants (see Table IV.4).

Children 1 to 3 Years. Limited data were available to identify a NOAEL or LOAEL for young children. The panel found just two case reports of hypervitaminosis A, both due to the administration of large doses of preformed vitamin A in the form of vitamin supplements and “health foods” by the child’s mother (Siegel and Spackman 1972; Smith and Goodman 1976). In one, a 30-month-old boy received approximately 17,000 mcg of preformed vitamin A on a daily basis for a year. The second case was a 4-year-old girl given 7,500 mcg/day of preformed vitamin A for two years.

Due to the lack of additional data for young children, the UL for preformed vitamin A was extrapolated from the adult UL. For adults (other than women of childbearing age), the critical adverse effect of excess vitamin A (preformed) intake used to set the UL was liver abnormalities. Toxicity has been demonstrated in numerous studies of adults, but the UL was based on two case reports of liver abnormalities due to long term (10 to 12 years) use of vitamin A supplements of 14,000 and 15,000 mcg/day (Minuk 1988; Zafrani et al. 1984). The LOAEL was set at the lower dose of 14,000 mcg/day, and the UF at 5. The sources of uncertainty cited were the severe, irreversible nature of the adverse effect; a LOAEL instead of a NOAEL; and inter-individual variability (Institute of Medicine 2001). The resulting UL for adults is 3,000 mcg/day of preformed vitamin A. After adjusting for relative body weight, the UL for children 1 to 3 years of age was set at 600 mcg/day of preformed vitamin A—the same as the UL for infants.

Discussion

Recent studies of usual dietary intake have shown that substantial proportions of non-breastfeeding infants and young children have intakes of preformed vitamin A above the UL. Dietary supplements play an important role but are not the only cause of high vitamin A (preformed) intakes in these age groups. The UL for preformed vitamin A for infants was

based on the lowest doses of supplemental vitamin A known to result in adverse effects. Due to a lack of data, the UL for preformed vitamin A for young children was extrapolated from the UL for adults.

In contrast to what might be inferred from the results of the dietary intake studies, the IOM panel characterized the risk associated with exceeding the UL for preformed vitamin A as small. Several issues emerge in reviewing the results of these studies and the methods used to set the ULs for preformed vitamin A. One is the possibility that the uncertainty factor used to derive the UL for infants was set too conservatively. The UF of 10 for infants is very large relative to the empirical finding from the study that generated the LOAEL; that is, the resulting UL is 10 times lower than the lowest intake of preformed vitamin A that has been reported to cause hypervitaminosis A in infants. The UF of 10 for infants is also higher than the UF of 5 for adults, yet the critical adverse effect in infants is not severe and is reversible (bulging fontanel), while the critical adverse effect for adults is severe and irreversible (liver damage).

Another issue is the lack of data on which to base a UL for young children. As a consequence, the UL for preformed vitamin A for children 1 to 3 years of age was extrapolated from the UL for adults, based on relative body weight. This method resulted in a UL that is the same as the UL for infants even though the reference body weight for young children is considerably greater than for infants. In addition, the adult UL for vitamin A (preformed) is based on liver abnormalities that have been documented in adults but may not provide an appropriate end point for children.

On the other hand, conservatism in setting the UL for preformed vitamin A for infants and children may be warranted. Tolerance to excess intake of preformed vitamin A has been shown to vary, and infants and children are more susceptible to the adverse effects (Carpenter et al. 1987; Coughlan and Cranswick 2001; Penniston and Tanumihardjo 2006). It is also possible that some infants and young children experience toxicity or “subclinical toxicity” at levels of vitamin A (preformed) intake between the UL and LOAEL. Cases of chronic hypervitaminosis A can go unnoticed although they are usually reversible upon cessation of supplement use (Bendich and Langseth 1989).

A further matter of importance is that dietary supplements and several foods commonly consumed by young children contain large amounts of preformed vitamin A. Data from NHANES III show that about three-quarters of children 1 to 3 years of age who were taking supplements exceeded the UL for preformed vitamin A from supplements alone. Daily multivitamins in the dose typically recommended for young children contain 2,500 International Units (IUs) or 750 mcg of preformed vitamin A, which exceeds the UL of 600 mcg/day (Allen and Haskell 2002). Briefel and colleagues (2006a) found that supplement use is relatively uncommon among young infants but increases to 19 percent of infants 6 to 11 months of age and 31 percent of toddlers age 12 to 24 months. They also demonstrated that the adequacy of total vitamin A intakes for toddlers does not depend on supplement

use. Thus, if the current ULs are accurate, providing supplemental preformed vitamin A may put healthy young children at risk of vitamin A toxicity unnecessarily.⁷

The major food sources of preformed vitamin A in the diets of infants and toddlers are infant formula, breast milk, cow's milk, and fortified ready-to-eat cereals (Fox et al. 2006). Fortified cereals usually contain at least 25 percent of the Daily Value for vitamin A per serving, or about 375 mcg of preformed vitamin A. A glass of low-fat milk provides another 150 mcg. These two foods together provide about 87 percent of the UL for young children. Thus it is very easy for a child to consume more than the UL for preformed vitamin A even without taking a vitamin supplement.

As with zinc, the possibility that usual intakes of preformed vitamin A have been overreported along with energy intake cannot be ruled out. However, this review raises some questions about the UL for preformed vitamin A. The uncertainty factor used to set the UL for infants may be too conservative given the limited severity of the critical adverse effect of excess preformed vitamin A intake chosen for this age group. In addition, the same value for the UL was set for young children, which seems conservative given their greater body weight relative to infants. The UL for preformed vitamin A for young children was based on a critical adverse effect demonstrated only in adults. Nevertheless, studies have shown that infants and children are more sensitive to the toxic effects of preformed vitamin A than adults. It is of particular concern that children's vitamin supplements contain an amount of vitamin A (preformed) that exceeds the UL and that a substantial share of infants and toddlers with adequate vitamin A intakes from food are receiving these vitamins. Although there has been no evidence of widespread vitamin A toxicity, biomarkers of vitamin A status were not measured for these age groups in NHANES, and clinical signs of toxicity may be underreported. The doses and forms of preformed vitamin A in supplements and food fortification may need to be reevaluated.

MAGNESIUM

Magnesium is an essential micronutrient that is integral to the healthy functioning of several physiological processes. It is a component of numerous metabolic reactions, including energy production, synthesis of carbohydrates and lipids, cell signaling and migration, and ion transport across cell membranes, among others. It also contributes to the structure of bones, cell membranes, and chromosomes. Magnesium is readily available in both plant and animal food sources such as leafy green vegetables, unrefined grains, and nuts, as well as meats and milk (Higdon 2003).

Magnesium deficiency is extremely rare among healthy individuals who consume a varied diet, but certain conditions, such as gastrointestinal and renal disorders, chronic

⁷A meta-analysis of hypervitaminosis A, which included 35 cases in children between 0 and 2 years of age, found that certain forms of vitamin A supplements (water-miscible, emulsified, and solid) are more toxic than others (oil-based) (Myhre et al. 2003). This information was not available at the time the ULs for preformed vitamin A were set.

alcoholism, and advancing age, can increase the risk of magnesium deficiency. Severe magnesium deficiency has been associated with hypocalcemia, neuromuscular hyperexcitability, metabolic disorders, and cardiovascular conditions, such as arrhythmias and atrial fibrillation. Epidemiological studies have also found a relationship between magnesium depletion and hypertension, postmenopausal osteoporosis, insulin resistance, and decreased insulin secretion (Institute of Medicine 1997).

Studies Assessing Usual Magnesium Intake

Studies that have assessed the usual intake of magnesium among adults, adolescents, and older children using 24-hour dietary recall data found that large proportions of these subgroups consumed magnesium at levels below the EAR (Table IV.5). The rates of inadequacy varied among age and gender subgroups, ranging from 14 percent of male children age 9 to 13 years to 91 percent of female adolescents age 14 to 18 years (Moshfegh et al. 2005; Sutor and Gleason 2002). In these studies, adolescents of both genders had the highest rates of magnesium inadequacy. Among older adults, children, and adolescents, females had higher rates of magnesium inadequacy than males. All of these analyses, which used either the 1994-1996, 1998 CSFII or the 2001-2002 NHANES data set, excluded intake of magnesium from supplements; thus, the estimates most likely overstate the true prevalence of inadequate magnesium intakes among the general population.

As discussed previously, adolescents and adults tend to underreport energy intake, which implies that magnesium intakes could be higher than these analyses suggest (Mertz et al. 1991; Johansson et al. 1998; Schoeller 2002). Underreporting alone, however, cannot explain the high rates of inadequacy observed in these dietary studies.

Clinical magnesium deficiency is quite rare among healthy individuals. A search of the literature that was published since the release of the DRIs for magnesium failed to reveal any cases of magnesium deficiency.

Method and Data Used to Derive the EAR for Magnesium

When selecting an indicator that would be appropriate for estimating the average magnesium requirement to ensure healthy functioning and decreased risk of chronic disease, the IOM Panel on Calcium and Related Nutrients considered various measures:

- ***Serum Magnesium Concentration.*** The concentration of magnesium in blood serum is sensitive to magnesium depletion due to dietary change. However, it was not considered the most accurate measure of magnesium status because the measure has failed to register below accepted normal values in clinical studies in which intracellular magnesium levels were low. Furthermore, higher risk for cardiovascular complications occurs at levels of serum magnesium at the lower end but within the normal range of serum magnesium concentration.

Table IV.5. Studies Assessing the Magnesium Intake of Older Children and Adults

Reference	Data Set	Supplements Included?	Key Results
Suitor and Gleason 2002	CSFII 1994-1996	No	<i>Female children age 9 - 13 years:</i> 33% had magnesium intakes below the EAR. <i>Male children age 9 - 13 years:</i> 16% had magnesium intakes below the EAR. <i>Female adolescents age 14 - 18 years:</i> 89% had magnesium intakes below the EAR. <i>Male adolescents age 14 - 18 years:</i> 62% had magnesium intakes below the EAR.
Foote et al. 2004	CSFII 1994-1996 day 1 data only	No	<i>Male adults over 18 years of age:</i> mean probability of adequacy for magnesium was 36%. <i>Female adults over 18 years of age:</i> mean probability of adequacy for magnesium was 34%.
Devaney et al. 2005	CSFII 1994-1996, 1998	No	Most adolescent and adult subgroups have inadequate intakes of magnesium. <i>Female adolescents:</i> 90% had magnesium intakes below the EAR. <i>Older adults over 60 years of age:</i> Between 70% and 75% had magnesium intakes below the EAR. <i>Low-income individuals:</i> high proportions of low-income individuals above 9 years of age had magnesium intakes below the EAR. <i>FSP and WIC participants:</i> high proportions of FSP and WIC participants over 9 years of age had magnesium intakes below the EAR.
Institute of Medicine 2006	CSFII 1994-1996, 1998	No	<i>Non-breastfeeding postpartum adolescent and adult women 14 - 44 years of age:</i> 88% had magnesium intakes below the EAR for women age 19 - 30 years.
Moshfegh et al. 2005	NHANES 2001-2002	No	<i>Female children age 9 - 13 years:</i> 44% had magnesium intakes below the EAR. <i>Male children age 9 - 13 years:</i> 14% had magnesium intakes below the EAR. <i>Female adolescents age 14 - 18 years:</i> 91% had magnesium intakes below the EAR. <i>Male adolescents age 14 - 18 years:</i> 78% had magnesium intakes below the EAR. <i>Female adults over 18 years of age:</i> 67% had magnesium intakes below the EAR. <i>Male adults over 18 years of age:</i> 64% had magnesium intakes below the EAR.
Gillis and Gillis 2005	Hamilton Children's Exercise and Nutrition Ctr.	No	<i>Non-obese and obese children age 5 - 13 years:</i> Over 25% of both non-obese and obese children had magnesium intakes below the EAR.

CSFII = Continuing Survey of Food Intake by Individuals; NHANES = National Health and Nutrition Examination Survey

IV. Review of Studies Used to Set the Dietary Reference Intakes for Selected Nutrients

- ***Plasma-Ionized Magnesium.*** The amount of magnesium in the blood plasma, as measured by ion-specific electrodes, appears to be a better measure of magnesium status than serum magnesium. Further study is required however before the procedure can be validated as an accurate measure of magnesium status.
- ***Intracellular Magnesium.*** Intracellular magnesium is a measure of the total magnesium contained in red blood cells, skeletal muscle, bone, and peripheral lymphocytes, among others. This measure also appears to be a more accurate indicator of magnesium status than serum magnesium yet also requires further evaluation.
- ***Estimates of Normal Tissue Accretion of Magnesium During Growth.*** It is possible to predict the amount of magnesium accumulation necessary to maintain healthy growth during childhood. However, there is not enough evidence available to establish an estimate of the amount of dietary magnesium required to ensure normal tissue accretion of magnesium throughout childhood.
- ***Magnesium Tolerance Tests.*** Tests to assess the renal excretion of non-orally administered magnesium have not been validated as an adequately sensitive measure of magnesium depletion in normal subjects. A magnesium tolerance test is also affected by renal function and is suboptimal due to its invasive nature.
- ***Epidemiological Studies.*** The available data from epidemiological studies linking magnesium intake to various positive and negative health outcomes were insufficient to establish causality and thus were not considered an adequate measure of magnesium deficiency.
- ***Balance Studies.*** Balance studies assess the amount of a nutrient that is absorbed by comparing observed intake to excretion. If individuals' intake exceeds excretion, they are said to have positive balance; if their excretion of the nutrient is greater than the amount consumed, they have negative balance. When intake matches excretion, individuals are considered to be in equilibrium or have zero magnesium balance. While it has been determined that adults require zero magnesium balance, with preference given to maintaining positive rather than negative balance over time, children and adolescents must maintain positive balance to amass the necessary levels of magnesium by adulthood.

After considering these options, the IOM panel chose to use magnesium balance studies as an indicator of magnesium requirements. Balance studies have been the primary measure of dietary magnesium status for the past several decades and are an attractive measure because most of these studies were conducted in a clinical setting where diet could be closely monitored and controlled. The panel acknowledged some of the balance studies' limitations,

which include inaccuracy in the measurement of intake and excretion (in stool and urine) and their failure to assess other bodily sources of magnesium loss. Because it has not been established that maximal retention of magnesium is beneficial (as is the case with calcium and bone mass accretion, for example), the panel chose to base the EAR on data from magnesium balance studies that were published after 1960, that had an adaptation period of at least 12 days or used self-selected diets, and that tested at least one level of magnesium intake below and one near the required level of magnesium.

Table IV.6 provides a summary of the studies and methods used to determine the EAR for magnesium for children, adolescents, and adults. The discussion below provides details on the derivation of the EAR for specific age and gender subgroups.

Children Age 1 to 13 Years and Adolescents Age 14 to 18 Years. The IOM panel assumed that a positive magnesium balance (accretion rate) of 8 to 10 mg/day for children and adolescents would be adequate, with older children requiring a balance of approximately 10 mg/day due to periods of rapid growth. This approximation was based on Andon and colleagues' (1996) estimate of a positive balance of 8.5 mg/day or more for girls age 10 to 12 years, at an intake equivalent to the 1989 RDA for magnesium. The results of the balance studies of children and adolescents reviewed by the panel were thus compared to this benchmark for positive balance.

The EARs for children and adolescents were based on the results of balance studies conducted in children that met the IOM panel's criteria, as described earlier. While adequate balance data were not available for the entire age range of 1 to 18 years, the panel determined that seven balance studies met the criteria and could be used to determine average requirements (Schofield and Morrell 1960; Abrams et al. 1997; Andon et al. 1996; Greger et al. 1978, 1979; Schwartz et al. 1973; Sojka et al. 1997). One of the seven studies assessed magnesium balance in children 7 to 9 years of age, and the remaining six included children between the ages of 10 to 14 years. Because this balance data only provided information on magnesium requirements for selected ages, the panel applied the findings of these seven studies to the rest of the child and adolescent subgroups based on the relevant age and gender groups represented in the studies.

The EARs for magnesium for children 1 to 3 and 4 to 8 years of age were based on one balance study conducted in 1960 on children 7 to 9 years of age and five balance studies of children 10 to 14 years of age conducted between 1973 and 1997, which were used to supplement the dearth of balance data on young children (Schofield and Morrell 1960; Abrams et al. 1997; Andon et al. 1996; Greger et al. 1978, 1979; Schwartz et al. 1973). The data from the balance studies of older children were extrapolated for the younger age group on the basis of reference body weights. The balance study of children age 7 to 9 years found that a positive magnesium balance was maintained on intakes of magnesium between 121 to 232 mg/day (Schofield and Morrell 1960). The IOM panel noted that this study, when viewed alongside the balance studies of older children, suggested that a daily intake of 5 mg per kilogram (kg) would result in a positive magnesium balance of approximately 10 mg/day for children age 1 to 8 years; however, there was uncertainty as to whether this standard would meet or exceed the needs of 50 percent of children in this age range. Using the

Table IV.6. Derivation of the Estimated Average Requirement (EAR) for Magnesium for Children and Adults

Life Stage Group	EAR	Method Used to Derive EAR
Young children	1 - 3 years: 65 mg/day 4 - 8 years: 110 mg/day	EARs were based on one magnesium balance study of children 7 to 9 years of age and data from five balance studies of older children and adolescents 10 to 14 years of age, extrapolating based on relative body weight. Assumed that a positive magnesium balance of 8 to 10 mg/day would result in adequate tissue accretion of magnesium in children 1 to 8 years of age, and that magnesium requirements do not differ by gender. An EAR of 5 mg/kg/day was set for this age group.
Older children	9 - 13 years: 200 mg/day	EAR was based on three magnesium balance studies of children and young adolescents 10 to 14 years of age. Assumed that a positive magnesium balance of 8 to 10 mg/day would result in adequate tissue accretion of magnesium in children 9 to 13 years of age, and that magnesium requirements do not differ by gender. An EAR of 5 mg/kg/day was set for this age group.
Adolescents	Boys 14 - 18 years: 340 mg/day Girls 14 - 18 years: 300 mg/day	EARs were based on six magnesium balance studies of children and young adolescents 10 to 14 years of age. Assumed that adolescents would require an additional magnesium intake of 0.3 mg/kg/day to maintain an adequate positive magnesium balance of 8 mg/day, and that magnesium requirements do not differ by gender. An EAR of 5.3 mg/kg/day was set for this age group.
Adults	Men 19 - 30 years: 330 mg/day Women 19 - 30 years: 255 mg/day Men 31 years and older: 350 mg/day Women 31 years and older: 265 mg/day	EAR for adult women was based on two magnesium balance studies; EAR for adult men was based on eight magnesium balance studies. Assumed that a zero magnesium balance is adequate for adults over 19 years of age, and that a positive balance is preferred over a negative balance over time. Also assumed a decline in renal functioning for women over 30 years of age, and increased fiber intake for men over 30 years of age. No balance data available for women over 50 years of age and men over 70 years of age.

reference weights for these age groups, the EAR for magnesium was set at 65 mg/day for children 1 to 3 years of age and 110 mg/day for children 4 to 8 years of age. This level of intake assumes that protein intake is adequate—dietary protein is thought to have a positive effect on magnesium absorption (Schwartz et al. 1973).

The EAR for magnesium for children 9 to 13 years of age was based primarily on three balance studies that assessed magnesium absorption and retention in children 10 to 14 years of age (Andon et al. 1996; Greger et al. 1978; Abrams et al. 1997). Two studies assessed magnesium balance in female subjects between 10.5 and 14.5 years of age, and one study involved male subjects averaging 10.9 years of age. All three studies allowed subjects to either consume their usual diet throughout the study or did not control the amount of magnesium consumed in prescribed diets; thus they did not assess multiple levels of magnesium intake. Abrams and coworkers (1997) found that boys and girls at this age share similar requirements for magnesium; however, the authors noted that their study did not adequately evaluate the balance of older pubescent boys. Given their identical reference weights and the IOM panel's estimate of required daily intake of 5 mg/kg for children 9 to 13 years, the EAR for both boys and girls in this age range was set at 200 mg/day.

The IOM panel based the EAR for adolescents 14 to 18 years of age on six balance studies in older children and young adolescents (Greger et al. 1978, 1979; Andon et al. 1996; Abrams et al. 1997; Schwartz et al. 1973; Sojka et al. 1997). Four of these balance studies included subjects between 12 and 14 years of age, one included subjects 9.5 to 14.2 years of age, and another included subjects that were only 10.5 to 12.5 years of age. None of these studies examined adolescents age 15 to 18 years, nor were the results for the older children extrapolated for the older adolescent group. Based on the findings of Abrams et al. (1997), the panel estimated that adolescents would need to consume an additional 0.3 mg/kg/day in order to achieve a positive balance of 8 mg/day of magnesium. Using this estimate, the panel established an EAR of 5.3 mg/kg/day for adolescent males and females age 14 to 18 years. This resulted in an EAR for magnesium of 340 mg/day for adolescent males and 300 mg/day for adolescent females.

One of the balance studies reviewed illustrated the positive effects of protein on magnesium absorption. Schwartz et al. (1973) found that an average intake of 240 mg/day (4.6 mg/kg/day) of magnesium resulted in negative balance among all of the boys who consumed a lower protein diet of 43 grams (g) per day; however, the same intake resulted in an average positive balance of 0.19 mg/kg/day among the boys who consumed a higher protein diet (93 g/day).

Adults Age 19 to 30 Years. As discussed earlier, the IOM panel assumed that a zero balance should be maintained in adults age 19 years and older, with preference given to a positive rather than a negative balance over time. Using this benchmark, the panel evaluated three studies of magnesium balance in men and two studies in women. These balance studies covered almost the entire age range of this subgroup, including adult subjects from 20 to 35 years of age.

Greger and Baier (1983) and Schwartz et al. (1986) tested relatively high levels of magnesium intake and found positive balance in their male subjects who had an average age

of 25 years and were between 22 and 32 years of age, respectively. While these studies used controlled diets, neither tested multiple levels of magnesium intake. Lakshmanan et al. (1984) allowed their male subjects between 20 and 35 years of age to consume self-selected diets. The average magnesium intake of 333 +/- 120 mg/day resulted in just under half of their subjects maintaining magnesium balance. Giving particular weight to the latter study, the IOM panel concluded that an EAR of 330 mg/day is appropriate for males age 19 to 30 years.

Two balance studies were used to set the EAR for women age 19 to 30 years. The Lakshmanan et al. (1984) study described above assessed balance in eight female subjects between 20 and 30 years of age who consumed self-selected diets. Similar to Schwartz et al. (1973), Wisker et al. (1991) explored the effect of protein intake on magnesium balance in women. They found that, although magnesium intakes of 243 mg/day combined with a lower protein diet (55.7 g/day) resulted in negative magnesium balance in German women, similar magnesium intakes (245mg/day and 252 mg/day) combined with a higher protein diet (73.8 g/day and 71.8 g/day, respectively) resulted in slightly positive magnesium balance. Because preference is given to maintaining a positive rather than a negative balance over time, the EAR was set at 255 mg/day.

Adults Age 31 to 50 Years. Four of the five balance studies used to set the EAR for men age 31 to 50 years examined interactions between other nutrients and magnesium balance. Some studies have suggested that high intakes of fiber decrease the absorption of magnesium (Siener and Hesse 1995; Wisker et al. 1991). Kelsay et al. (1979) and Kelsay and Prather (1983) found that in controlled low fiber diets, magnesium intakes of 308 to 356 mg/day were adequate to maintain magnesium balance in men; however, those subjects who consumed similar levels of magnesium as part of a high fiber diet had negative balance. In contrast to the finding of Schwartz et al. (1973) and Wisker et al. (1991), a controlled diet study of 10 men age 19 to 64 years found that average magnesium intakes that ranged from 229 to 258 mg/day were adequate to achieve magnesium balance, regardless of the level of protein (65 mg/day or 94 mg/day) (Mahalko et al. 1983). Spencer et al. (1994) varied magnesium and calcium intakes in five men between 38 and 75 years of age and found that subjects on extremely high magnesium diets (798 and 826 mg/day) had positive balance regardless of the level of calcium, whereas those on the low magnesium diets (240 and 264 mg/day) had negative balance, independent of calcium intake. Thus, the IOM panel set the EAR at 350 mg/day, higher than that for men age 19 to 30 years, based on greater evidence of negative balance in the intake range of 300 to 350 mg/day and the assumption that the consumption of fiber increases with age.

The IOM panel used only one study to set the EAR for women. Lakshmanan et al. (1984) found that 4 of the 10 female subjects age 35 to 53 years on self-selected diets were in equilibrium or positive magnesium balance, with intakes that ranged from 182 to 258 mg/day; the remaining six were in negative balance, with intakes that ranged from 164 to 301 mg/day. The EAR was set at 265 mg/day, which is higher than that of women age 19 to 30 years because renal function, which contributes to magnesium status, deteriorates with age, and a larger proportion of the older women studied were in negative balance.

Adults 51 Years and Older. The IOM panel used the results of five balance studies to set the EAR for magnesium for men 51 to 70 years of age. No balance studies were available for women 51 to 70 years of age, nor were there any balance studies available for either men or women age 70 years or older.

Four of the balance studies used to set the EAR for men age 51 to 70 years were also used to set the EAR for men age 31 to 50 years. These studies all had sample sizes of fewer than 13 subjects and included men between 19 and 75 years of age. The fifth study, Schwartz et al. (1984), examined magnesium balance in men with an average age of 53 years; this study found a positive balance associated with an average intake of 381 mg/day. The IOM panel set the EAR for men age 51 to 70 years at 350 mg/day, which matches the EAR for men age 31 to 50 years.

The EAR for women 51 to 70 years of age was set at 265 mg/day; it is identical to the EAR for women 31 to 50 years of age because there were no additional balance data available for the older age group. The EAR for the women age 51 to 70 years was not set at a higher level due to decreased renal functioning because this decline was already incorporated into the EAR for women age 31 to 50 years.

The IOM panel was unable to find any acceptable magnesium balance studies of individuals over the age of 70, so they evaluated data from one magnesium tolerance test and two intracellular studies of institutionalized and non-institutionalized elderly subjects (Gullestad et al. 1994; Touitou et al. 1987; Paolisso et al. 1992). None of these studies provided conclusive evidence that could be used to set an EAR for this age group; however, their results were relatively consistent with the balance studies described above. Thus, the IOM panel chose to apply the estimated magnesium requirements for adults age 51 to 70 years to this elderly age group. Nonetheless, they noted that urinary magnesium excretion increases with age.

Discussion

Studies of usual intakes of magnesium suggest that high proportions of older children, adolescents, and adults consume inadequate amounts of this essential nutrient. These results are mirrored across age and gender divisions; however, there is a lack of evidence of widespread magnesium deficiency in the general public. The EARs for magnesium were determined on the basis of available balance study findings for subgroups of children and adults.

There are several issues to consider when reviewing the derivation of the EAR for magnesium. There is a paucity of balance data for multiple age and gender subgroups. For example, no balance studies were available to help determine the appropriate average magnesium requirements for children under 7 years of age, adolescents 15 to 18 years of age, older female adults over 50 years of age, or the elderly. In addition, the balance data from children 10 to 14 years of age were applied, rather than extrapolated on the basis of relative weight, to older adolescents age 15 to 18 years; and four out of the five balance studies used

to set the EAR for men 31 to 70 years of age had small sample sizes ($N < 13$), so they may not provide a reliable estimate of the average magnesium requirements for this subgroup.

Besides a lack of available balance data for particular subgroups, some of the balance studies have certain limitations that should be taken into consideration. The IOM panel concluded that two of the three balance studies used to set the EAR for men age 19 to 30 years assessed levels of magnesium intake that were too high to obtain an estimate of average magnesium requirements; furthermore, none of the three studies evaluated more than one level of magnesium intake. The latter issue was true for many of the balance studies used. Despite the stipulation that a balance study must assess at least two levels of intake to be included in the analysis, several of the studies used to set the EARs failed to do so.

More important, however, balance studies may not provide an accurate assessment of magnesium requirements. Hegsted (1973) concluded that balance studies overestimate the retention of nutrients. Other research has also suggested that balance studies systematically overestimate intake and underestimate output of nutrients. Horwitt (1986) suggested that balance studies are often inappropriately used to determine nutrient requirements, and that short-term balance studies may inaccurately assess nutrient retention due to gradual changes in nutrient status. Horwitt also noted that mineral balance, in particular, is affected by variation in hormonal and activity levels.

The interaction between protein and magnesium absorption seems to play an important role in determining magnesium adequacy. While the EAR for males age 14 to 18 years was set at 340 mg/day, Schwartz et al. (1973) found that adolescent males who consumed a diet that contained 240 mg/day of magnesium and 93 g/day of protein maintained an average positive magnesium balance of between 6 and 15 mg/day during the first and second years of the study, respectively. At a lower level of protein (43 g/day), the same amount of magnesium resulted in negative balance. While the IOM panel used this as evidence of the need for a higher EAR, the usual intake of protein in this age group may suggest an alternative interpretation. Given an average daily intake of protein among males age 14 to 18 years of 1.42 g/kg/day and a reference weight of 64 kg, their average protein intake is approximately 91 g/day (Moshfegh et al. 2005). Thus, if the findings of Schwartz et al. (1973) are accurate, current usual intake data suggest that a lower level of magnesium may be adequate to maintain a positive balance in this subgroup.

Given the apparent negative effect of fiber consumption on magnesium absorption, intake of fiber influences whether individuals maintain magnesium balance. Studies that have examined magnesium balance at different levels of fiber intake have found that men who consume 355 mg/day of magnesium maintain a positive magnesium balance on 9 g/day of fiber but display negative magnesium balance on 59 g/day of fiber (Kelsay et al. 1979). A similar relationship between fiber and magnesium absorption was found in a study of women under the age of 30 years (Wisker et al. 1991). Because it is assumed that men over 30 years of age consume higher levels of fiber than younger men, the IOM panel set a higher EAR for men age 31 to 50 years of age (350 mg/day) than for men 19 to 30 years of age (330 mg/day). The average usual dietary fiber intake in the general population, however, falls

far below the high levels of fiber tested in these balance studies. The average usual dietary fiber intake is 18 g/day and 14.3 g/day for men and women 19 years of age and older, respectively (Moshfegh et al. 2005). These average usual intakes fall far below the AI for fiber and suggest that despite high rates of dietary magnesium inadequacy, adults may be able to maintain magnesium balance on intakes below the EAR because they have low intakes of fiber. This does not imply, however, that the EAR for magnesium should be lowered to compensate for inadequate intake of fiber in the general population.

In summary, while usual intake data suggest widespread magnesium inadequacy among older children, adolescents, and adults, there is a paucity of evidence of deficiency to support these findings. New evidence on magnesium requirements based on other potential indicators of magnesium status might be useful for assessing whether the current derivation of the EAR for magnesium is appropriate. Currently, however, it is unclear whether the other indicators discussed earlier provide more accurate assessments of magnesium status. Furthermore, it may be important to give attention to the current average intake levels and effects of other nutrients that affect magnesium absorption in order to accurately estimate average magnesium requirements.

VITAMIN E

The essential functions of vitamin E in human nutrition are still being studied. At present, vitamin E is best known for its role as an antioxidant. It intercepts free radicals formed during normal metabolism and environmental exposures, preventing damage to cell membranes and low density lipoproteins. The antioxidant activity of vitamin E has been associated with a lowered risk of heart disease, diabetes, cancer, cataracts, and Alzheimer's disease. In addition, vitamin E appears to inhibit platelet aggregation, dilate blood vessels, and affect cell signaling and immune and inflammatory responses (Packer 1993; Institute of Medicine 2000; Brigelius-Flohe et al. 2002).

The term vitamin E describes a group of eight naturally occurring substances: the α -, β -, γ -, and δ -tocopherols, and the α -, β -, γ -, and δ -tocotrienols. All forms of vitamin E have historically been thought to exert vitamin E activity. Currently, the evidence suggests that only α -tocopherol is recognized by the protein that regulates levels of α -tocopherol in the blood. The other forms of vitamin E are not convertible to α -tocopherol, are preferentially excreted from the body, and, hence, are no longer considered to contribute to vitamin E activity (Institute of Medicine 2000; Traber 2001; Higdon 2003).

Food sources of α -tocopherol include most vegetable oils—sunflower, safflower, and cottonseed oil are particularly rich sources—sunflower seeds, nuts and nut butters, whole grains, avocados, and green leafy vegetables. Vitamin E in the form of α -tocopherol is also found in fortified foods, like ready-to-eat cereals, and in most vitamin E supplements. Vitamin E supplements may be made from natural sources of α -tocopherol, but synthetic forms are also used. Synthetic α -tocopherol is less bioavailable and has only half the potency of natural forms (Higdon 2003).

Vitamin E deficiency is very rare in the U.S., occurring only in premature newborns, in individuals with fat malabsorption syndromes, or as a result of a genetic mutation of the α -tocopherol transfer protein (Institute of Medicine 2000; Traber 2001; Brigelius-Flohe et al. 2002). If not treated in the early stages, vitamin E deficiency leads to peripheral neuropathy. No cases of Vitamin E deficiency have ever been reported in individuals with low dietary intakes of vitamin E. The potential toxicity of long-term supplementation with α -tocopherol has not been well studied. In some individuals, excess α -tocopherol may increase the risk of hemorrhagic stroke (Institute of Medicine 2000).

Studies Assessing Usual Vitamin E Intake

Diet assessment studies have found that a large share of the U.S. population has usual intakes of vitamin E that are below the EAR (Suitor and Gleason 2002; Devaney et al. 2005; Maras et al. 2004; Foote et al. 2004; Ahuja et al. 2004; Devaney et al. 2005; Moshfegh et al. 2005; Institute of Medicine 2006; Briefel et al. 2006a, 2006b). As shown in Table IV.7, this finding holds true across all life stage and gender subgroups for which EARs have been established, though data on vitamin E intake from dietary supplements were not available for the majority of the subgroups studied. Until recently, vitamin E values in nutrient databases were expressed as α -tocopherol equivalents, which included all naturally-occurring forms of vitamin E. The EARs for vitamin E, however, are based only on the α -tocopherol form of the vitamin. Therefore, the studies shown in Table IV.7 that analyzed vitamin E as α -tocopherol equivalents overstate vitamin E intake, and the prevalence of inadequacy is actually underestimated. Based on data from NHANES III, α -tocopherol intakes in the U.S. are, on average, approximately 80 percent of the reported intake of α -tocopherol equivalents (Institute of Medicine 2000).

Focusing on results from the studies that analyzed α -tocopherol only, the proportions of adolescents and adults with usual vitamin E intakes below the EAR, from food alone, ranged from 89 to 100 percent (Maras et al. 2004; Ahuja et al. 2004; Moshfegh et al. 2005). The percentages of younger children with usual vitamin E intake below the EAR were slightly lower than that of the older age groups. Ahuja and colleagues (2004) reported rates of inadequacy from food alone ranging from 75 percent for children 4 to 8 years of age to 97 percent for females age 9 to 13 in the 1999-2000 NHANES. Females of all ages had higher rates of vitamin E intake below the EAR than their male counterparts in this data set, while the more recent 2001-2002 NHANES data reveal gender differences only among adults (Moshfegh et al. 2005). Virtually all female adolescents had inadequate usual intakes of vitamin E from food alone, regardless of the data set used.

Data from FITS, which included vitamin E from food *and* supplements, provides some indication of the potential contribution of supplements to vitamin E intake. Devaney and colleagues (2004) found that 58 percent of all toddlers 12 to 24 months of age had vitamin E intakes below the EAR. However, Briefel and coworkers (2006a) reported a large difference in the rate of vitamin E inadequacy between toddlers who used supplements (9 percent) and those who did not (65 percent). The prevalence of usual supplement use among toddlers in this study was 31 percent, and supplements contributed 25 percent of their total vitamin E intake (Fox et al. 2006). Given these findings, the available studies (which are based on

Table IV.7. Studies Assessing the Vitamin E Intake of Children and Adults^a

Reference	Data Set	Supplements Included?	Key Results
Sutor and Gleason 2002	CSFII 1994-1996	No	<i>Female children age 6 - 8 years:</i> 68% had usual vitamin E intakes below the EAR. <i>Male children age 6 - 8 years:</i> 48% had usual vitamin E intakes below the EAR. <i>Female children age 9 - 13 years:</i> 85% had usual vitamin E intakes below the EAR. <i>Male children age 9 - 13 years:</i> 70% had usual vitamin E intakes below the EAR. <i>Female adolescents age 14 - 18 years:</i> 99% had usual vitamin E intakes below the EAR. <i>Male adolescents age 14 - 18 years:</i> 84% had usual vitamin E intakes below the EAR.
Foote et al. 2004	CSFII 1994-1996 day 1 data only	No	<i>Female adults over 18 years of age:</i> mean probability of adequacy for vitamin E was 7%. <i>Male adults over 18 years of age:</i> mean probability of adequacy for vitamin E was 14%.
Maras et al. 2004	CSFII 1994-1996, with α -tocopherol values from USDA National Nutrient Database for Standard Reference 15	No	<i>Female adults over 19 years of age:</i> 97 - 98% had usual vitamin E intakes below the EAR. <i>Male adults over 19 years of age:</i> 90 - 95% had usual vitamin E intakes below the EAR.
Devaney et al. 2005	CSFII 1994-1996	No	<i>FSP participants age 4 - 8 years:</i> 42% had usual vitamin E intakes below the EAR. <i>FSP eligible nonparticipants age 4 - 8 years:</i> 57% had usual vitamin E intakes below the EAR. <i>Female adolescents age 14 - 18 years:</i> 100% had usual vitamin E intakes below the EAR. <i>Older adult females 60 - 70 years:</i> 95% had usual vitamin E intakes below the EAR. <i>Older adult males age 60 - 70 years:</i> 78% had usual vitamin E intakes below the EAR. <i>Low-income males over 71 years of age:</i> 95% had usual vitamin E intakes below the EAR. <i>Non-low-income males over 71 years of age:</i> 77% had usual vitamin E intakes below the EAR.
Institute of Medicine 2006	CSFII 1994-1996, 1998	No	<i>WIC children age 1 - 1.9 years:</i> 55% had usual vitamin E intakes below the EAR. <i>WIC children age 2 - 4.9 years:</i> 47% had usual vitamin E intakes below the EAR. <i>Non-breastfeeding, postpartum adolescent and adult women age 14 - 44 years:</i> 99.8% had usual vitamin E intakes below the EAR.

^a Vitamin E measured as *a*-tocopherol equivalents, unless otherwise noted.

CSFII = Continuing Survey of Food Intake by Individuals

FITS = Feeding Infants and Toddlers Study

NHANES = National Health and Nutrition Examination Survey

Reference	Data Set	Supplements Included?	Key Results
Ahuja et al. 2004	NHANES 1999-2000, with values for vitamin E as <i>a</i> -tocopherol	No	<p><i>Children age 1 - 3 years: 81% had usual vitamin E intakes below the EAR.</i></p> <p><i>Children age 4 - 8 years: 75% had usual vitamin E intakes below the EAR.</i></p> <p><i>Female children age 9 - 13 years: 97% had usual vitamin E intakes below the EAR.</i></p> <p><i>Male children age 9 - 13 years: 91% had usual vitamin E intakes below the EAR.</i></p> <p><i>Female adolescents age 14 - 18 years: 99.6% had usual vitamin E intakes below the EAR.</i></p> <p><i>Male adolescents age 14 - 18 years: 92% had usual vitamin E intakes below the EAR.</i></p> <p><i>Female adults over 18 years of age: 96% had usual vitamin E intakes below the EAR.</i></p> <p><i>Male adults over 18 years of age: 90% had usual vitamin E intakes below the EAR.</i></p>
Moshfegh et al. 2005	NHANES 2001-2002, with values for vitamin E as <i>a</i> -tocopherol	No	<p><i>Children age 1 - 3 years: 80% had usual vitamin E intakes below the EAR.</i></p> <p><i>Children age 4 - 8 years: 80% had usual vitamin E intakes below the EAR.</i></p> <p><i>Female children age 9 - 13 years: 95% had usual vitamin E intakes below the EAR.</i></p> <p><i>Male children age 9 - 13 years: 97% had usual vitamin E intakes below the EAR.</i></p> <p><i>Female adolescents age 14 - 18 years: > 97% had usual vitamin E intakes below the EAR.</i></p> <p><i>Male adolescents age 14 - 18 years: > 97% had usual vitamin E intakes below the EAR.</i></p> <p><i>Female adults over 18 years of age: 97% had usual vitamin E intakes below the EAR.</i></p> <p><i>Male adults over 18 years of age: 89% had usual vitamin E intakes below the EAR.</i></p>
Devaney et al. 2004	FITS 2002	Yes	<i>Toddlers age 12 - 24 months: 58% had usual vitamin E intakes below the EAR.</i>
Briefel et al. 2006a	FITS 2002	Yes	<p><i>Toddlers age 12 - 24 months (supplement users): 9% had usual vitamin E intakes below the EAR.</i></p> <p><i>Toddlers age 12 - 24 months (supplement non-users): 65% had usual vitamin E intakes below the EAR.</i></p>
Briefel et al. 2006b	FITS 2002	Yes	<p><i>Hispanic toddlers age 12 - 24 months: 39% had usual vitamin E intakes below the EAR.</i></p> <p><i>Non-Hispanic toddlers age 12 - 24 months: 50% had usual vitamin E intakes below the EAR.</i></p>

^a Vitamin E measured as *a*-tocopherol equivalents, unless otherwise noted.

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IV. Review of Studies Used to Set the Dietary Reference Intakes for Selected Nutrients

datasets that do not include the contributions from dietary supplements) probably also overestimate the prevalence of vitamin E inadequacy among older children and adults. A recent analysis of data from the 1999-2000 NHANES found that 11.3 percent of adults age 20 years and over consumed at least 400 IU of vitamin E per day from supplements or approximately 12 to 18 percent of the adult RDA⁸ (Ford et al. 2005).

The high prevalence of apparently inadequate vitamin E intakes in the absence of signs of vitamin E deficiency is curious, even after taking into account the lack of data on supplement use among older children and adults. While underreporting of energy intake may play a role, it is unlikely that underreporting alone explains the very high rates of vitamin E intakes below the EAR. There have been no reports of low blood levels of α -tocopherol from NHANES data. In addition, a search of the literature published since the DRIs were released did not find any new reports of clinical or biochemical signs of vitamin E deficiency among individuals of any age or gender.

Methods and Data Used to Derive the EAR for Vitamin E

The IOM Panel on Dietary Antioxidants considered both the antioxidant function and the reduction of chronic disease risk in setting the DRIs for vitamin E. Because vitamin E deficiency is so rare, studies correlating the neurologic symptoms of deficiency with dietary intakes were not available. The panel considered the following alternative indicators for estimating the α -tocopherol requirement:

- ***Lipid Peroxidation Markers.*** Blood indicators of the extent of oxidation of lipids are generally elevated during states of vitamin E depletion and return to normal with vitamin E repletion. However, these measures are also sensitive to the intake of other antioxidants so were not used to assess α -tocopherol requirements.
- ***Oxidation Products of DNA or Proteins.*** Indicators that reflect free radical damage to DNA and proteins are available, but vitamin E has not been shown to prevent oxidation of DNA or proteins.
- ***Vitamin E Metabolite Excretion.*** Only one study has shown an increase in the urinary excretion of a product of vitamin E metabolism with increased vitamin E intake. The substance identified reflects only a fraction of the α -tocopherol consumed daily, and could not be used as a basis for setting the requirement.

⁸The amount of α -tocopherol in vitamin E supplements depends on the source. A natural form of 400 IUs of vitamin E provides 268 mg of α -tocopherol whereas the equivalent dose of a synthetic form provides only 180 mg α -tocopherol (Institute of Medicine 2000). Though most vitamin E supplements contain only α -tocopherol, a few “mixed tocopherol” supplements also contain the β -, γ -, and δ forms.

- ***Vitamin E Biokinetics.*** Biokinetics have not yet been studied sufficiently to determine the amount of vitamin E required to maintain pool size or tissue concentrations of vitamin E.
- ***Plasma α -Tocopherol Concentration.*** The level of α -tocopherol in blood plasma does not correlate well with intake of vitamin E, except when supplements are given to vitamin E-depleted subjects. Although serum α -tocopherol is measured in NHANES, it could not be used as the basis for determining the vitamin E requirement.
- ***Hydrogen Peroxide-Induced Hemolysis.*** Hydrogen peroxide-induced hemolysis and breath ethane are measures of the sensitivity of red blood cells to oxidative destruction in vitro. They have been correlated with plasma levels of α -tocopherol in vitamin E deficient children and adults and are corrected with supplemental vitamin E.

A large number of epidemiologic and intervention studies of the relationship between vitamin E intake and risk for chronic disease were also reviewed. These included the Cambridge Heart Antioxidant Study (CHAOS), the GISSI-Prevenzione Trial, the Heart Outcomes Prevention Evaluation (HOPE), and the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. The panel concluded that results of these studies were not consistent enough to serve as the basis for determining requirements.

The criterion of vitamin E adequacy ultimately selected for children and adults was based on induced vitamin E deficiency and the intake that correlated with in-vitro hydrogen peroxide-induced hemolysis and plasma α -tocopherol levels. No indicator of vitamin E status was identified for infants, so recommendations for vitamin E intakes for this age group were set as an AI (Institute of Medicine 2000).

Children and Adolescents 1 to 18 Years of Age. There were no data found on which to base the EAR for vitamin E in healthy children or adolescents. Consequently, the EARs were extrapolated from adult values. Table IV.8 illustrates the metabolic formula that was used to make the adjustments.

Adults 19 Years and Older. The EAR for adults is largely based on one set of experimental studies of healthy men who were depleted of vitamin E for 6 years and then repleted. The studies were part of the Elgin Project conducted by Horwitt and others in the 1950s and 1960s. Nineteen adult men were fed a diet containing very small amounts of α -tocopherol plus vitamin E-free lard. After 2.5 years, the lard was replaced with oxidized corn oil, increasing the subjects' total intake of polyunsaturated fatty acids and putting an additional burden on their remaining vitamin E stores. The subjects were followed for another 4 or so years. As plasma tocopherol levels decreased, peroxide-induced hemolysis increased. A group of subjects were repleted after 54 months by giving them each a different amount of supplemental vitamin E over a period of 138 days (Horwitt et al. 1956, 1963; Horwitt 1960).

Table IV.8 Derivation of the Estimated Average Requirement (EAR) for Vitamin E for Children and Adults

Life Stage Group	EAR ^a	Method Used to Derive EAR
Children	1-3 years: 5 mg/day 4-8 years: 6 mg/day Boys 9-13 years: 9 mg/day Girls 9-13 years: 9 mg/day	No data on which to estimate requirements. EARs extrapolated from adult values, based on relative body weight and needs for growth: $EAR_{child} = EAR_{adult} (F)$, where $F = (Weight_{child} / Weight_{adult})^{0.75} (1 + \text{growth factor})$ Assumed that average vitamin E requirement for growth is comparable to that for protein and does not differ by gender.
Adolescents	Boys 14-18 years: 12 mg/day Girls 14-18 years: 12 mg/day	No data on which to estimate requirements. EARs extrapolated from adult values, based on relative body weight and needs for growth, as shown above. Assumed that average vitamin E requirement for growth is comparable to that for protein.
Adults	Men over 19 years of age: 12 mg/day Women over 19 years of age: 12 mg/day	Selected criterion for adequacy as the lowest plasma α -tocopherol level known to limit in vitro hydrogen peroxide-induced hemolysis to 12 percent or less. Determined the vitamin E intake sufficient to achieve this plasma α -tocopherol concentration (12 $\mu\text{mol/L}$) based on one study of vitamin E-depleted adult men, generating an EAR of 12 mg/day α -tocopherol. Data not available to determine whether requirements differ for women, adults 51 years and older, or pregnant women.

^a As α -tocopherol.

The panel set the criterion of vitamin E adequacy as the plasma α -tocopherol level that restricted hydrogen peroxide-induced hemolysis to 12 percent or less. Based on data from four of the vitamin E-depleted and six control subjects, the plasma α -tocopherol levels that met this criterion were 12 micromoles per liter ($\mu\text{mol/L}$) or less; when averaged over six subjects with less than 12 percent hemolysis the concentration was 16.2 $\mu\text{mol/L}$. These values were compared to results of hydrogen peroxide-induced hemolysis tests conducted in children with cystic fibrosis. Farrell and colleagues (1977) found that a slightly lower plasma α -tocopherol of 14 $\mu\text{mol/L}$ was high enough to prevent hemolysis. To be prudent, the lowest plasma α -tocopherol level associated with normal hydrogen peroxide-induced hemolysis was estimated at 12 $\mu\text{mol/L}$. Based on the repletion of seven subjects, the vitamin E intake sufficient to increase plasma α -tocopherol to 12 $\mu\text{mol/L}$ or above was 12 mg/day α -tocopherol. This value was used as the EAR for adult males. Data were not available to determine whether requirements differ for women, adults 51 years and older, or pregnant women. The EAR for these groups is the same as for males 19 through 50 years of age.

Discussion

Recent dietary assessment studies that consider vitamin E intake from food alone have reported a high prevalence of inadequate intakes of vitamin E for virtually all age and gender subgroups of the population. The estimates are even higher from studies that used nutrient databases that had been updated to exclude tocopherols that do not contribute to vitamin E activity, though supplement use was not taken into account. The EARs for vitamin E for all age and gender groups are based on a study of vitamin E-depleted adult males. Given that vitamin E deficiency is very rare in the U.S. and has been linked to specific health conditions rather than inadequate dietary intakes, these findings have raised questions about both the EARs for vitamin E and the assessment of vitamin E intakes.

As noted above, the EAR for vitamin E was based on a long-term experimental study in vitamin E-depleted adult men. Due to limited data for the other life stage groups, the EAR for adult males was used for adult females and older adults, and the EARs for children and adolescents were extrapolated from the adult EAR. The Elgin Project studies on which the EAR was based have two notable limitations. First, the peroxide-induced hemolysis test used in those studies was conducted *in vitro*—outside the body. Results obtained can be highly variable depending on the procedures used (Bieri 2002; Traber 2002, 2001; Horwitt et al. 1956). Farrell and coworkers (1977) improved on the reliability of the peroxide-induced hemolysis test and confirmed its relationship to plasma α -tocopherol in vitamin E-deficient cystic fibrosis patients. However, even with better methods, the peroxide hemolysis test is not a marker of the clinical signs of vitamin E deficiency (peripheral neuropathy or hemolytic anemia), which were absent in these patients.

A second limitation relates to the experimental diets consumed by the vitamin E-depleted subjects. In a critique of the DRIs for vitamin E, Horwitt (2001) suggests that the large amounts of vitamin E-free unsaturated fats that were fed to his subjects increased their requirement for vitamin E relative to free-living adults. If these fats had not been included in the diets, the minimum requirement for vitamin E would have been too small to study. Vitamin E requirements have been shown to increase as the amount of polyunsaturated fatty acids in the diet increase (Institute of Medicine 2000).

Given the drawbacks of the Elgin Project studies, it is possible that the EAR for adults was set too high. Since the EARs for all other age groups were extrapolated from the adult value, it follows that they also would be high. However, the real issue seems to be that the criterion of adequacy selected for vitamin E is not an appropriate marker of overt deficiency or reduced risk of chronic disease. It is important to note that the IOM panel recognized that, for all of the antioxidant nutrients, the EARs are higher than the amount needed to prevent overt deficiencies and are based on limited data (Institute of Medicine 2000).

Aside from the lack of studies, there are a number of practical constraints and complexities to establishing the vitamin E requirement on the basis of preventing overt deficiency. One is that it is difficult to assess vitamin E adequacy because it can take decades for an adult to show the neurologic abnormalities associated with vitamin E depletion. Another is that the true function of vitamin E has not yet been identified—the antioxidative properties of vitamin E are not what make it “essential” for humans (Brigelius-Flohe et al.

2002; Traber 2001). Horwitt and others have also shown that the amount of α -tocopherol required by humans is dependent on the amount of fats circulating in the blood and stored in the body.⁹ For example, individuals with above-normal serum lipid levels may require more vitamin E (Horwitt 1960).

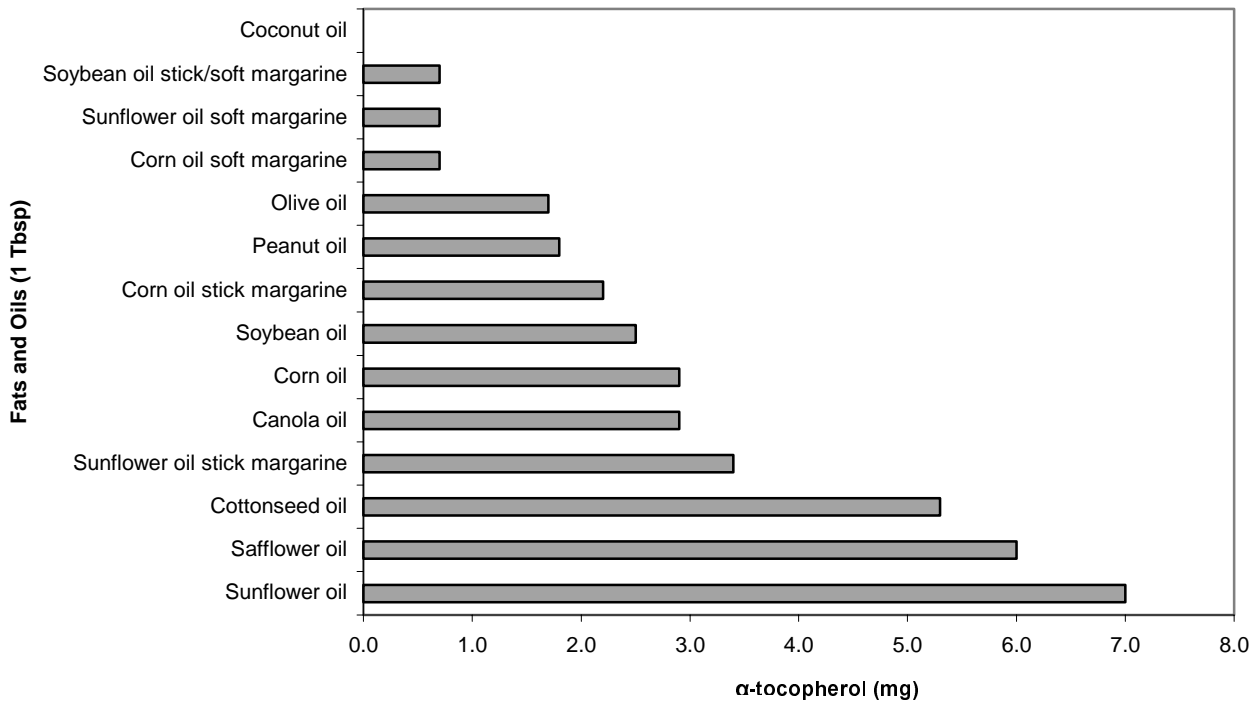
The lack of consistent findings across studies prevented the panel from establishing the vitamin E requirements on the basis of reducing the risk of chronic disease. In considering possible indicators of vitamin E adequacy on which to base the EAR, the panel did review studies of the effects of vitamin E on chronic disease. Only one of four double-blind controlled studies of vitamin E and coronary heart disease prevention had a positive outcome. The data for other diseases were even less convincing. Results from other trials of vitamin E that were in progress when the DRIs were being set may now be available and could provide the data needed to update the criterion of adequacy for vitamin E.

Aside from the issues related to the method used to derive the EARs, current methods of dietary assessment tend to underestimate vitamin E intake. The IOM panel identified four potential sources of error:

1. Energy intake is known to be underreported in dietary surveys, and intake of dietary fat (which is a carrier for vitamin E) is likely to be disproportionately underreported (Briefel et al. 1997).
2. The amounts of fats and oils used in food preparation and ultimately taken up by the cooked food are difficult to measure using the dietary recall method.
3. Lack of information on the specific types of fats and oils consumed, which is especially likely for commercially-prepared products, requires that defaults be used in coding. (As shown in Figure IV.1 below, fats and oils vary considerably in their α -tocopherol content.)
4. The number of available food samples analyzed for vitamin E content was small; therefore, the vitamin E values in nutrient databases are highly variable or have been imputed (Obarzanek et al. 1997).

In spite of the problems of measuring dietary intakes of vitamin E, α -tocopherol intake has likely decreased over time. Efforts to improve our diets relative to the prevention of chronic disease have resulted in changes in the types of oils used in food preparation and manufactured foods to favor vegetable sources. About half of the vitamin E content of safflower oil, canola oil, and olive oil is α -tocopherol, but corn and soybean oil have about 10 times more γ -tocopherol than α -tocopherol. Although γ -tocopherol is the most common

⁹The intake of α -tocopherol required to limit oxidation may range anywhere from 5 mg to 30 mg or more per day (Horwitt 1960).

Figure IV.1. Vitamin E (α -tocopherol) Content of Fats and Oils

Source: Food and Nutrition Science Alliance 2000.

form of vitamin E in the American diet, its function in humans is unclear (Traber 2001; Institute of Medicine 2000).

A recently published study by Bruno and others (2006) provides some support for the current EAR for vitamin E. They cite research showing that very low-fat diets for the purposes of weight control are associated with a 50 percent reduction in vitamin E intake and suggest that fortifying low-fat foods may be one solution. The Bruno study estimated vitamin E requirements in five adult subjects. The subjects consumed apples fortified with α -tocopherol in breakfasts with varying amounts of fat. Using plasma α -tocopherol kinetics, they found that the mean dietary vitamin E requirement was approximately $15 \text{ mg} \pm 6 \text{ mg}$ per day.

In summary, the EAR for vitamin E may warrant reassessment. The diets of the majority of the U.S. population do not meet current estimates of vitamin E requirements. This can be attributed in part to both limitations of the data used to set the EAR and to problems with the assessment of vitamin E intake. One question is whether the level of evidence currently available for vitamin E may be more appropriately used to set an AI. However, the extent of underreporting of vitamin E intake may be too great to reliably determine an AI. Vitamin E deficiency is rare and the challenges to better defining physiologic requirements are great, but it is not yet known what levels of vitamin E intake promote optimal health. An updated review of results from experimental studies of the effect of various amounts of vitamin E on the reduction of chronic diseases may shed light on this question. Data on supplement use from the current NHANES will help establish the true prevalence of apparently suboptimal vitamin E intakes.

IV. Review of Studies Used to Set the Dietary Reference Intakes for Selected Nutrients

FIBER

Fiber has been found to have numerous health benefits, which include the reduction of serum cholesterol and blood sugar levels as well as the prevention and treatment of constipation. In addition, a number of studies have found that high fiber intakes have a moderating impact on the risk of cardiovascular disease, type 2 diabetes, diverticular disease, and certain types of cancers. Some research also suggests that high fiber intake may help control weight, since consumption of fiber leads to a feeling of fullness (Institute of Medicine 2002/2005; Higdon 2003).

Prior to establishing the DRIs for fiber, the IOM Panel on the Definition of Dietary Fiber defined two major categories of fiber: dietary and functional. **Dietary fiber** includes naturally occurring nondigestible carbohydrates and lignin from plants. Isolated or synthetic, nondigestible carbohydrates can be considered **functional fiber** if shown to have beneficial health effects. **Total fiber** is defined as the sum of dietary fiber and functional fiber (Institute of Medicine 2001). Legumes, nuts, whole grains, bran products, fruits, and non-starchy vegetables are all good sources of dietary fiber. Isolated fibers that are used as food additives or dietary supplements and also meet the definition for functional fiber include pectins, gums, cellulose, and psyllium.

Fiber differs from the other dietary components discussed in this report—it is not digested or absorbed into the body, nor is it considered an essential nutrient. While a potential functional consequence of low fiber intake is constipation, inadequate intakes of fiber do not result in clinical signs of deficiency. Few adverse effects of consuming large amounts of fiber have been reported, and they are usually associated with insufficient fluid intake while increasing fiber consumption.

Studies Assessing Usual Intake of Dietary Fiber

The IOM Panel on Macronutrients established an AI for total fiber. To date, however, most studies of dietary intake have assessed only dietary fiber. These studies show that large proportions of adults, adolescents, and children have usual intakes of dietary fiber that fall far below the AI (Table IV.9). As noted in Chapter I, for nutrients and other dietary components with an AI, such as fiber, only limited inferences can be made regarding the prevalence of inadequacy (Institute of Medicine 2000a). While no conclusions can be drawn about the prevalence of inadequacy if mean intakes are less than the AI, there is cause for concern if the vast majority of individuals have intakes that fall far below the AI, as is the case with fiber.

Devaney and colleagues (2005) found that average dietary fiber intakes fell substantially below the AI for total fiber for all population subgroups examined, which included older adults, overweight individuals, adolescent females, and low-income individuals, among others. Recent analyses of the 2001-2002 NHANES found that children age 1 to 13 years also have dietary fiber intakes far below the AI (Moshfegh et al. 2005). Analyses of data from FITS showed similar results for toddlers 12 to 24 months, who had mean usual intakes of dietary fiber from food and supplements that were far below the AI (Devaney et al. 2004;

Table IV.9. Studies Assessing the Dietary Fiber Intake of Children and Adults^a

Reference	Data Set	Supplements Included?	Key Results
Devaney et al. 2005	CSFII 1994-1996, 1998	No	<i>Children age 2 years and over and adults:</i> Mean dietary fiber intakes of all subgroups examined were far below the AI.
Institute of Medicine 2006	CSFII 1994-1996, 1998	No	<i>WIC children age 1 - 1.9 years:</i> mean usual intake of dietary fiber was far below the AI. <i>WIC children age 2 - 4.9 years:</i> mean usual intake of dietary fiber was far below the AI. <i>Women, non-breastfeeding postpartum age 14 - 44 years:</i> mean usual intake of dietary fiber was far below the AI
Moshfegh et al. 2005	NHANES 2001-2002	No	<i>All age and gender subgroups over 1 year of age:</i> mean usual intake of dietary fiber was far below the AI.
Devaney et al. 2004	FITS 2002	Yes	<i>Toddlers age 12 to 24 months:</i> mean usual intake of dietary fiber was far below the AI.
Briefel et al. 2006a	FITS 2002	Yes	<i>Toddlers age 12 to 24 months:</i> mean usual intake of dietary fiber was far below the AI for both supplement and non-supplement users.
Briefel et al. 2006b	FITS 2002	Yes	<i>Toddlers age 12 to 24 months:</i> mean usual intake of dietary fiber was far below the AI for both Hispanic and non-Hispanic toddlers.

^a Intake data are for dietary fiber only. The AI is for total fiber (dietary + functional).

CSFII = Continuing Survey of Food Intake by Individuals

FITS = Feeding Infants and Toddlers Study

NHANES = National Health and Nutrition Examination Survey

Briefel et al. 2006a, 2006b). Although the percentage with *total fiber* intakes at or above the AI may be underestimated, regardless of subgroup even the 90th percentile of dietary fiber intake was below the AI in each of these studies.

Method and Data Used to Derive the AI for Fiber

Since fiber is not an essential nutrient and there are no biochemical assays that reflect an individual's fiber status, a definition of fiber deficiency could not be established. Hence, to determine fiber needs, the IOM Panel on Dietary Reference Intakes for Macronutrients limited its review to studies of the potential health benefits of dietary and functional fiber. Most of these studies measured intakes of dietary fiber only, which was generally more available in nutrient databases (Institute of Medicine 2002/2005).

IV. Review of Studies Used to Set the Dietary Reference Intakes for Selected Nutrients

A large number of epidemiologic studies and intervention trials have evaluated the relationship between fiber intake and risk of chronic disease. The panel reviewed studies of the role of fiber in the prevention of hyperlipidemia; hypertension; coronary heart disease (CHD); and colon, breast, and other cancers. Studies relating fiber intake to gastrointestinal health, weight maintenance, and diabetes were also considered. Findings are summarized below:

- ***Fiber Intake and Risk of CHD.*** The evidence from a large number of epidemiologic studies supports a protective effect of dietary fiber on the risk of CHD. Cereal fibers had a stronger protective effect than fruit or vegetable fiber, and women benefited somewhat more than men from increasing their fiber intake. Results of intervention trials show that certain viscous functional fibers and food sources of viscous fiber, such as oats and beans, lower serum total and low density lipoprotein (LDL) cholesterol.
- ***Fiber Intake and Cancer.*** Several observational, case-control, and epidemiologic studies have found that high fiber diets are protective against colon cancer. However, more recent prospective cohort studies and clinical trials demonstrated no effect. Although fiber has been shown to lower serum estrogen levels, the available data do not support the hypothesis that high fiber intakes lower the risk of endometrial, ovarian, prostate, or breast cancer.
- ***Fiber Intake and Gastrointestinal Health.*** The beneficial role of certain fibers in promoting laxation and preventing constipation is well-documented. The data from several types of studies supports a negative relationship between fiber intake and diverticular disease, which is fairly common among older adults. The consumption of nonviscous dietary fiber, and cellulose in particular, was the most protective.
- ***Fiber Intake and Diabetes.*** There is strong epidemiologic evidence of a protective effect of dietary fiber against type 2 diabetes. Viscous fibers from foods and supplements, such as pectin and guar gum, have been shown to reduce the glycemic response and serum lipid levels. It may be that viscous fiber delays gastric emptying, slowing the absorption of glucose from food.
- ***Fiber Intake and Obesity.*** A few epidemiologic studies have shown that dietary fiber intake is negatively correlated with body mass index in both men and women. Some observational and prospective cohort studies have concluded that high fiber diets are effective in weight loss, although results from clinical trials have been mixed. The hypothesis that consuming soluble fibers low in energy can delay gastric emptying, thereby prolonging satiety, has not been confirmed.

The panel concluded that a recommended level of intake could be set for fiber based on its role in the prevention of CHD. The greatest benefit appears to come from cereal fibers

and viscous functional fibers such as gums and pectins. It was not possible to set an EAR because the beneficial effect of fiber takes place over a range of intakes (Institute of Medicine 2002/2005). Table IV.10 summarizes the methods used to set the AI for fiber, which are further described below.

No recommendations for fiber intake were made for infants for three reasons: (1) there are no functional indicators of fiber intake in infants, (2) human milk is recommended as the sole source of nourishment from birth through 6 months of age and is devoid of fiber, and (3) there were no data on the fiber intakes of infants 7 to 12 months of age.

Children and Adolescents Age 1 to 18 Years. Constipation is a fairly frequent problem for children, and it is often treated with a high fiber diet. A small number of studies have found that children with constipation consume substantially less dietary fiber, on average, than healthy controls (McClung et al. 1993, 1995; Morais et al. 1999; Roma et al. 1999). Recognizing that the data were limited, the panel set the AI for fiber for children based on data for adults that showed that 14 g of dietary fiber per 1,000 kcal per day reduced the risk of CHD. The AI was set for each age and gender group by multiplying the 14 g/1,000 kcal by the median energy intake for the group as reported in the CSFII.

Adults Age 19 Years and Older. The AI for fiber for adults was based on the intake level observed to protect against CHD in three large-scale, prospective cohort studies (Pietinen et al. 1996; Rimm et al. 1996; Wolk et al. 1999). These studies were chosen

Table IV.10. Derivation of the Average Intake (AI) for Total Fiber

Life Stage Group	AI	Method Used to Derive the AI
Children and Adolescents	Children 1 - 3 years: 19 g/day	Data on fiber intake and constipation in children were limited. Therefore, the AI was based on data for adults, which showed that 14 g of dietary fiber per 1,000 kcal per day reduced the risk of CHD. The AI was set for each age and gender group by multiplying the 14 g/1,000 kcal/day by the median energy intake for the group, as reported in the CSFII. For example, the median energy intake for children 1- to 3-year-old children is 1,372 kcal/day. The AI is then $14 \text{ g} \times 1,372/1,000 \text{ kcal} = 19 \text{ g/day}$ of total fiber.
	Children 4 - 8 years: 25 g/day	
	Boys 9 - 13 years: 31 g/day	
	Boys 14 - 18 years: 38 g/day	
	Girls 9 - 18: 26 g/day	
	Adults	

CHD = coronary heart disease

CSFII = Continuing Survey of Food Intake of Individuals

because they showed a statistically significant inverse relationship between dietary fiber and the relative risk of CHD; had adequate power; used multivariate models to control for other dietary and behavioral factors related to CHD (saturated fat intake, smoking, body mass index, etc.); and provided quintiles of fiber and associated energy intakes. Dietary fiber intake was assessed at baseline with validated, semi-quantitative food frequency questionnaires. Thus it was possible to relate the number of grams of dietary fiber to the decrease in coronary morbidity and mortality.

The Health Professionals Follow-Up Study documented myocardial infarction and fatal coronary disease among 43,757 U.S. male health professionals 40 to 75 years of age. After a 6-year follow-up period, Rimm and coworkers (1996) reported a significant difference in the relative risk for CHD for men with dietary fiber intakes of 29 g/day compared with the lowest quintile of about 12 g/day. Fiber intakes were energy-adjusted to 2,000 kcal/day, so this translated to 14.5 g dietary fiber per 1,000 kcal.

In the Nurses' Health Study, a 10-year study of 68,782 U.S. women age 37 to 64 years, the median dietary fiber intakes were 23 g/day at the highest quintile and 11.5 g/day at the lowest quintile (Wolk et al. 1999). Based on the normalized energy intake of 1,600 kcal/day, the reduction in risk of coronary events was maximized at an intake of about 14 g of dietary fiber per 1,000 kcals.

While the main objective of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was to examine the effect of vitamin supplementation on lung cancer risk, Pietinen and colleagues (1996) also monitored CHD outcomes. The study was conducted with 21,930 Finnish men 50 to 69 years of age who were followed for six years. A significant negative trend with risk of CHD was observed for men in the highest quintile of fiber intake (35 g/day) compared with the lowest quintile of intake (16 g/day). Based on a median energy intake in the highest quintile of 2,705 kcal/day, this equated to about 13 g of dietary fiber per 1,000 kcal.

The findings from these three studies were averaged, resulting in a recommended intake of 14 g of dietary fiber per 1,000 kcal per day. The data from a number of other epidemiologic studies and clinical trials of CHD were supportive of this recommendation. In addition, positive effects on type 2 diabetes were seen with the same amount of dietary fiber in two large, prospective cohort studies (Salmerón et al. 1997a, 1997b). The panel set the AI for *total fiber* equal to the recommended intake for dietary fiber based on the assumption that functional fibers as ingredients in food were, at the time, only a minor proportion of total fiber intake; it also wanted to recognize the beneficial role of functional fiber. The AI for younger and older adults was set by multiplying the 14 g of dietary fiber per 1,000 kcal by the highest median energy intake for each gender-specific age group from the 1994-96, 1998 CSFII.

There are several ways in which recommendations for fiber intake have been expressed in the past—for example, as age plus number of grams per day or grams per kilogram of body weight. The AIs for fiber are expressed relative to energy intake because the beneficial effects are most likely related to the total amount of food (and thus fiber) consumed, not to

age or body weight. No data were found to indicate that the fiber recommendation relative to energy intake would differ by life stage.

Discussion

Virtually all age and gender subgroups of the population have mean usual intakes of dietary fiber that fall far below the AI for total fiber. Fiber is not an essential nutrient; however, it is generally accepted that adequate fiber is an important component of a healthy diet, given its apparently beneficial impact on a variety of health outcomes. The AI for fiber is 14 g of total fiber per 1,000 kcal per day, which was determined on the basis of prospective cohort studies that found a consistent association between high intakes of dietary fiber and significant reductions in CHD risk among adults.

There are several issues of significance with regard to the derivation of the AI for fiber and the measurement of fiber intake. First, misreporting of energy intake, assuming fiber-containing foods make some contribution, would not explain the high levels of fiber intakes below the AI. Since the AI for each life stage group is calculated on the basis of median energy intake, if energy intake is underreported, the AI would also be under-estimated.

Secondly, estimates of fiber intake in the studies reviewed here may be lower than actual intakes of fiber. Total fiber includes both dietary fiber and functional fiber, yet both the studies used to set the AI and to assess fiber intake only measured dietary fiber. In addition, an analysis conducted by Moshfegh and colleagues (1999) showed that compounds such as inulin and oligofructose, which were not previously included in nutrient databases, contributed an additional 5 g per day more fiber, on average, than reported in the CSFII. Furthermore, for individuals consuming fiber supplements, both dietary and total fiber intake have been underestimated.

Additionally, the AI was established for total fiber yet the fiber AI is based on studies where intakes of dietary fiber were associated with reductions in CHD. Since the physiological effects of fiber appear to vary based on the type, it is not clear whether 14 g/1,000 kcal of a mix of dietary and functional fiber will confer the same benefits as 14 g of dietary fiber per 1,000 kcal per day. Therefore, at present, comparisons of dietary fiber intake to the AI seem to provide a better indication of the adequacy of fiber intake with respect to CHD risk than total fiber intake.

Some researchers have questioned whether CHD risk is an appropriate criterion for determining recommended fiber intakes for all life stage groups. The AI for fiber was based on studies in adults between the ages of 37 and 75 years. As mentioned previously, data were not available to determine whether fiber needs relative to total energy differ for younger adults or children. Since the risk for most chronic degenerative diseases increases with age, it is possible that the optimal intake of fiber as a function of energy intake is lower for younger adults and children. Furthermore, the AIs for fiber represent a substantial increase from the previous “age-plus-5-grams” recommendation for dietary fiber suggested by Williams and colleagues (1995), which was based on promoting normal laxation. For

young children 1 to 3 years of age, the current AI of 19 g/day of total fiber is more than two-and-a-half-fold higher than this recommendation.

Note also that the recommended intake of 14 g of total fiber per 1,000 kcals was translated into a set of AIs for each life stage group using data on median energy intakes from the 1994-96, 1998 CSFII. A disadvantage of this approach is that the AIs for fiber may be too high for those who consume less than median energy intake for their life stage group. Although the IOM panel recommended scaling back the AI for individuals consuming less than the median energy intake, these adjustments have not been made in studies comparing fiber intake to the AI. In addition, the data on median energy intakes from the CSFII are now close to 10 years old.

Finally, in setting the AI for fiber, the IOM panel used the data from the highest quintile of fiber intake from the three cohort studies to calculate the recommended level of intake. Although this represents the intake of dietary fiber where the maximum reduction in CHD risk was achieved, some benefits were observed at lower intake levels. For example, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study a relative risk for CHD of 0.84 was associated with a median fiber intake of 34.8 g/day; however, a median intake of 28.3 g/day (10 g/1,000 kcal) produced similar results (relative risk of 0.86; Pietenen et al. 1996). On the other hand, findings from large cohort studies of the effects of fiber on type 2 diabetes corroborated the recommendation of 14 g of fiber per 1,000 kcal. Therefore, this amount of *dietary fiber* may be a reasonable goal, at least for older adults.

In conclusion, the large gap between current dietary fiber intakes and the AI for fiber implies that the majority of Americans do not consume enough *dietary fiber*. Little is known about total fiber intakes or the relationship between total fiber and heart disease, diabetes, cancer, and other chronic conditions that affect the health of a large share of U.S. population, yet the AI was established for total fiber. The method used to set the AI may also have overstated the optimal fiber intake for individuals who consume less than the median energy intake for their age-gender group and for children and young adults. If additional dose-response data to ascertain the level of fiber intake required to promote normal laxation become available, the amelioration of constipation could be explored as an alternative endpoint to the reduction of CHD risk for determining recommended fiber intakes in children. In the meantime, using individual energy intakes to calculate fiber requirements would provide a more accurate assessment of individual fiber needs than the median for the life-stage group. Alternatively, the AIs for each life stage group could be recalculated and revised, as needed, using data from the more recent NHANES. This review suggests that the current recommendation for fiber intake could be revisited and that our understanding of the relationship between fiber and health outcomes for children, adolescents, and adults would benefit from further research.

POTASSIUM

Potassium, an intracellular cation that is found primarily in fruits and vegetables, is vitally important for normal cellular function in the human body. The electrochemical gradient caused by the difference in concentration between sodium and potassium across cell membranes is called the membrane potential and is involved in nerve impulse transmission,

muscle contraction, and heart function. Potassium is also a cofactor for certain enzymes, including pyruvate kinase, which plays an important role in carbohydrate metabolism (Higdon 2003).

Hypokalemia, which occurs at a serum potassium concentration of less than 3.5 millimoles per liter (mmol/L), is caused by severe potassium deficiency. Severe deficiency, however, is quite rare due to the availability of potassium in commonly consumed foods (Demigné et al. 2004). Certain conditions increase the risk of hypokalemia, including the use of diuretics, alcoholism, severe vomiting or diarrhea, excessive use of laxatives, eating disorders, magnesium depletion, and congestive heart failure. The symptoms of hypokalemia include fatigue, muscle weakness, cramps, intestinal paralysis, bloating, constipation, abdominal pain, and in more serious cases, muscular paralysis or potentially fatal arrhythmias. While low dietary intakes of potassium typically do not lead to hypokalemia, research suggests that potassium inadequacy can increase the risk of chronic diseases, including high blood pressure, salt sensitivity, kidney stones, bone turnover, and stroke (Higdon 2003; Institute of Medicine 2005).

The crucial balance between sodium and potassium has been altered in modern western diets, which have much higher intakes of sodium than potassium—the inverse of prehistoric dietary patterns. This has led to claims that the modern ratio of sodium to potassium intake is one of the key causes of the prevalence of some chronic diseases (Higdon 2003; Demigné et al. 2004).

Studies Assessing Usual Potassium Intake

While few studies have assessed potassium intake, those studies that have evaluated the adequacy of potassium intake in the general population have found that the vast majority of individuals have intakes of potassium that are far below the AI (Table IV.11). The one exception to this finding is infants up to 12 months of age, almost all of whom have potassium intakes that exceed the AI (Institute of Medicine 2006). As discussed earlier, widespread evidence of intakes below the AI for potassium does not necessarily imply that the majority of Americans have a deficiency of potassium; however, it is important to note that adolescent and adult respondents in the 90th percentile of potassium intake in both the 1994-1996, 1998 CSFII and 2001-2002 NHANES had intakes of potassium that fell below the AI (Moshfegh et al. 2005; Institute of Medicine 2006). Underreporting alone cannot explain the low potassium intakes observed among these age groups. Toddlers 12 to 24 months surveyed in FITS also had mean intakes of potassium that fell far below the AI (Heird et al. 2006).

Method and Data Used to Derive the AI for Potassium

The IOM Panel on Dietary Reference Intakes for Electrolytes and Water considered numerous indicators of insufficient dietary intake of potassium:

- **Potassium Balance.** As described earlier, balance studies assess nutrient absorption by comparing nutrient consumption to excretion. Intake of other

Table IV.11. Studies Assessing the Potassium Intake of Children and Adults

Reference	Data Set	Supplements Included?	Key Results
Moshfegh et al. 2005	NHANES 2001-2002	No	<i>All age and gender subgroups over 1 year of age: mean usual intake of potassium was far below the AI.</i>
Institute of Medicine 2006	CSFII 1994-1996, 1998	No	<i>WIC children age 1 - 1.9 months: mean usual intake of potassium was far below the AI. WIC children age 2 - 4.9 years: mean usual intake of potassium was far below the AI. Non-breastfeeding, postpartum adolescent and adult women age 14 - 44 years: mean usual intake of potassium was far below the AI.</i>
Heird et al. 2006	FITS 2002	Yes	<i>Toddlers age 12 - 24 months: mean usual intake of potassium was far below the AI.</i>
Briefel et al. 2006a	FITS 2002	Yes	<i>Toddlers age 12 to 24 months: mean usual intake of potassium was far below the AI for both supplement and non-supplement users.</i>
Briefel et al. 2006b	FITS 2002	Yes	<i>Toddlers age 12 to 24 months: mean usual intake of potassium was far below the AI for both Hispanic and non-Hispanic toddlers.</i>

CSFII = Continuing Survey of Food Intake by Individuals

FITS = Feeding Infants and Toddlers Study

NHANES = National Health and Nutrition Examination Survey

nutrients can affect potassium balance. For example, increases in dietary fiber intake result in increased fecal excretion of potassium, and extremely high levels of sodium intake that exceed 6.9 g/day produce a net loss of potassium. Non-hypertensive subjects who consumed at least 1.6 g/day of potassium maintained potassium balance but had serum potassium concentrations at the lower end of the normal range (Sebastian et al. 1971).

- ***Serum Potassium Concentration.*** Serum potassium concentration measures the potassium concentration in the blood. Plasma concentrations of potassium are tightly controlled and thus are not very responsive to large increases in potassium intake. Even though individuals may consume enough potassium to fall within the acceptable range of serum potassium concentration (greater than 3.5 mmol/L), their intakes would nevertheless be considered inadequate if

increased potassium intake would decrease their risk of chronic disease. Because the IOM panel was concerned with ameliorating the risk of chronic disease, it did not consider serum potassium an acceptable measure of potassium adequacy.

- ***Hypokalemia.*** Evidence of moderate potassium deficiency and related chronic conditions does not always correspond to the development of hypokalemia; thus, it was not considered an sufficiently sensitive measure of adequacy.
- ***Salt Sensitivity.*** Individuals whose blood pressure increases with a rise in the consumption of sodium chloride are considered “salt sensitive.” Salt sensitivity has been shown to be strongly correlated to potassium intake, and the therapeutic effects of increased potassium intake on salt sensitivity are particularly evident in African American men (Morris et al. 1999; Price et al. 2002).
- ***Blood Pressure.*** Several epidemiological studies have found an inverse relationship between blood pressure and potassium intake, and intervention studies have also suggested that potassium can reduce blood pressure in both non-hypertensive and hypertensive subjects. None of these intervention studies evaluated the effects of more than two levels of potassium, preventing dose-response assessments. Furthermore, the studies that increased potassium intake through dietary adjustments did not parse out effects due to potassium and other nutrients, such as fiber and magnesium. A meta-analysis of a large number of clinical trials showed statistically significant reductions in systolic and diastolic blood pressure among the potassium treatment groups (Whelton et al. 1997). In several of these trials, the moderating effects of potassium were evident only when sodium intake was high. The effect of potassium on blood pressure was more pronounced in trials with a majority of African American subjects than in those with subjects who were predominantly white.
- ***Cardiovascular Disease.*** Rodent studies have found that potassium has reduced the occurrence of stroke and related mortality, although there has been significant debate over the effect of the type of accompanying anion on the moderating effects of potassium intake. Several, but not all of the epidemiological studies reviewed by the IOM panel found an inverse relationship between baseline potassium intake and stroke-induced morbidity and mortality among multiple population subgroups. Analyses of NHANES I data found a significant inverse relationship between potassium intake and stroke mortality, but the effect was only present in hypertensive and African American men (Fang et al. 2000).
- ***Bone Demineralization.*** Multiple epidemiological studies have found a significant positive relationship between potassium intake and bone mineral density in men, women, and children.

- ***Kidney Stones.*** Several large-scale epidemiological studies have found an inverse relationship between potassium intake and risk of kidney stones. A Finnish study observed beneficial effects of increased potassium intake on kidney stone formation until potassium intakes exceeded 4.6 g/day, at which point increased potassium intake did not seem to impact the risk of kidney stones (Hirvonen et al. 1999). Evidence from one clinical trial of the effects of potassium citrate on kidney stone formation supports these observational findings (Barcelo et al. 1993).
- ***Pulmonary Function.*** Mixed evidence suggests that potassium intake might increase relaxation of bronchial smooth muscles in adults and children.

Several factors can increase potassium requirements in healthy subjects, including exercise and exposure to high temperatures and diuretics. The beneficial impact of potassium on certain chronic conditions, such as blood pressure and kidney stones, also seems to be affected by sodium chloride intake; however, the IOM panel determined that there were not enough data available to set different recommendations for potassium intake based on sodium intake levels. Race also seems to play a role in determining the impact of potassium on certain chronic conditions; the positive effects of potassium on salt sensitivity and blood pressure appear to be more pronounced among African Americans than among other racial groups. Nevertheless, the IOM panel concluded that there is insufficient evidence to set specific potassium requirements for different racial and ethnic groups.

Table IV.12 provides a summary of the studies and methods used to determine the AI for potassium for children and adults. The discussion below provides details on the derivation of the AI for specific age and gender subgroups.

Children and Adolescents Age 1 to 18 Years. There was a lack of evidence on which to base an AI for children age 1 to 18 years. Few studies have assessed whether potassium has the same positive effects on health outcomes that have been found in studies of adults. An observational study of Dutch children age 5 to 17 years found that increased blood

Table IV.12. Derivation of the Average Intake (AI) for Potassium

Life Stage Group	AI	Method Used to Derive the AI
Children and Adolescents	1 - 3 years: 3.0 g/day 4 - 8 years: 3.8 g/day 9 - 13 years: 4.5 g/day 14 - 18 years: 4.7 g/day	AI for children and adolescents was extrapolated from the adult AI using the average of median energy intake levels for these age groups, as reported in the CSFII.
Adults	Men and women over 19 years of age: 4.7 g/day	AI for adults was based on epidemiological studies and clinical trials that suggest an inverse relationship between potassium intake and risk of chronic health conditions, including blood pressure, salt sensitivity, kidney stones, bone demineralization, and stroke.

CSFII = Continuing Survey of Food Intake by Individuals

pressure was inversely related to potassium intake and the dietary sodium:potassium ratio. Two clinical trials found no significant effect of potassium supplementation on blood pressure in children; however, both trials had extremely small sample sizes. The IOM panel concluded that the chronic health conditions that have been associated with inadequate potassium intake in adults are the result of inadequate intake of potassium over time, beginning in childhood. Therefore, the panel chose to extrapolate the AI for potassium for adults to children, on the basis of average median energy intake for each age range. They noted, however, that the best means of extrapolation is unclear. Energy intake was selected because the panel believed that extrapolation based on body weight would yield recommended intakes that were too low and that energy intake was a more appropriate method because children consume a high level of energy (and thus sodium) compared to their weight. Given their median energy intakes, the AI was set at 3.0 g/day for children age 1 to 3 years, 3.8 g/day for children age 4 to 8 years, 4.5 g/day for children age 9 to 13 years, and 4.7 g/day for adolescents age 14 to 18 years.

Adults Age 19 to 50 Years. The AI for adults 19 to 50 years of age is based on the clinical and epidemiological evidence described above, which suggests that increased potassium intake has several beneficial health outcomes, including decreased salt sensitivity and reduced risk for bone loss, kidney stones, and high blood pressure. Meta-analyses of clinical trials have found that potassium chloride reduces blood pressure (Cappuccio and MacGregor 1991; Geleijnse et al. 2003; Whelton et al. 1997). Potassium bicarbonate has been shown to reduce salt sensitivity and potassium citrate appears to reduce risk of kidney stone formation (Morris et al. 1999; Barcelo et al. 1993).

While dose-response trials that test multiple levels of potassium intake are not available, significant reductions in blood pressure in normotensive individuals occurred at intake levels that ranged from 3.1 to 4.7 g/day in clinical trials. Morris et al. (1999) found that potassium bicarbonate intakes of 4.7 g/day lessened severe salt sensitivity and abolished moderate salt sensitivity in normotensive African American male subjects (only African American male subjects displayed severe salt sensitivity), while intakes of 2.7 g/day diminished moderate salt sensitivity to a similar degree in both normotensive African American and white male subjects. None of the white subjects in this study received the 4.7 g/day diet.

Large-scale observational studies of adult men and women have shown that individuals who consume greater amounts of potassium experience lower rates of kidney stone formation (Curhan et al. 1993, 1997; Hirvonen et al. 1999). While the Health Professionals Study found a 20 percent decrease in the relative risk for kidney stones when potassium intakes increased from 3.8 g/day up to greater than 4.0 g/day, the Nurses' Health Study showed only a 2 percent decrease in the relative risk for kidney stones when potassium intake increased from 3.7 to 4.0 g/day (Curhan et al. 1993, 1997). Hirvonen et al. (1999) found no further reductions in relative risk of kidney stones at intake levels higher than 4.6 g/day. Other epidemiological studies suggest that higher potassium intake is related to decreased bone loss in both men and women (Tucker et al. 1999; New et al. 1997).

None of the studies used to set the AI offered information about gender differences in potassium requirements. The same AI was applied to both men and women, even though

the panel noted that variation in body composition and energy consumption may lead to different requirements for men and women. Furthermore, all of the studies evaluated the effects of potassium in conjunction with high sodium intake; thus, the AI for potassium could be lower for individuals who consume a reduced sodium diet.

Adults Over 50 Years of Age. Because few studies have assessed the effects of aging on potassium requirements in humans, the IOM panel relied on rodent studies to supplement the paucity of human data. Urinary excretion of potassium does not increase with age in rats; however, high levels of potassium intake seem to decrease the efficiency of urinary excretion of potassium chloride and increase plasma potassium concentration in older rats (Friedman and Friedman 1957; Rowe et al. 1992). The consequences of these results for older adults are unknown. Total body potassium and total exchangeable potassium decline with age, particularly in women (Davis et al. 1989; Rowe et al. 1992); however, hormonal regulation of potassium homeostasis outside of the kidneys does not appear to vary with age (Minaker and Rowe 1982; Rowe et al. 1992). Despite consuming less energy than younger adults, older adults have an increased risk of high blood pressure. While somewhat inconclusive, the panel determined that the available evidence and elevated risk of high blood pressure warranted applying the AI for adults age 19 to 50 years to older adults; thus, the AI was set at 4.7 g/day for both men and women over the age of 50.

Discussion

Studies that have assessed the usual intake of potassium in the U.S. population suggest that the majority of children, adolescents, and adults have intakes of potassium that fall far below the AI. While widespread evidence of potassium deficiency is lacking, habitually low levels of intake could play a role in the prevalence of certain chronic health conditions that have been tied to potassium intake.

There are several aspects of the derivation of the AI for potassium that are important to bear in mind when considering recent analyses of usual potassium intake in the general population. Most importantly, the AI for potassium was derived not on the basis of risk of deficiency—defined as hypokalemia—but rather on the basis of reducing the risk of chronic disease.

In addition, there appear to be significant differences in the amount of potassium required to achieve certain health states among various population subgroups. As noted earlier, differences in body composition and energy consumption between men and women may result in different potassium requirements by gender. Many of the studies used to set the AI for adults did not present separate results by gender; such information would be useful for determining whether potassium requirements differ for men and women. In addition, there is some evidence that the trends in relative risk reduction associated with increased potassium intake differ between men and women. For example, while the relative risk of kidney stones decreased by 20 percent between the fourth (3.8 g/day) and fifth (> 4.0 g/day) quintiles of potassium intake in a large epidemiological study of men, the relative risk of kidney stones only decreased by 2 percent between the fourth (3.7 g/day) and fifth (4.7 g/day) quintiles of potassium intake in a similarly large epidemiological study of women

(Curhan et al. 1993, 1997). Substantial differences in the significance and directional consistency of the trends in the relative risk of stroke among men and women can also be found in the same studies. In addition, Morris et al. (1999) found that non-hypertensive African American men experience more severe salt sensitivity than non-hypertensive white men. Their severe salt sensitivity was reduced by intakes of potassium of 4.7 g/day. Both non-hypertensive African American and white men with moderate salt sensitivity responded positively to intakes of potassium of 2.7 g/day, which is well below the established AI. Furthermore, some studies have suggested that the effect of potassium on blood pressure may be more pronounced in African Americans (Brancati et al. 1996; Obel 1989).

The AIs for children age 1 to 18 years were extrapolated from adult recommendations on the basis of average energy intakes because the chronic conditions that have been linked to potassium in adults were assumed to begin in childhood. It is important to determine whether this is an appropriate basis for extrapolation, in part due to possible misreporting of energy intakes, but also because it is not known whether inadequate potassium intake during childhood does in fact play a role in determining chronic disease during adulthood. Jones et al. (2001) found that increased potassium intake reduced urinary calcium excretion in adults, which may decrease the risk of kidney stones. The same relationship between potassium and calcium excretion was not observed in the children studied.

The relationship between potassium and chronic health outcomes also requires further study. As discussed earlier, many of the intervention studies that supplemented potassium intake through dietary changes failed to determine the effects of potassium on blood pressure, independent of the effects of other nutrients that were also prevalent in the treatment diets, such as fiber and magnesium. In addition, three epidemiological studies were cited in the derivation of the AI for adults age 19 to 50 years that were said to support an inverse relationship between potassium intake and risk of kidney stones (Curhan et al. 1993, 1997; Hirvonen et al. 1999). The most recent study, Hirvonen et al. (1999), however, found that this association was greatly attenuated and became non-significant ($p=0.34$), when magnesium intake was controlled. Potassium intake is also positively associated with intake of other essential nutrients (Curhan et al. 1993). Thus, the effects of potassium intake, independent of its correlation with dietary and other confounding factors, still need to be explored through future research.

In sum, it appears that more research would help to better understand the effects of potassium on health outcomes, determine whether intake requirements differ among various subgroups, and establish levels of potassium intake that would ensure adequacy for the majority of individuals. Dose-response trials would be useful in determining the effect of multiple levels of intake on various health outcomes. At present, studies that have assessed usual intakes of potassium have documented that the majority of Americans consume levels of potassium far below the AI, but the implications of this finding are unclear. Additional research is needed to determine whether chronic, widespread consumption of potassium below the AI has contributed to the prevalence of certain health conditions in modern society, including high blood pressure and stroke, among others.

CHAPTER V

CONCLUSIONS

Given the importance of nutrient reference standards to the design of food and nutrition assistance programs and policy, it is critical to examine carefully the DRIs and findings from dietary assessment studies to determine whether these programs are meeting their nutritional objectives. Moreover, understanding the DRIs is important for applications of the group planning framework, which is based on findings from dietary assessment studies and nutritional goals related to the DRIs (Institute of Medicine 2003). This study provides an in-depth examination of the models and methods used to set the DRIs for food energy and six selected nutrients—zinc, vitamin A, magnesium, vitamin E, fiber, and potassium. It originated in response to the results of recent dietary assessment studies that indicate some substantial inadequacies or excesses in intakes of these nutrients, seemingly unaccompanied by adverse health effects.

Earlier efforts to prioritize nutrients of public health concern required evidence of accompanying biochemical, clinical, or anthropometric adverse health effects. However, given that the DRIs incorporate the goal of reducing the risk of chronic disease (where data are available), rather than simply preventing deficiency, it is possible that short-term measures of biochemical, clinical or anthropometric adverse health effects may not be present even though the long-term health impact may still be important. Nonetheless, some findings from dietary assessment studies suggest dramatic dietary concerns that are not widely acknowledged by the nutrition research and policy community.

Of particular importance for the design and evaluation of food and nutrition assistance programs is the extent to which problems identified in dietary assessment studies represent important public health concerns or are the result of methodological shortcomings in either dietary assessment methods or the DRIs. Three scenarios are possible in interpreting findings of dietary assessment studies:

1. ***Some DRIs are flawed.*** In the case of flawed DRI values, results of dietary assessment studies should be interpreted cautiously, and policymakers may want to delay any policy changes or recommendations. A process for revising the DRI based on updated scientific evidence might be the priority.

2. ***The DRI values have a sound scientific basis, but the dietary recall data have limitations.*** If a probable explanation of dietary assessment concerns is the quality of the dietary recall data—for example, problems measuring vitamin E intakes—caution may also be advised in interpreting the results of the dietary recall studies, and efforts might be directed to improving the quality of the dietary data.
3. ***Both the DRIs and dietary recall data are considered scientifically sound.*** When there is confidence in both the DRI values and dietary recall data, dietary problems identified may indicate a real dietary concern, and policy considerations might be warranted—for example, restricting the amount of vitamin A in dietary supplements.

STUDY FINDINGS AND RESEARCH NEEDS

This review of the methods and studies underlying the DRIs suggests several issues to consider in interpreting the results of dietary assessment studies (Table V.1). Two general issues apply to all of the nutrients summarized in the table. First, errors in dietary recall data—either underreporting of intakes by adults or overreporting of intakes by young children—partially, but not fully, explain both the inadequacies and excessive intake findings summarized in the table. Second, the lack of sensitive and specific biochemical markers of inadequacy or toxicity for the nutrients in Table V.1 (with the exception of food energy) has resulted in DRIs for these selected nutrients to be based on studies or indicators that are less than optimal.

Food Energy. Recent analyses of usual energy intakes have found that mean usual intake exceeds mean EER for infants and young children by a substantial margin. In a re-analysis of doubly labeled water data measuring TEE, alternative specifications of TEE equations for infants and young children did not produce estimates of EERs that differed substantially from those presented in the IOM macronutrient report. The analysis indicates that other characteristics beyond body weight are significant predictors of TEE. Nonetheless, neither the inclusion of these factors nor a different estimation strategy materially changes the EER predictions.

The finding that the EERs estimated here are similar to those in the IOM report suggests that other explanations drive the large difference between energy requirements and intakes. One possibility would be that intakes truly do exceed requirements by a substantial margin. However, the magnitude of the difference between reported intakes and requirements suggests that this cannot be the only factor. Instead, the reason for the disparity is most likely (1) overreporting of children's energy intakes, (2) underreporting of children's weights, or (3) some combination of these two factors.

Zinc. Several studies have found that a high percentage of non-breastfeeding infants and young children have usual intakes of zinc that exceed the UL. The zinc ULs for infants and young children were set to prevent copper deficiency. Yet despite a very high prevalence of usual intakes above the UL, only one documented case of copper deficiency due to excessive zinc consumption has been reported for young children.

V. Conclusions

Table V.1. Review of the DRIs for Selected Nutrients: Study Findings and Research Needs

Nutrient	Subgroup	Results of Dietary Assessment Studies	Issues for Consideration
Food Energy	Infants and young children	Mean usual intake > EER by substantial margin	Overconsumption of food and beverages Overreporting of consumption Underreporting of body weight
Zinc	Infants and young children	High prevalence of usual intake > UL	Lack of data on adverse effects of excessive zinc intake Extrapolating the UL upward from the value for very young infants rather than downward from the value for adults Narrow margin between RDA and UL UL for zinc refers to intakes from all foods and supplements, yet adverse effects reported from supplements only Certain fortified foods and dietary supplements for children contain high levels of zinc UL for zinc does not take into account copper intake Overreporting of energy intakes may result in overestimates of zinc intake
Preformed Vitamin A	Infants and young children	High prevalence of usual intake > UL	UF used to set the UL for infants is high, but infants and children may be more susceptible to toxic effects Chronic hypervitaminosis A can go unnoticed Certain fortified foods and dietary supplements for children contain high levels of preformed vitamin A Overreporting of energy intakes may result in overestimates of preformed vitamin A intake
Magnesium	Older children and adults	High prevalence of usual intake < EAR	Limitations of balance data in determining magnesium requirements Other indicators of magnesium status may improve the accuracy of the EARs Nutrient interactions may affect magnesium requirements Underreporting of energy intakes for adults may result in underestimates of magnesium intakes
Vitamin E	Children and adults	High prevalence of usual intake < EAR	Lack of dose-response data Criterion of adequacy used to set EAR may not be a biomarker of vitamin E status Requirements vary based on amount of polyunsaturated fat consumed Current methods of dietary assessment underestimate vitamin E intake Vitamin E values in nutrient databases are highly variable or have been imputed Underreporting of energy intakes for adults may result in underestimates of vitamin E intakes
Fiber	Children and adults	Mean usual intake far less than AI	Studies used to determine AI based on dietary fiber, yet AI set for total fiber Effects of fiber may differ between children and adults AI for fiber depends on energy intakes, which are subject to underreporting or overreporting
Potassium	Children and adults	Mean usual intake far less than AI	Potassium requirements may differ by gender Effects of potassium may differ between children and adults Lack of dose-response data Effects of potassium on health outcomes may be confounded by other dietary factors

The in-depth review and analysis of the methods and studies used to set the UL for zinc suggested several issues to consider: (1) lack of data on the adverse effects of excessive zinc consumption in infants and young children; (2) differences in the ULs when extrapolating upward from the infant value versus extrapolating downward from an adult value; (3) the narrow margin between recommended zinc intake levels and the ULs; and (4) the application of the UL to naturally occurring zinc from food, despite no evidence of adverse effects.

The apparent problem of high zinc intake may be related to the consumption of zinc-fortified foods, particularly infant formula, infant cereals, and ready-to-eat breakfast cereals, some of which contain an amount of zinc that exceeds the UL for this age group. In addition, if parents overreport energy intakes of infants and young children, it seems plausible that the proportions of these subgroups with zinc intakes above the UL are overestimated. With infant formula ranking as the most important source of food energy for infants and ready-to-eat cereals fortified with zinc an important source of food energy for young children, it is likely that zinc intake is also overreported.

To strengthen the basis upon which to re-evaluate the UL for zinc for infants and young children, research is needed to identify (1) improved biomarkers of zinc and copper status, (2) intake levels and sources of zinc associated with adverse effects, and (3) the feasibility of defining a zinc UL that takes into account copper intake. In the meantime, zinc fortification practices and levels of zinc in children's dietary supplements might be re-evaluated, given their high content of zinc relative to the UL. The potential benefits of adding copper to zinc-fortified ready-to-eat cereals, common practice for infant formulas, could also be explored.

Preformed Vitamin A. Recent dietary assessment studies have shown that substantial proportions of non-breastfeeding infants and young children have intakes of preformed vitamin A above the UL. Although overreporting of intakes likely plays a role, several issues emerged in reviewing the methods used to set the ULs for preformed vitamin A. One is the possibility that the UF of 10 used to derive the UL for infants was set too conservatively, given the empirical findings used to determine the LOAEL and the reversibility of the critical adverse effect (bulging fontanel) on which it is based. The UL for young children was extrapolated from the UL for adults and resulted in a value that is the same as the UL for infants, even though the reference body weight for young children is considerably greater than for infants.

On the other hand, conservatism in setting the UL for preformed vitamin A for infants and children may be warranted. Infants and children are more susceptible to the adverse effects of excess vitamin A than adults, and some infants and young children experience toxicity at levels of preformed vitamin A intake between the UL and LOAEL. Cases of chronic hypervitaminosis A can go unnoticed. While the critical adverse effect for infants (bulging fontanel) is reversible, other adverse effects may be irreversible and little is known about the long-term effects of excessive vitamin A intake on young children.

Dietary supplements and several foods commonly consumed by young children contain large amounts of preformed vitamin A. Data from NHANES III show that about three-quarters of children 1 to 3 years of age who were taking supplements exceeded the UL for

performed vitamin A from supplements alone. Daily multivitamins in the dose typically recommended for young children contain an amount of preformed vitamin A in excess of the UL. If the current ULs are accurate, providing supplemental preformed vitamin A may put healthy young children at risk of vitamin A toxicity unnecessarily.

It would be useful to consider the possibility of extending the assessment of vitamin A status (plasma retinyl esters) in NHANES to infants and children under 4 years of age. This may shed light on whether young children are experiencing subclinical or unreported vitamin A toxicity at current levels of preformed vitamin A intake. As with zinc, it might be useful to reevaluate the levels of preformed vitamin A in children's dietary supplements and fortified foods.

Magnesium. Studies of usual intakes of magnesium suggest that high proportions of older children, adolescents, and adults consume inadequate amounts of this essential nutrient. These results were found for most age and gender subgroups; however, there is a lack of evidence of widespread magnesium deficiency in the general public. The EARs for magnesium were determined on the basis of available balance study findings for subgroups of children and adults.

There are several issues to consider when reviewing the derivation of the EARs for magnesium. In addition to a lack of balance data for multiple age and gender sub-groups, some of the balance studies that were available had significant limitations. More important, however, balance studies may be problematic when used to determine nutrient requirements because they may inaccurately assess nutrient retention. By overestimating intake and underestimating output, the values for nutrient requirements derived from balance studies may be inflated.

New evidence on magnesium requirements based on other potential indicators of magnesium status might be useful for assessing whether the current derivation of the EAR for magnesium is appropriate. Currently, however, it is unclear whether the other indicators of magnesium status discussed in Chapter IV provide more accurate estimates of magnesium status. Furthermore, to accurately estimate average magnesium requirements, it may be important to consider the effects of other nutrients that affect magnesium absorption.

Vitamin E. The diets of nearly all of the U.S. population do not meet current estimates of vitamin E requirements. This can be attributed in part to (1) limitations of the data used to set the EAR, and (2) problems with the assessment of vitamin E intake. The EARs for vitamin E for all age and gender groups were based on one study in adult males that is now more than 40 years old. While it was a long-term experimental study, the subjects were fed large amounts of polyunsaturated fats to increase their vitamin E requirements, and the tests used to determine adequacy were conducted outside the body and have not been correlated with vitamin E deficiency.

Current methods of dietary assessment also tend to underestimate vitamin E intake. Four general sources of error in dietary recalls result in underreporting of vitamin E intakes: (1) disproportionate underreporting of foods with high levels of dietary fat, which also are important contributors of vitamin E; (2) difficulty collecting reliable data on the amounts of

fats and oils used in food preparation; (3) use of default coding procedures because of lack of information on the specific types of fats and oils consumed; and (4) highly variable and imputed data on vitamin E values in nutrient databases.

Additional research is needed to determine what levels of vitamin E intake promote optimal health across the life span. Vitamin E deficiency is rare, and the challenges to better defining physiologic requirements are great. However, the IOM panel noted that several experimental studies of the effect of various amounts of vitamin E on the reduction of chronic diseases were in progress while the DRIs were being developed. An updated review of results from these studies may provide additional evidence on which to base the DRIs for vitamin E in the future. One question is whether the level of evidence currently available for vitamin E may be more appropriately used to set an AI. Another question is whether the nutrition research community might give high priority to improvements in dietary assessment methodologies with respect to (1) data on fat intake and (2) obtaining additional food composition data for vitamin E.

Fiber. The large gap between current dietary fiber intakes and the AI for fiber implies that most Americans do not consume enough fiber. The AI for fiber—14 g of *total fiber* per 1,000 kcal per day—was determined on the basis of studies that found an association between high intakes of *dietary fiber* and significant reductions in CHD risk among adults. The average dietary fiber intake that was associated with maximal CHD risk reduction in these studies was 14 g per 1,000 kcal per day. Since the AI includes both dietary and functional fiber, an even larger share of individuals is not consuming the amount of dietary fiber considered optimal according to the findings of these studies. Overall, little is known about the exact relationship between total fiber (dietary fiber plus functional fiber) and heart disease, diabetes, cancer, or other chronic health conditions that affect the health of a large share of the U.S. population.

One important issue is whether CHD risk is an appropriate criterion for determining recommended fiber intakes for all life stage groups. The AI for fiber was based on studies in adults between the ages of 37 and 75 years, and data were not available to determine whether fiber needs relative to total energy differ for younger adults or children. Because the risk for most chronic degenerative diseases increases with age, it is possible that the optimal intake of fiber as a function of energy intake is lower for younger adults and children. The method used to set the AI may also have overstated the optimal fiber intake for people who consume less than the median energy intake for their age-gender group.

The review suggests that the current recommendation for fiber intake could be revisited and that our understanding of the relationship between *total* fiber and health outcomes for children, adolescents, and adults would benefit from further research. In particular, additional dose-response data are needed to ascertain the level of fiber intake required to promote normal laxation in children. This would enable the amelioration of constipation to be explored as an alternative endpoint to the reduction of CHD risk for determining recommended fiber intakes for children. In the meantime, researchers and practitioners may want to individualize their estimates of fiber needs by using actual energy intakes (and 14 g

per 1,000 kcal), rather than the AIs for an entire life-stage group. Finally, studies that assess total fiber intakes would be useful in making comparisons to the current AI for fiber.

Potassium. Studies that have assessed the usual intake of potassium in the U.S. population suggest that most children, adolescents, and adults have intakes of potassium that fall far below the AI. While widespread evidence of potassium deficiency is lacking, habitually low levels of intake could play a role in the prevalence of certain chronic health conditions that have been tied to potassium intake such as salt sensitivity, high blood pressure, and kidney stones.

The relationship between potassium and health outcomes also requires further study. More research is needed to better understand the effects of potassium on health outcomes, independent of its correlation with potential confounding factors, and whether these effects vary between children and adults. Studies are also needed to determine whether optimal potassium intake differs among various subgroups (for example, by gender) and to establish levels of potassium intake that would be best for most people. To this end, dose-response trials would be useful in determining the effect of multiple levels of intake on various health outcomes.

CONCLUDING DISCUSSION

Development of the DRIs was an intensive effort to advance our knowledge and documentation of nutrient requirements. This effort spanned more than a decade and involved IOM panels of experts who reviewed and synthesized the scientific research and data on nutrient function and absorption, effects of inadequate or excessive intakes, potential indicators of inadequate or excessive intakes, and other factors that may influence requirements. In many instances, available data were often sparse or drawn from studies with significant limitations, and only limited evidence was available to guide the development of specific DRIs. The panels often pieced together many data sources and studies to produce a synthesis that represented their best knowledge of the human requirements for nutrients. Thus, although governed by scientific rationale, informed judgments were often required in setting these nutrient reference values.

Policymakers, nutrition and public health researchers, and the professional dietetics community need to understand the issues involved in deriving the DRIs and how to interpret the results of studies assessing nutrient adequacy using the DRIs. This study is a first attempt to undertake such a critical look and to identify and document the factors that explain the study results.

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