6

Guiding Principles for the Discretionary Addition of Nutrients to Food

As discussed in Chapter 3, fortification practices in the United States differ from those in Canada. The United States permits the discretionary fortification of food (with the exception of fresh produce, meats, poultry, and egg products) following Food and Drug Administration (FDA) guidelines (FDA, 1980; 21 C.F.R. 104.20). Canada has a more controlled approach.

The Dietary Reference Intake (DRI) reports clearly indicate that the potential exists for over- or underexposure to some nutrients for specific population groups or subgroups. The various reference values that comprise the DRIs were developed in part to provide benchmarks and comparison points that could be used by government agencies in the United States and Canada to set policies to improve the general health of their populations. The Tolerable Upper Intake Levels (ULs), in particular, were developed in partial response to concerns about the risks of overconsumption of nutrients in these two countries where nutrient deficiency diseases have significantly declined in the general population (IOM, 1997). With the decline in deficiency diseases, the relationship of nutrient and food intake to long-term health and the reduction in risk of chronic diseases has become an area of emphasis in nutrition programs and policies in the United States and Canada. A particular recent focus has been on those conditions related to the growing problem of overweight and obesity in the population (Joint Steering Committee, 1996; USDA/DHHS, 2000).

Some populations throughout North America, however, are still at risk for specific nutrient inadequacy in their diets because they

consume an insufficient amount of food to meet energy needs, they consume food with low nutrient density, or they omit one or more food groups. Historically, enrichment or fortification[1] of food targeted to specific populations has been used to reduce these types of inadequacies. Through fortification the specific nutrient content in food products can be minimally enhanced to restore naturally occurring nutrients lost during processing or it can be increased above the level found in comparable food to serve as a significant source of the specific nutrient.

The committee has approached discretionary fortification of food within the parameters of its limited charge from the study sponsors. This charge states:

> As a result of identifying approaches to using the DRIs as the basis for reference values for the food label, [the committee is to] determine principles for discretionary fortification or addition of nutrients to foods as well as the suitability of using reference values for the food label for discretionary fortification.

Thus the committee focused its deliberations on the suitability of applying the DRIs and the guiding principles recommended in Chapter 5 to the issues surrounding discretionary fortification. In doing so, the committee focused on the DRIs and, as also requested by the sponsors, considered FDA's 1980 fortification policy and specific vulnerable groups in the population. This chapter presents six principles, based on the scientific information contained in the DRI reports, that are intended to guide future discretionary fortification practices. The committee's approach has not been to review individual types of food, but rather to develop principles that would be applicable for all food, including meat and poultry products.

The committee has also approached its task on discretionary fortification with the assumption that the resulting guiding principles are scientific criteria that the sponsoring agencies would review and apply as they deem appropriate to identify situations where fortification is justified. While the historic and current approaches to fortification in the United States and in Canada differ, the committee has developed these principles with the anticipation they will serve as guidance to facilitate compatibility of discretionary fortification practices between the two countries.

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[1]Throughout this chapter the term "fortification" refers to the addition of nutrients to food.

SCIENTIFIC JUSTIFICATION AND CRITERIA

GUIDING PRINCIPLE 11. The scientific justification for discretionary fortification of food should be based on documented public health needs, particularly on dietary inadequacy that is determined by assessing the prevalence of nutrient inadequacy in the population. Regulatory agencies should develop criteria for determining when the evidence of dietary inadequacy indicates a documented public health need for the increased availability of nutrients in the food supply.

The committee recommends that discretionary fortification be based on public health need. The committee realizes the importance of fortification and its impact on disease prevention and the potential for problems if there are no policies that govern the fortification levels for nutrients. The fortification policies of the United States (21 C.F.R. 104.20) and the proposed policies of Canada (Health Canada, 1999, 2002) warn of over- or underfortification and the potential for nutrient imbalances that may occur as a result of random and excessive fortification of food.

The committee discussed what defines a "need" that can be met through discretionary fortification. This situation might occur when the nutrient content of the general diet does not meet the needs of all segments of the population or when the need might be less widespread. Within these broad situations of public health need, clearly the promotion of the health of the population can play an important role.

As a first step in identifying whether there is a public health need that might provide scientific justification for discretionary fortification, federal agencies should estimate the level of dietary inadequacy in life stage and gender subgroups of the population for any nutrient of concern. The DRIs can be used to assess the proportion of a group that has a usual intake of a nutrient that is less than the requirement. In addition, the health and nutritional status of groups or individuals need to be assessed through use of biochemical, clinical, and anthropometric indicators (IOM, 2000a). The appropriate method for assessing the prevalence of nutrient inadequacy for groups using the DRIs is presented in Section III of *Dietary Reference Intakes: Applications in Dietary Assessment* (IOM, 2000a). As discussed in that report, assessment is a two-step process. First, the distribution of usual nutrient intakes in the population from both food and supplements must be estimated using appropriate dietary intake assessment methods to determine actual intakes (i.e., 24-hour dietary intake recalls or food records). Then, by applying standard

statistical procedures, the effect of day-to-day variation can be discounted and an estimated distribution of usual intakes can be derived. For most nutrients the Estimated Average Requirement (EAR) cut-point method[2] can be applied to estimate the proportion of the population with usual intakes that are insufficient to meet their nutrient requirements. A probability approach is required for iron and protein, however, because the requirement distributions of these nutrients are not symmetrical. These assessment methods are outlined in the DRI reports for these nutrients (IOM, 2001, 2002a).

As noted in the DRI assessment report (IOM, 2000a), it is not possible to estimate the population prevalence of inadequacy for a nutrient for which there is an Adequate Intake (AI) and no EAR. Since AIs have been determined using different methodologies and assumptions, consideration must first be given to how the AI was established. Only when the AI was set as the median intake of the nutrient by a healthy population (i.e., for pantothenic acid, vitamin K, chromium, manganese, and *n*-6 and *n*-3 polyunsaturated fatty acids) can any degree of inadequacy be determined, and then only in a very limited way. Groups with mean intakes at or above the AI can generally be assumed to have a low prevalence of inadequate intakes. When mean intakes are below the AI, assumptions about adequacy cannot be made unless intakes approach zero. For all other AIs no quantitative measure of adequacy can be made. However other evidence, such as a direct measure of inadequacy with biological tests and measures of long-term health benefits with other biomarkers, should be used to validate intake data and as the basis for assessing adequacy in the absence of other information.

Once the prevalence of inadequacy for a particular nutrient has been assessed in a nationally representative sample of individuals, further review is required to determine whether there is sufficient evidence of public health need to scientifically justify the addition of a nutrient to the food supply through discretionary fortification. There is little published research on the impact of discretionary fortification practices on nutrient intakes or on the prevalence of nutrient inadequacy or excess. Although there is a growing body of literature on the effect of mandatory fortification (enrichment) (e.g., the addition of folic acid to standardized cereal and grain products) (Bailey et al., 2003; Mills et al., 2003; Quinlivan and Gregory,

[2]"With this method, the population prevalence of inadequate intakes is simply the proportion of the population with intakes below the median requirement (EAR)" (IOM, 2000a, p. 81).

2003; Ray et al., 2002a, 2002b, 2003), it would be premature to draw inferences about all discretionary fortification from these studies.

The committee cannot recommend guidelines about the impact of discretionary fortification on nutrient inadequacy and the distribution of inadequate intakes in the population without empirical data on discretionary fortification. Instead, the committee presents four key issues that should be considered as regulatory agencies appraise the public health need for discretionary fortification: the magnitude of the estimated prevalence of inadequacy, the reliability and validity of the prevalence estimate, the health risks associated with the determined inadequacy, and the indications that the nutrient inadequacy can possibly be ameliorated by increasing the availability of the nutrient in the food supply.

Magnitude of the Estimated Prevalence of Inadequacy

Regulatory agencies need to develop criteria to assess the public health importance of prevalence estimates in the context of concerns about discretionary fortification. For example, if the population prevalence of inadequacy for a nutrient is estimated to be 5 percent, questions can be raised about whether this prevalence level is sufficient to justify discretionary fortification. Although 5 percent of the population is a significant number of individuals, unless there is adequate information about this 5 percent of the population that enables fortified food products to be targeted to them, it is unlikely that discretionary fortification would have a discernible impact on the usual nutrient intakes. With a higher prevalence of inadequacy in clearly defined target groups, discretionary fortification might be a more viable strategy. Before considering this option, however, it would be necessary to examine data on the potential impact this discretionary fortification would have on nutrient intake levels in the population. Such prevalence information would need to be determined on the basis of total nutrient intake from food and dietary supplements.

Reliability and Validity of the Prevalence Estimate

There is imprecision associated with all prevalence estimates, but estimates may also be biased by particular methodological problems. In appraising the estimated prevalence of inadequacy for a particular nutrient in the population, the direction and magnitude of measurement errors in the assessment of dietary inadequacy need to be considered. The problems of measurement error associated

with dietary intake assessment have been discussed at length in the DRI assessment and planning reports (IOM, 2000a, 2003). Briefly, errors can arise in the estimation of usual food and nutrient intakes because of random and systematic errors in self-reporting of intakes (particularly systematic underreporting of intakes), estimation of usual intake levels from observed intakes, and determination of the nutrient content of a particular food (because of incomplete or erroneous food composition data).

Although knowledge of these measurement errors continues to grow and methods have been proposed to assess the accuracy of self-reported dietary intakes, there are limited tools with which to identify and correct such errors in population survey data. Because the determination of dietary inadequacy rests on an evaluation of the adequacy of usual nutrient intake levels in the population, errors in the measurement of usual intake levels pose a serious threat to this process. The prevalence of nutrient inadequacy could be grossly overestimated if there are high levels of underreporting in the dietary intake data or if the food composition database includes incomplete or erroneous data on the levels of a particular nutrient in food. Errors also are introduced into measurements of dietary supplement intake because formulations change frequently, and individuals who participate in surveys often have difficulty identifying the exact supplement brand or formulation they used, as well as the duration and regularity of use. Such problems need to be addressed before dietary intake assessments alone are used as a basis for discretionary fortification.

Given the limitations of dietary intake data, evidence of nutrient inadequacy from dietary intake assessments should be verified whenever possible by comparisons with other biochemical or clinical evidence of nutrient inadequacies at the population level. Congruence between dietary and biochemical indices of nutrient inadequacy is particularly valuable in establishing that problems of dietary inadequacy identified through dietary assessments are indeed of public health importance. Conversely, conflicting evidence of dietary insufficiencies need to be carefully reviewed before discretionary fortification could be scientifically justified as providing a potential public health benefit.

Health Risks Associated with Nutrient Inadequacy

Evidence of dietary inadequacy also needs to be weighed against the criteria used to determine the requirements for a particular nutrient. A prevalence of nutrient inadequacy based on nutrient

requirements as defined in the DRIs does not necessarily indicate a prevalence of nutrient deficiency. For example, two different indicators for estimating an average requirement were identified for vitamin A. One was the reversal of night blindness. The other, for which an EAR was calculated, was the minimum acceptable liver vitamin A reserve. A 10 to 15 percent prevalence of usual intakes below the calculated value required to prevent night blindness would indicate a more serious public health problem than a similar prevalence of intakes below the value required to maintain liver stores in healthy individuals. Vitamin A is the only nutrient for which there are two approaches for establishing requirements to address two different endpoints. This nutrient, however, highlights the importance of considering the severity of the consequences of not meeting requirements for particular nutrients when interpreting prevalence estimates to justify the need for discretionary fortification. In addition, based on such factors as geographic location, access to food, patterns of intake, and demographics, not meeting the requirements for one nutrient (e.g., vitamin D) in a given population may pose more of a health risk than not meeting the requirements of another nutrient. Depending on the prevalence of inadequacy and the severity of the health consequences associated with inadequate intakes of a particular nutrient, regulatory agencies may wish to encourage discretionary fortification or to consider population-level interventions (similar to the approach taken with folate) rather to address identified problems.

Selecting the Most Effective Strategy to Address Nutrient Inadequacy

Before an observed prevalence of nutrient inadequacy can be interpreted to scientifically justify the need for increased availability of the nutrient in the food supply, some analysis of the dietary correlates and sociodemographic characteristics associated with inadequate intakes in the population is required. Since discretionary fortification is first and foremost a strategy to increase nutrient density, it is important not to embark on this intervention without some indication that increased nutrient density might help to ameliorate the identified nutrient inadequacy. For example, if inadequate nutrient intakes are observed in the context of inadequate energy intakes, strategies to increase total food intake may be more important than strategies to increase the nutrient levels in food. An association between inadequate energy and nutrient intakes might also be indicative of an underreporting problem in the dietary intake data,

particularly if there is no corroborating evidence of energy inadequacy in the population.

A CONCEPTUAL MODEL

Use of the Tolerable Upper Intake Levels

When the UL was first introduced in the DRI report on calcium and related nutrients, one rationale for its development was concern about ". . . the increased fortification of foods with nutrients and the use of dietary supplements by more people and in larger doses" (IOM, 1997, p. 26). As mentioned in the original description of the model for the ULs (IOM, 1997), nutrients can be viewed like other chemical agents as having the potential to produce adverse health effects from excessive ingestion via the various sources available: conventional food, dietary supplements, and drugs. The UL is specifically defined as ". . . the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the specified life stage group" (IOM, 2002a). After discussing several possible approaches, the DRI Subcommittee on Upper Reference Levels of Nutrients determined that the science bases for nutrients and toxicology at the time best lent itself to a risk assessment framework for deriving ULs. The term "tolerable" was included as part of the name for this reference value because it connotes a level of intake that can be biologically tolerated, yet with regular intake above the UL there is the potential for increased risk of adverse health effects. The definition of an adverse effect underlying the ULs is broad. This breadth has led to significant diversity in the severity of the adverse effects, the typical ingestion sources (e.g., food, supplements, pharmaceutical preparations), and the rationale for intake (e.g., nourishment, treatment regime, prevention) that have been used as the basis for the ULs. These factors, as well as the specific details of the derivation of the UL, must be taken into account when considering discretionary fortification.

Discretionary Fortification Decision Making

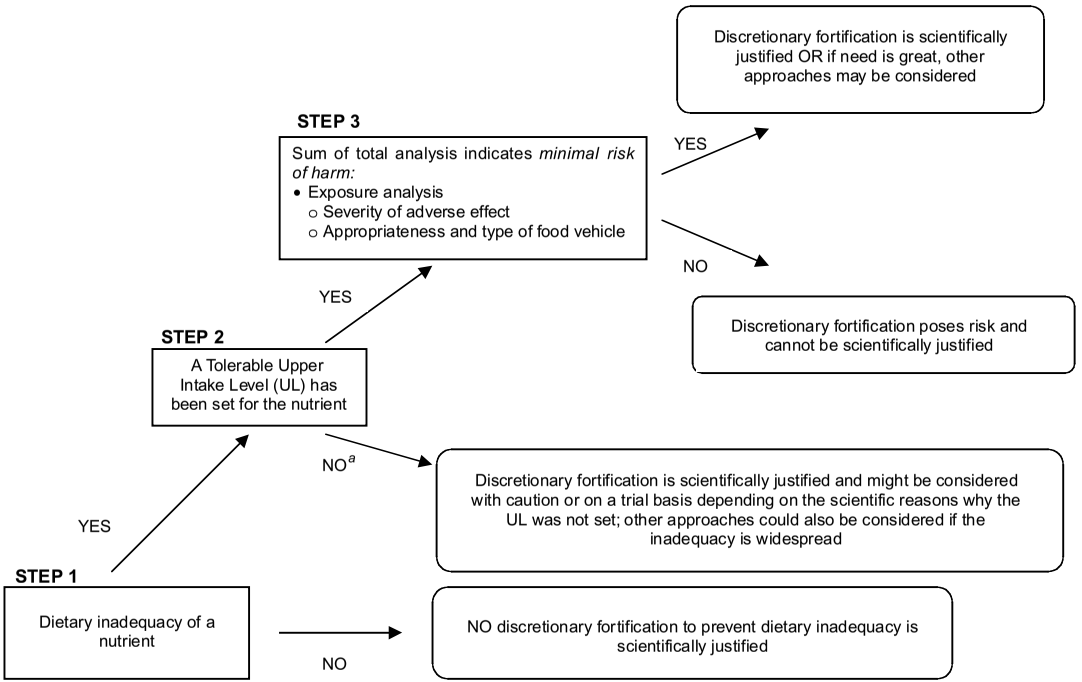
Guiding Principle 11 implies that existing food- and supplement-intake databases should be used to determine exposure of population groups to the nutrient proposed for fortification, and that the EAR should be used as a basis for this determination. The committee also made the following assumptions:

- Regardless of how the data are accumulated, decisions about the presence of dietary inadequacy and the level of public health need should reside with the regulatory agencies.
- If it is determined that there is no dietary inadequacy or that the inadequacy is at such a level that it does not constitute a public health risk, discretionary fortification would not be scientifically justified.
- If it is determined that there is dietary inadequacy of a nutrient in the population, discretionary fortification with that nutrient would be scientifically justified but, depending on the level of the public health need, the agencies may wish to consider other approaches to address the inadequacy. The scientific justification for discretionary fortification would most likely be composed of several steps, and optimally different groups (e.g., regulatory agencies, food manufacturers, federal research institutions, and university scientists) would have responsibility for these steps. The committee therefore recommends increased communication among these groups to share information about dietary and supplement intake and their potential effects on health.

GUIDING PRINCIPLE 12. In situations where discretionary fortification is scientifically justified, intake data should be used with the Tolerable Upper Intake Level (UL) to provide evidence, using a careful modeling approach, to explain how current exposure to the nutrient in question would be altered by discretionary fortification.

The committee recommends that intake data and the UL be used to model how exposure to potential fortification with a nutrient would alter the population's exposure to that nutrient. This modeling would use the amount of the nutrient under consideration for fortification to be provided to the population as a whole, to be provided to the population groups targeted by the food, and to be provided to the population groups at potential risk for overexposure to the nutrient.

To provide a documented public health justification for discretionary fortification, the committee recommends the three-step conceptual approach to decision making as illustrated in the flow diagram in Figure 6-1. This approach indicates how scientific information, including the DRIs, might justify four different outcome decisions with regard to discretionary fortification: no documented scientific justification for the discretionary fortification of food, fortification poses a significant safety risk and therefore cannot be scientifically



[a] For a number of nutrients no UL was set because there was insufficient documentation of adverse effects and the Dietary Reference Intake (DRI) reports language does not include a statement of concern of safety. For example, "There are no reports available of adverse effects from consumption of excess thiamin by ingestion of food and supplements. Because the data are inadequate for a quantitative risk assessment, no Tolerable Upper Intake Level (UL) can be derived for thiamin" (IOM, 1998, p. 81). For several other nutrients the UL was not set because there was insufficient documentation of adverse effects; however the DRI report language indicated a concern about safety. For example, "No adverse effects have been convincingly associated with excess intake of chromium from food or supplements, but this does not mean that there is no potential for adverse effects resulting from high intakes. Since data on the adverse effects of chromium intake are limited, caution may be warranted" (IOM, 2001, p. 216).

FIGURE 6-1 Flow diagram for decisions about discretionary food fortification.

justified, discretionary fortification needs additional scientific study or proceeds on a trial basis while more information is gathered, or discretionary fortification is scientifically justified. If the public health need is sufficient, agencies may consider approaches other than discretionary fortification as a means to increase a nutrient in the food supply, including the use of supplements.

Step One. Determine whether a dietary inadequacy of a specific nutrient has been documented scientifically in at least one segment of the population and if there is sufficient public health need. If *no* dietary inadequacy of a specific nutrient has been documented scientifically in at least one segment of the population, there is no demonstrated public health need for increased availability of the nutrient, and no discretionary fortification is justified. However, if there is a documented inadequacy and sufficient need, the next step is consideration of the UL.

Step Two. If a UL has not been set by the DRI reports for the nutrient being considered for discretionary fortification because there are no reports of adverse effects,[3] then discretionary fortification to address the inadequacy would be scientifically justified. Different approaches might be taken depending upon the language in the DRI reports.

For a number of nutrients no UL was set because there was insufficient documentation of adverse effects and the DRI report language does not include a statement that indicates a concern about safety. For example, "There are no reports available of adverse effects from consumption of excess thiamin by ingestion of food and supplements. Because the data are inadequate for a quantitative risk assessment, no Tolerable Upper Intake Level (UL) can be derived for thiamin" (IOM, 1998, p. 81). For several other nutrients the UL was not set because there was insufficient documentation of adverse effects; however the DRI report language indicated a concern about safety. For example, "No adverse effects have been convincingly associated with excess intake of chromium from food or supplements, but this does not mean that there is no potential for adverse effects resulting from high intakes. Since data on the adverse effects of chromium intake are limited, caution may be warranted"

[3]A UL was not set for the following nutrients for the population 4 years of age and older: vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, carotenoids, arsenic, chromium, silicon, and vanadium.

(IOM, 2001, p. 216). When there is no cautionary language in the DRI report, discretionary fortification might be considered. When caution is expressed as part of the UL discussion for the nutrient in a DRI report, then according to the decision model discretionary fortification would be considered only after more detailed scientific review and modeling or, on a trial basis while more data are collected, similar to the temporary marketing authorization used in Canada (Health Canada, 1999) and the temporary marketing permits used for variation from standardized food in the United States (21 C.F.R. 130.17). If sufficient public heath need is demonstrated, the regulatory agencies may consider other approaches to increase the availability of the nutrient. If the nutrient has a UL, then the next step is to proceed with modeling of the impact of fortification on the appropriate populations.

Step Three. An exposure analysis would be prepared using the appropriate populations. The analysis would include an evaluation of the severity of the adverse effect and whether the effect is observed with food, fortified food, supplements, or dosages designed for pharmacological purposes. If the totality of evidence from the exposure analysis indicates that fortification of a food item poses a *significant risk* of adverse effects to at least one segment of the population, then discretionary fortification at the proposed level would not be scientifically justified. If the exposure analysis indicates a *minimal risk of harm* and/or the effects are not noted at the levels proposed to be provided in food and supplements, discretionary fortification might be scientifically justified. In all cases appropriate records of the analyses should be maintained in the event adverse effects occur. If sufficient public health need is demonstrated, other approaches may be considered to increase the availability of the nutrient to the population.

Selected Nutrient Examples Using the Discretionary Fortification Decision Approach

Use of the decision flow diagram presented in Figure 6-1 is necessarily dependent upon many factors, such as the food that is being considered for fortification, the form of the food, the form and amount of the nutrient to be included in the food, and the exposure/modeling data. Below are four hypothetical examples that illustrate how the approach might be used. These examples are highly abstract because the necessary data specifics are not included.

Iron

The need for iron varies greatly among life stage and gender groups. Some groups, such as adult men and postmenopausal women, meet their relatively low needs for iron very easily. For example, men in a study conducted on Prince Edward Island, Canada, had a prevalence of inadequacy for iron of less than 1 percent (Taylor et al., 2002). In contrast, women of childbearing age and young children show vulnerability to iron deficiency. Women ages 19 to 50 years in the same Prince Edward Island study had a prevalence of inadequacy for iron of 29 percent (Taylor et al., 2002). Discretionary fortification with iron requires selection of the appropriate food vehicles that will be consumed preferentially by those in need of enhanced iron intake. A further complication is that many dietary assessment programs calculate total dietary iron, but not bioavailable iron. Finally, the needs of one group (e.g., women of child-bearing age) must be balanced against the risk of exceeding the UL for other groups (e.g., individuals with iron storage disease). According to the decision flow diagram in Figure 6-1, under these circumstances there might be sufficient scientific information to justify discretionary fortification with iron or to consider other approaches to supply iron to the specific subgroups that are iron deficient.

Vitamin D

Since publication of the DRIs for vitamin D (IOM, 1997), studies have shown that the current recommended intake levels are inadequate to maintain nutrient status in the absence of substantial cutaneous production (Heaney et al., 2003). Other recent studies demonstrated that the levels of vitamin D already added to food are not high enough or are not found in enough different food products to prevent vitamin D inadequacy (Looker et al., 2002; Nesby-O'Dell et al., 2002; Rucker et al., 2002; Tangpricha et al., 2002; Vieth et al., 2001). Since the DRI value established for vitamin D is an AI, calculation of the prevalence of inadequacy using this reference value is not possible. The studies cited above used biological indicators of vitamin D status to demonstrate that current dietary intakes are not adequate. According to the decision flow diagram in Figure 6-1, vitamin D might be another example of a nutrient for which discretionary fortification might be scientifically justified. At the same time, while the UL for vitamin D for the general population is 50 μg/day, a number of studies have documented vitamin D toxicosis in elderly individuals consuming a healthful diet and multiple sup-

plements (Marriott, 1997). Therefore, depending on the most current information regarding risk to specific populations, it might be decided that the scientific justification for discretionary fortification necessitated a more in-depth scientific review process or was more congruent with a trial period of fortification while more data was collected.

Vitamin A

The UL for vitamin A (as retinol) is 3,000 μg for pregnant women 19 to 50 years of age and 2,800 μg for pregnant women 18 years of age and younger. These values are approximately four times the Recommended Dietary Allowance (RDA). Some foods are highly concentrated sources of preformed vitamin A (e.g., liver). Other common food products, such as fortified low-fat milk, butter, or margarine, can provide additional preformed vitamin A. Thus preformed vitamin A may pose a significant risk of adverse effects to women of childbearing age who may become pregnant. According to the decision flow diagram in Figure 6-1, vitamin A could possibly be an example when discretionary fortification would not be scientifically justified or would necessitate careful study.

Alternatively fortification could be considered using provitamin A carotenoids, such as β-carotene, rather than retinol to increase vitamin A content. Provitamin A carotenoids are converted to retinol at an estimated rate of 12 μg as β-carotene or 24 μg as other provitamin A carotenoids (e.g., α-carotene and β-cryptoxanthin) to 1 retinol activity equivalent (RAE) (IOM, 2001). These conversation rates, however, assume that the carotene is bound in a fruit or vegetable matrix, so food fortified with carotenes may provide more RAEs than corresponding endogenous carotenes. Carotenes have no known level of toxicity and no UL, and there is no cautionary language about them in the DRI report (IOM, 2000b). Therefore, assuming that a public health need has been demonstrated, fortification might be scientifically justified.

Vitamin C

Vitamin C is a nutrient that is added to food not only for fortification purposes, but also for its in vitro antioxidant effects. Vitamin C has a UL of 2,000 g for adults. This value decreases to 650 mg for children ages 4 to 8 years. In considering the risk of harm based on the decision flow diagram in Figure 6-1, two factors emerge as important in assessing the scientific justification about fortification

with vitamin C: the severity of the adverse effects and a complete exposure analysis. Many potential risks of excess vitamin C have been identified. In the DRI report (IOM, 2000b) the relatively mild adverse effect, osmotic diarrhea, was chosen as the endpoint for the UL for vitamin C. The DRI report explained "[the] effects are generally not serious and are self-limiting." However the ULs for children for vitamin C were extrapolated based on body weight differences and therefore the risk of harm for children may warrant additional consideration.

The other important factor is that an exposure analysis would be needed that estimated vitamin C inclusion in food under all circumstances. For example, attention should be paid to the potential for vitamin C to increase iron absorption in instances where this effect is not desired, that is, when iron intakes are not inadequate or limited. While healthy people do not increase iron absorption in response to high doses of vitamin C, it is not known whether individuals with hereditary hemochromatosis could be adversely affected by the long-term ingestion of vitamin C (IOM, 2000b). Therefore, depending on the most current information regarding risk to specific populations, it might be decided that the scientific justification for discretionary fortification necessitated a more in-depth scientific review process or was more congruent with a trial period of fortification while more data were collected.

ISSUES IN IMPLEMENTING A LEVEL OF DISCRETIONARY FORTIFICATION

Role of Existing Practices in Maintaining Adequacy

GUIDING PRINCIPLE 13. Currently there is limited research on the impact of discretionary fortification on the distribution of usual intakes in the population. Consideration should be given to fortification with nutrients up to the amount for products to meet the criteria as "good" or "excellent" sources of the nutrients,[4] consistent with the modeling approach described in Guiding Principle 12.

[4]In the United States, for a food to qualify to serve as a "good source" of a nutrient, it must contain 10 to 19 percent of the Daily Value (DV) per reference amount customarily consumed. An "excellent" or "high" food source must contain at least 20 percent of the DV.

There is currently an absence of empirical data on the impact of discretionary fortification on the distribution of usual nutrient intakes in the population. This lack of data makes it difficult to estimate the amount of a nutrient that must be added to food to have the desired effect on an identified nutrient inadequacy. As a temporary alternative, fortification levels could be matched to the criteria for meeting nutrient content claims as "good" or "excellent" sources of nutrients, consistent with the modeling approach recommended in Guiding Principle 12. Recognizing that the defining conditions for these claims may change in the future, the committee recommends using these criteria with outcome modeling as a potentially effective approach to increasing the availability of selected nutrients in the food supply and facilitating communication of this benefit to consumers. The committee recommends using these criteria as a scientifically sound approach, even if the defining criteria for claims should change.

GUIDING PRINCIPLE 14. Potential changes to certain long-standing discretionary fortification practices should be carefully reviewed because they may be central to the maintenance of nutrient adequacy in the population.

Discretionary fortification of the food supply has evolved over time in the United States. This evolution has created a dynamic relationship between the micronutrient content of the food supply and the dietary adequacy and nutritional status of population groups. For example, in the United States many breakfast cereals have been fortified with vitamins and minerals at about 15 to 25 percent of the DV per serving since the 1970s. Since the 1980s some orange juice products have been fortified with calcium at 30 percent of the DV per 8 fl oz, an amount equivalent to that contained in 8 oz of milk. Regular use of these products could contribute meaningfully to nutrient intake in many segments of the population. Berner and colleagues (2001) demonstrated that discretionary fortification of some food products moved the ". . . median or the 25th percentile intakes from below to above the RDA . . ." for a number of different nutrients.

As indicated previously the committee recommends the use of existing food composition and dietary supplement databases to assess the level of dietary adequacy in selected population groups. It is the committee's understanding that individual food items that have been fortified under discretionary fortification policies in the United States cannot be readily identified as such in the current U.S.

Department of Agriculture food composition databases (Moshfegh, 2002). Thus it is presently difficult to analyze the impact of current discretionary fortification on usual nutrient intakes in the population. However, it is imperative that the contribution of existing fortification practices and dietary supplements to current intakes be understood before regulations are introduced that would dramatically alter these practices Given this situation, the agencies may decide that it important to support the continuation of certain longstanding discretionary fortification practices for the general nutritional well-being of the population.

Severity of the Adverse Effect

GUIDING PRINCIPLE 15. The severity of the adverse effect on which the Tolerable Upper Intake Level (UL) is based should be reviewed when considering discretionary fortification with a nutrient using the conceptual decision approach presented in Figure 6-1.

An important consideration in using the ULs is the heterogeneity of the severity of the adverse effects on which they are based. The definition of a UL includes the phrase ". . . is likely to pose no risk of adverse health effects . . ." (IOM, 1997, 1998, 2000b, 2001, 2002a). The DRI reports define the term adverse effect as ". . . any significant alteration in the structure or function of the human organism (Klaassen et al., 1986) or any impairment of a physiologically important function that could lead to a health effect that is adverse."[5] This definition provides wide latitude in identifying adverse effects. Often the effect identified for a nutrient is the first effect noted, regardless of its severity, which may not be evidenced from the consumption of food, but only from the consumption of nonfood sources or highly fortified food sources. Selected examples of the diversity of adverse effects identified as the basis for ULs for several nutrients are included in Box 6-1. The committee acknowledges that the paucity of direct data and diversity of adverse effects are limitations to the UL concept.

Therefore in evaluating the potential for overexposure to a specific nutrient, it is necessary to carefully consider the basis for esti-

[5]This definition is ". . . in accordance with the definition set by the joint World Health Organization, Food and Agriculture Organization of the United Nations, and International Atomic Energy Agency (WHO/FAO/IAEA) Expert Consultation on *Trace Elements in Human Nutrition and Health* (WHO, 1996)" (IOM, 1997, p. 52).

BOX 6-1 Examples of the Diversity of Adverse Effects as the Basis for Tolerable Upper Intake Levels (ULs) of Nutrients

Magnesium:

Magnesium, when ingested as a naturally occurring substance in foods, has not been demonstrated to exert any adverse effects. However, adverse effects of excess magnesium intake have been observed with intakes from nonfood sources such as various magnesium salts used for pharmacological purposes. Thus, a Tolerable Upper Intake Level (UL) cannot be based on magnesium obtained from foods. . . . The primary initial manifestation of excessive magnesium intake from nonfood sources is *diarrhea* (Mordes and Wacker, 1978; Rude and Singer, 1980). (IOM, 1997, p. 242)

Niacin:

Flushing is the adverse effect first observed after excess niacin intake and is generally observed at lower doses than are other effects. Flushing that results in patients deciding to change the pattern of niacin intake (i.e., reduce the amount taken at a time or withdraw from treatment) was selected as the most appropriate endpoint on which to base a UL. Although nicotinamide appears not to be associated with flushing effects, a UL for nicotinic acid that is based on flushing is considered protective against potential adverse effects of nicotinamide. The data on hepatotoxicity are considered less relevant to the general population because they involve large doses taken for long periods of time for the treatment of a medical condition. (IOM, 1998, p. 142)

Vitamin A:

Based on considerations of causality, quality, and completeness of the database, *teratogenicity* was selected as the critical adverse effect on which to base a UL for women of childbearing age. For all other adults, liver abnormalities were the critical adverse effects. Abnormal liver pathology, characteristic of vitamin A intoxication (or grossly elevated hepatic vitamin A levels), was selected rather than elevated liver enzymes because of the uncertainties regarding other possible causes such as concurrent use of hepatotoxic drugs, alcohol intake, and hepatitis B and C. Bone changes were not used because of the conflicting findings and the lack of other data confirming the findings of Melhus et al. (1998). (IOM, 2001, pp. 132–133)

Vitamin D:

Hypervitaminosis D is characterized by a *considerable increase in plasma 25(OH)D* concentration to a level of approximately 400 to 1,250 nmol/liter (160 to 500 ng/ml) (Jacobus et al., 1992; Stamp et al., 1977). Because changes

continued

BOX 6-1 Continued

in circulating levels of $1,25(OH)_2D$ are generally small and unreliable, the elevated levels of 25(OH)D are considered the indicator of toxicity. . . . The adverse effects of hypervitaminosis D are probably largely mediated via hypercalcemia, but limited evidence suggests that direct effects of high concentrations of vitamin D may be expressed in various organ systems, including kidney, bone, central nervous system, and cardiovascular system (Holmes and Kummerow, 1983). (IOM, 1997, p. 278)

NOTE: Words in *italics* are the adverse effects that form the basis for the UL for the nutrient.

mating the UL for that nutrient. In many instances the ULs are based on the intake of a nutrient from food, fortified food, and supplements. By definition, the ULs apply to chronic or usual intake levels. Assessments of overexposure thus need to be based on distributions of usual intake, and in cases where the UL applies to the total intake of a nutrient from food and supplements, the estimate of usual intake must incorporate intake from both sources.

Exposure Analysis of Dietary Supplements

Dietary supplements contribute substantially to the nutrient intake of large segments of the North American population (Balluz et al., 2000; Radimer et al., 2000; Vitolins et al., 2000). These contributions must be captured in the assessment of the total intake exposure of populations. While a number of studies have shown minimal to significant improvements in nutritional status with supplements targeted to at-risk groups in Western countries (Fiatarone Singh et al., 2000; Kiely et al., 2001; Stang et al., 2000; Stratton and Elia, 2000), emerging research demonstrates possible risks. This research indicates that the amounts of certain nutrients in some dietary supplements, coupled with adequate dietary intake, may result in total intake levels that approach and sometimes exceed the ULs (Allen and Haskell, 2002; O'Brien et al., 2001). The committee recognizes that FDA is prohibited by statutory provision from limiting the composition of the levels at which a specific nutrient is included in a dietary supplement other than for safety reasons. Because it is necessary

to know total nutrient intake in the diet relative to the UL, exposure estimates analogous to those for conventional foods need to be developed for dietary supplements.

Modifications for Special Purposes

GUIDING PRINCIPLE 16. Where discretionary fortification is scientifically justified for special-use products, the intended use of the targeted food should be the standard against which the nutrient content is assessed.

The committee's discussion of food marketed for special purposes focused on three types: those specially formulated for targeted populations at risk, meal replacements, and food designed as alternative sources of nutrients. In the United States some small children require relatively high amounts of nutrients that are inadequate in their diets. In this situation foods are formulated to ameliorate the nutrient inadequacy. For example, the Special Supplemental Nutrition Program for Women, Infants and Children has used cereals highly fortified with iron as a cornerstone of its efforts to decrease anemia among at-risk children. These special cases may require the use of higher amounts of discretionary fortification than might be suitable for more general-purpose food products.

Meal replacements are single foods—in bar, powdered mixes for reconstitution, or ready-to-drink form—that are intended to replace one or more meals or to serve as a sole source of nourishment. These products are marketed to or "represented for use" by a variety of individuals, such as those seeking a convenient meal or snack, those trying to manage their weight, and those at nutritional risk due to involuntary weight loss or recovery from illness or surgery.

In the United States FDA does not regulate the nutrient composition of meal replacements, but how a product is represented for use plays an important role in determining appropriate fortification goals for these products. FDA's current general fortification policy (FDA, 1980; 21 C.F.R. 104.20) states that nutrients must be added to food in proportion to caloric content. FDA recognizes that this policy may not be appropriate if a food is represented for use as a substitute for one made to resemble a traditional food. For example, a product represented to be used in a weight-reduction program is more appropriately fortified to replace the vitamins and minerals normally provided by a traditional meal that contains more calories.

In Canada "special purpose foods," which include meal replacements and nutritional supplements, are handled separately from

other foods in order that the food is appropriate for its intended purpose. Health Canada has recommended that manufacturers be given "the flexibility to develop new products targeted to groups or individuals with special needs" (Health Canada, 1999, p. 24). The manufacturer, however, would be required to provide the scientific rationale for both the target group and the nutrient composition. In Canada the composition of meal replacements is regulated under the Food and Drug Regulations to provide nutrients in accordance with the Recommended Nutrient Intakes (RNIs) and the *Nutrition Recommendations* (Canada, 1990). Meal replacements must contain approximately 25 percent of the RNIs of 12 vitamins and 10 minerals in a serving, and the quantity and quality of protein and the quantity of fat and essential fatty acids are controlled.

Meal replacements represent a special situation with respect to fortification, be it discretionary as in the United States, or regulated as in Canada. The important consideration is that a meal replacement be fortified with a defined variety of nutrients in quantities appropriate for the meal it replaces.

Another type of special-purpose food, sometimes called a substitute food, is a food product designed specifically to provide an alternative source of a nutrient. Examples include orange juice or soy- and rice-based beverages intended to provide a milligram equivalent amount of calcium per reference serving for persons with lactose intolerance or food allergy, for vegetarians, or for personal choice to meet calcium needs. When discretionary fortification is used for special purposes, the intended use of the targeted food should determine the amount of the proposed nutrient addition.