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Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silver, Vanadium, and Zinc[1]

In this session, Robert Russell of Tufts University, former chair of the panel on micronutrients, focused attention on research related to 4 of the 14 disparate nutrients that were covered in the DRI Micronutrients Report (IOM, 2001), namely vitamin A, vitamin K, iron, and zinc.[2] Dr. Janet Hunt of Grand Forks Human Nutrition Research Center, former member of the Subcommittee on Interpretation and Uses of Dietary Reference Intakes, provided research perspectives related to the report.

DISCUSSION OF RESEARCH RECOMMENDATIONS

Presenter: Robert M. Russell

To set the stage for considering research recommendations, this presentation provided background information on Dietary Reference Intakes (DRIs). Then Dr. Russell identified and discussed what he considered to be the four most important research recommendations made in the DRI Micronutrients Report.

[1]This chapter is based on a transcript and slides from the workshop.
[2]Dr. Russell's comments incorporate input from a majority of the other micronutrient panel members.

Background Information

The background information provided here is intended to illustrate the major knowledge gaps that have posed challenges for setting DRIs for the micronutrients covered in the DRI Micronutrients Report. The Estimated Average Requirements (EARs) for vitamin A, iron, and zinc were all based on factorial considerations including percent absorption, bioavailability, excretion, turnover, and utilization of the nutrient. The panel had considered using indicators for setting the EARs for these nutrients. Examples of indicators the panel considered when setting the EAR for vitamin A include:

- immune function,
- conjunctival impression cytology,
- relative dose–response and modified relative dose–response,
- isotope dilution,
- serum/plasma retinol concentration, and
- dark adaptation.

The first three indicators were not selected either because most of the work was done in animals or because the observations were made in developing countries where the total nutritional profiles were uncertain. Insufficient data were available on isotope dilution studies to obtain a good prediction of body stores of vitamin A. Neither serum nor plasma retinol concentrations could be used because retinol is under homeostatic control.

By pooling data from four studies on dark adaptation, encompassing 13 individuals, the EAR would have been set at 300 retinol activity equivalents (RAEs), Because the coefficient of variation was 40 percent, however, it was judged that the Recommended Dietary Allowance (RDA) could not be established using dark adaptation (the preferred indicator). Thus, the factorial method rather than dark adaptation was used to set the EAR. Doing this resulted in an EAR that was about twice as high—625 RAE/day.

For vitamin K, an Adequate Intake (AI) was set rather than an EAR. This decision was a result of two factors: lack of dose–response data and some uncertainty about the physiologic relevancy of carboxylated osteocalcin as an indicator for vitamin K status.

Four Key Research Recommendations

Dr. Russell identified four research recommendations in the DRI Micronutrients Report that he viewed as of highest priority. These recommendations appear below. These four research recommendations cut across many of the nutrients and remain major research gaps.

1. Identification of new functional and biochemical end points that indicate sufficient and insufficient body stores (vitamin A, vitamin K, iron, chromium)
2. Identification of new functional and biochemical end points that indicate nutrient toxicity (iron and oxidative status, iron content of ferritin, hepcidin, vitamin A and bone toxicity, zinc and immune function)
3. The identification and (quantified) effects of interactions between micronutrients and other food components: calcium and zinc, zinc and phytate
4. Determination of the effects of age, sex, race, pregnancy, and lactation on nutrient utilization and turnover: vitamin A, vitamin K, zinc

Status of These Research Needs

The Identification of New Functional and Biochemical End Points

As an example of the first recommendation, studies are needed of the relationship between early childhood iron deficiency and cognitive function with an eye toward identifying the best indicators of risk. Some progress has been made on vitamin K, and studies are underway. For example, three clinical intervention trials are investigating the specific role of phylloquinone in bone in postmenopausal women. At least one is addressing the beneficial effects of pharmacologic dosing of menaquinone 4 in the treatment of osteoporosis. (Menaquinone 4 has been used to treat osteoporosis for more than 10 years in Japan, with reported benefits]Cockayne et al., 2006].) These three intervention studies should provide useful information about the physiologic significance of undercarboxylated osteocalcin and could be helpful in providing data useful for establishing EARs.

New studies suggest roles for vitamin K in coronary artery disease and in brain function, and these topics warrant further research. For example, strong animal data support a role for vitamin K-dependent proteins as an inhibitor of calcification. In particular, mice lacking the gene coding for matrix Gla protein show calcification of their arteries that leads to hemorrhagic death due to vessel rupture. As another example, animal studies of neurodegeneration hold promise and need to be expanded. In addition, parallel human studies are needed to examine links of neuropsychological outcome measures or other measures of cognitive function with vitamin K status. Because high intakes of vitamin K are associated with high-quality diets, prospective intervention trials using the isolated vitamin will be needed to distinguish the action of vitamin K from that of other nutrients, such as folate.

End Points that Indicate Nutrient Toxicity

A number of functional and biochemical endpoints that indicate nutrient toxicity offer promising avenues of research:

- Iron and oxidative status, iron content of ferritin, and hepcidin;
- The relationship between iron status, serum ferritin, and the metabolic syndrome and the putative risk for cardiovascular diseases related to oxidative damage;
- The examination of which systems become dysfunctional with excess zinc, considering the immune system as a prime target of investigation; and
- The relationship of vitamin A intake with bone demineralization—Feskanich and coworkers (2002) provide evidence that this adverse effect occurs at intakes that are close to the RDA, but some inconsistent findings also have been reported.

Interactions

Of particular interest are studies of interactions between calcium and zinc and between zinc and phytate. Related is study of the quantity of endogenous zinc excreted by the intestine versus the quantity absorbed (i.e., studies on human zinc homeostasis) at various intake levels.

Effects of Age, Sex, Race, and Physiological Status on Nutrient Utilization

The DRI values set for children (by the use of extrapolation) merit attention. Table 6-1, which covers vitamin A values, illustrates this point.

One can see that the Tolerable Upper Intake Levels (ULs) for the younger children equal the RDAs for adolescents—a situation that calls for closer examination. Similarly for the younger children, the UL for zinc is very close to the RDA; and it could be easy for young children to exceed the UL for zinc.

The investigation of lactating women's iodine requirements is another topic still in need of research.

TABLE 6-1 Selected Dietary Reference Intake Values for Vitamin A and the Criteria Used to Set Them, by Life Stage

Life Stage	Criterion	EAR	RDA	AI	UL
		←μg of vitamin A/day→			
0–6 months	Human milk content			400	
7–12 months	Extrapolated from 0–6 months			500	
1–2 years	Extrapolated from adults	210	300		600
4–8 years	Extrapolated from adults	275	400		900
9–13 years, M	Extrapolated from adults	445	600		
9–13 years, F	Extrapolated from adults	420	600		
14–18 years, M	Extrapolated from adults	630	900		
14–18 years, F	Extrapolated from adults	485	700		
> 18 years, M	Adequate body stores	625	900		
> 18 years, F	Adequate body stores	500	700		

M = Male; F = Female; EAR = Estimated Average Requirement; RDA = Recommended Dietary Allowance; AI = Adequate Intake; UL = Tolerable Upper Intake Level .

SOURCE: IOM (2001).

Research Gaps for Which New Data Are Available

More data are available now to address a number of research questions identified by the panel on micronutrients, including the following:

- The effect of vitamin A status on plant carotene conversion. The lower the vitamin A nutriture, the better humans break down and utilize the plant carotene (Ribaya-Mercado et al., 2000).
- The vitamin A activity of different plant foods (Haskell et al., 2004; Tang et al., 1999; 2005). For example, the conversion ratio of beta-carotene to vitamin A would be 21 μg to 1 μg for spinach and 15 to 1 for carrots. Research is still needed on how this conversion is affected when the plant food is eaten as a part of a whole meal.
- The vitamin A content of foods
- Classifications of iron-loading syndromes with identification of the central role of hepcidin, which is a down-regulator of iron transport. There is great hope that hepcidin could be used in setting an EAR and/or in considering iron overload.

Potential New Research Questions

Dr. Russell posed a set of topics for investigation that have arisen since the writing of the DRI Micronutrients Report:

- Vitamin A and gene expression profiles, especially gene expressions that control certain functions
- The bioavailability and metabolism of menaquinones and the roles of menaquinones and phyloquinones in sphingolipid metabolism. Animal data published since the DRI Micronutrients Report completion points to roles for vitamin K in the form of menaquinone for brain function: it stimulates sphingolipid synthesis and improves cognition.
- The relationship between iron status and infections, such as human immunodeficiency virus (HIV) and tuberculosis
- Food-specific bioavailability questions, such as the bioavailability of iron or beta-carotene in cereal and legume crops produced

by varietal selection or genetic engineering to improve iron nutrition

- Biomarkers of zinc status, primarily genomic or proteomic, to correlate with functional outcomes such as immunity. For example, a gene product derived from zinc-influenced systems (such as zinc transporter proteins) might serve as a biomarker.

Status of Research on Chromium, Copper, and Ultra-Trace Minerals

No substantial progress has been made on the bioavailability and turnover of chromium, copper, or the ultra-trace minerals (arsenic, boron, manganese, molybdenum, nickel, silicon, and vanadium). Furthermore, no substantial data have been published to date on physiologic and psychologic functional consequences of deficiencies of these minerals. A research question might be, "What is the effect of boron deficiency in bone health?"

Summary

In summary, for vitamin K, much progress has occurred and more is expected over the next several years—probably enough on which to base an EAR. For vitamin A, there has been substantial progress as well. Despite good progress for iron, much remains to be done, especially regarding hepcidin as a marker of iron status. For the other minerals, much work still needs to be done.

RESEARCH PERSPECTIVES

Presenter: Janet R. Hunt

The DRI process can be related to the circular process of assessment, planning, implementation, and evaluation (Figure 6-1). Following the steps in Figure 6-1 can help to identify research needs.

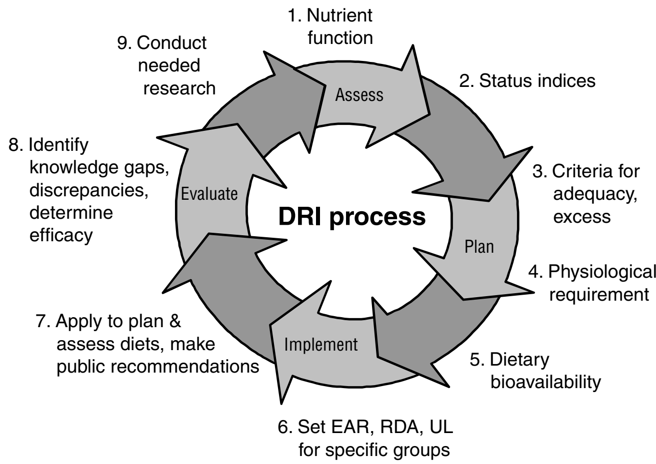

FIGURE 6-1 Dietary Reference Intakes process in relation to the circular assessment, planning, implementation, and evaluation process.

Steps 1 and 2: Nutrient Function and Status Indicators

There is a need to identify the functional roles related to good health for the micronutrients. Even though zinc is widely known for its importance for immune function and for wound healing, it is not yet possible to identify a specific immune function, chemical, or indicator that can be used to indicate adequate zinc intake.

Sensitive status indices are lacking for the micronutrients covered in the DRI Micronutrients Report, with the possible exceptions of vitamin A, iron, and iodine. For example, beyond the prevention of anemia and having adequate levels of transferrin saturation, there currently is no clear cut point for measurement indicators of iron stores. It is notable that since the DRI Micronutrients Report was completed, Cook and colleagues (2003) have developed a measure of body iron stores by using an algorithm based on the ratio of serum transferrin receptor (TfR) and serum ferritin. However, the measure does not provide a clear cut point for adequacy. In intervention studies in developing countries, this algorithm using TfR and serum ferritin has been very sensitive. In contrast to using hemoglobin as an end point, this algorithm-based method of measuring body iron stores can be used in intervention studies to reduce the number of subjects and shorten the observation time. However, there is a strong need for standardization of the measurement of TfR between different commercial assays.

As Dr. Russell indicated, hepcidin is a very promising general indicator of iron status—namely, as a regulator of iron absorption in the body (Nemeth and Ganz, 2006). However, most hepcidin data have been limited to genetic expression in animals, and the measurement of hepcidin peptide in serum poses challenges. Research is needed to develop the methodology and to apply hepcidin to the assessment of iron status in humans (Hadley et al., 2006). Dr. Hunt also agreed that status indices related to iron and cognition are needed, especially to address concerns about childhood iron deficiency and its impact on cognition and possibly mood and affect.

Further research on zinc transport proteins (Liuzzi and Cousins, 2004) may provide a more specific indicator of nutritional adequacy that could contribute to setting the EAR for zinc. This area of research requires more animal as well as human studies to identify sensitive and specific indicators.

The few functional indices available do not provide evidence that the use of mineral supplements will affect performance, as concluded in a recent review of mineral requirements for military personnel (IOM, 2006b); but the identification of functional indices continues to be an area of research that would support the development of DRIs.

Steps 3 and 4: Criteria and Physiological Requirement

The ability to set criteria for adequacy and excess is limited when the criteria cannot be based on function. This is the case, for example, when one must rely on factorial estimations of nutrient requirements.

Basing an EAR or AI on factorial estimations of the requirement relies largely on the use of data from balance studies and the replacement of estimated daily excretion. To the extent that such studies must serve as the basis of requirements, Dr. Hunt supports the report's recommendations for research methods that call for balance studies that (1) are sufficiently long to reach a new steady state, and (2) are designed so that the intakes bracket the requirements. When making factorial estimations, an additional consideration is the handling of nutrient loss through sweat. Specific situations of heat and humidity affect sweat losses of nutrients, but they are very difficult to measure accurately, and data are lacking regarding how adaptation affects such losses (IOM, 2006b).

Step 5: Dietary Bioavailability

Accounting for the Bioavailability of Iron

The bioavailability of iron merits special attention as related to the EAR and RDA. In particular, the EAR for iron was based on an estimated 18 percent iron bioavailability from a typical North American dietary intake. However, a diet consistent with the recently released *Dietary Guidelines for Americans 2005* (DHHS/USDA, 2005) may reduce the bioavailability of iron to approximately 11 percent, (Hunt, unpublished calculation). This estimate is based on the much higher fiber content recommended by *Dietary Guidelines for Americans 2005* (which is consistent with the AI for dietary fiber). An 11 percent bioavailability suggests that the dietary iron requirement would be 60 percent larger than if the bioavailability were 18 percent. Given that the same amount of iron consumed can result in vastly different amounts of iron absorbed, perhaps iron recommendations need to incorporate bioavailability considerations and suggestions for improving iron bioavailability rather than be limited to the amount of iron to be consumed.

Progress Made

Since 2002, some progress has been made regarding the bioavailability of both zinc and iron. The International Zinc Nutrition Consultative Group has developed an algorithm that predicts zinc bioavailability from the whole diet (International Zinc Consultative Group, 2004). It is based on two factors: the zinc content of the diet and the phytate content of the diet. Recognition has increased that the oral zinc dose or the amount of zinc in a meal affects zinc absorptive efficiency (International Zinc Nutrition Consultative Group, 2004). Work also has progressed on the bioavailability of different forms of zinc, including indication that zinc oxide is bioavailable and could be useful for fortification (Herman et al., 2002; de Romana et al., 2003).

Step 6: Setting EARs, RDAs, and ULs for Specific Groups

Problems posed by the need to extrapolate to set DRIs for children have, in several instances, resulted in setting a UL that is lower than typical intakes of specific age groups. In particular, based on data from the Continuing Survey of Intakes by Individuals, substantial percentages of formula-fed infants and of children up to age 8 years have zinc intakes that exceed the UL. Similarly, high percentages of children have iodine intakes that exceed the UL. Reported intakes of vitamin A also commonly exceed the UL for children younger than the age of 4 years.

Step 7: Applying Dietary Reference Intakes in Planning and Assessing Diets

Apparent discrepancies have been discovered when applying the new DRIs to the planning and assessment of diets. For example, discrepancies between intakes and the UL for manganese appear for subgroups of individuals. Typical diets of some groups, such as pregnant women and vegetarians, may not be adequate for iron. Because of lower dietary iron bioavailability, the benefit of iron supplementation of vegetarian diets is unclear.

Steps 8 and 9: Identifying Knowledge Gaps and Discrepancies and Conducting Needed Research

A number of knowledge gaps and discrepancies were identified above. In addition, knowledge of the usefulness of different supplemental forms of iron, including different elemental iron powders and chelated forms of iron, has increased (Hurrell et al., 2002; Swain et al., 2003; Hoppe et al., 2003; Zimmerman et al., 2005). In Vietnamese and Chinese studies, sodium iron ethylendiaminetetra-acetic acid (EDTA) has been shown to be very effective in addressing iron deficiency anemia (Chen et al., 2005; Van Thuy et al., 2005).

For elements such as boron, there is potential that further research information, probably beginning with animal models, might lead to inclusion as a nutrient. Boron is demonstrated to be essential for most of the plant world (Devirian and Volpe, 2003).

DISCUSSION

Comments and questions following this presentation were of a general nature and are summarized in Chapter 13, "Wrap-up Session."