Dietary Reference Intakes: Concepts and Approaches Underlying Protein and Energy Requirements

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Abstract

Nutrient reference values provide guidance for maintaining and enhancing health via standard setting and development of nutritionally improved products to decrease the risk of disease. Since 1941, the Food and Nutrition Board (FNB) of the National Academy of Sciences in the United States has developed and periodically revised recommendations for nutrients; the last (10th) edition of the Recommended Dietary Allowances (RDA) was released in 1989. In 1994 the FNB initiated an expanded approach to develop dietary reference intakes (DRI), quantitative nutrient intakes that include concepts of chronic disease risk and multiple reference values more specifically suited to various applications. In concert with Canadian scientists, 10 DRI reports have been completed since 1997 and are available for review at www.nap.edu. The DRI reports explicitly review possible functional endpoints considered in determining the adequacy of each nutrient, and differentiate between the statistical basis for assessing the adequacy of intakes for individuals and groups and providing recommended intakes, as well as levels of nutrient intake that should not be exceeded. Recommended intakes for infants are based on average volumes of intake by healthy, full-term, exclusively breast-fed infants and nutrient analysis of human milk; the recommended intake also includes nutrients contributed by complementary foods consumed during the second 6-month period of life.

Introduction

Nutrient reference values provide guidance to maintain and enhance health via standard setting and development of nutritionally improved products to decrease the risk of disease. Quantitative reference values for nutrients used in food and nutrition planning have been available since the early 1900s when recommended intakes for protein were included in early United States
Department of Agriculture bulletins [1]. At the beginning of World War II, the Food and Nutrition Board (FNB) of the National Academy of Sciences established a set of nutrient standards in 1941: the Recommended Dietary Allowances (RDAs) [2]. Over the following five decades, these have been periodically revised and by 1989, served as tools to assess the adequacy of diets, as goals for intake, and as the basis for food and nutrition programs and policies in the US and other countries.

By the 1980s, research in nutrition and health had expanded beyond initial concerns focused on deficiency diseases to looking at chronic disease relationships. Such research broadened the definition of nutrient ‘deficiency’ and supported the release of two companion reports by the FNB in 1989, the 10th edition of the Recommended Dietary Allowances [3] and a new report evaluating the role of nutrients and diet on chronic disease [4].

The definition of RDA has remained markedly constant over many revisions: the levels of intake of essential nutrients that were considered, in the judgment of the FNB and on the basis of available scientific knowledge, to be adequate to meet the known nutritional needs of practically all healthy persons for nutrients known to be required [3]. Past concerns about nutrient toxicity, of consuming too much of a nutrient, were typically not significant, with major exceptions being products such as infant formulas, which might well be the sole source of nutrients for an important period of growth and development, or substances such as cod liver oil.

In 1994 the FNB proposed expanding the approach of its previous work in establishing RDAs to include concepts of disease risk beyond traditional deficiency signs and symptoms [5]. Following the approach used by Great Britain in 1991 [6] and based on the diverse situations in which RDAs were increasingly being used as the reference values (table 1), it also became increasingly important to provide multiple reference values more specifically suited to the application and which could be scientifically supported [5]. This expansion of the RDAs to provide additional reference values, termed dietary reference intakes (DRIs), has resulted in a series of 10 DRI reports since 1997. This has been a joint activity with Canadian scientists, supported by US governmental agencies, Health Canada, private foundations, and industry.

**Conceptual Basis of Dietary Reference Intakes**

Brief descriptions of each category of reference intakes included in the DRI reports are provided in table 2, along with their typical uses. Initially, only three categories of DRIs for each nutrient were planned: an estimated average requirement (EAR), an RDA, and a tolerable upper intake level (UL). Early on, however, it became apparent that for nutrients with little dose-response data, a reference value would still be needed as a recommended level of intake, established on a different basis than the RDA (fig. 1). This
surrogate recommended intake, the adequate intake (AI), was not called an RDA to explicitly show that it was less conclusive and that more judgment was involved in its determination.

Model for Establishing Recommended Intakes

The DRI reports explicitly review the usefulness and limitations of all possible functional endpoints considered in determining adequacy, justifying those selected in establishing the requirement for the nutrient. Typically animal data are not used. While attention is paid to observed intakes in healthy populations, recommended intakes are based on epidemiological observations, human balance study data, depletion/repletion studies, and accepted surrogate markers or biochemical indicators of adequacy, when functional outcomes, such as decreased risk of chronic disease, are not available.

The basis of both the RDA and the use of the EAR in the assessment of adequacy of group intakes requires establishing a dose response (fig. 1). A normal or symmetrical distribution of requirements in a group of individuals with similar age and gender is also needed [7] (fig. 2). The departure from past derivations of most nutrient recommendations (with the exception of protein) is that in order to have an RDA as the recommended intake for an individual, there must be data available to establish an EAR. The EAR is defined as the best estimate of the average (actually, median) requirement for a group of similar individuals. Thus, half of individuals in the subgroup will have their needs met...
### Table 2. Dietary reference intakes: definitions and uses

<table>
<thead>
<tr>
<th>Category of dietary reference intake (DRI)</th>
<th>Use to assess dietary adequacy¹/excess</th>
<th>plan diets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate intake² (AI) = the recommended average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate – used when an RDA cannot be determined</td>
<td>XX</td>
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<tr>
<td>Recommended dietary allowance (RDA) = the average daily nutrient intake level sufficient to meet the nutrient requirement of nearly all (97–98%) healthy individuals in a particular life stage and gender group</td>
<td>XX</td>
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<tr>
<td>Acceptable macronutrient distribution range (AMDR) = the range of intakes for an energy yielding macronutrient associated with reduced risk of chronic disease while providing adequate intakes of essential nutrients; given as a percent of energy intake</td>
<td>XX</td>
<td></td>
</tr>
<tr>
<td>Tolerable upper intake level (UL) = the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase</td>
<td>XX</td>
<td></td>
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<tr>
<td>Estimated average requirement³ (EAR) = the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group</td>
<td>XX</td>
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<tr>
<td>Estimated energy requirement (EER) = the EER is defined as the average dietary energy intake that is predicted to maintain energy balance in a healthy adult of a defined age, gender, weight, height, and level of physical activity consistent with good health. In children and pregnant and lactating women, the EER is taken to include the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health</td>
<td>XX</td>
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**References:**

¹ Dietary Reference Intakes: 2000

² Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride

³ Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Protein, and Chloride
Table 2. (continued)

<table>
<thead>
<tr>
<th>Category of dietary reference intake (DRI)</th>
<th>Use to assess dietary plan adequacy&lt;sup&gt;1&lt;/sup&gt; excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMDR: use to estimate the proportion of the population that falls outside the range to assess adherence to recommendations and determine concern level about adverse consequences</td>
<td>XX</td>
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</table>

<sup>1</sup>Evaluating an individual’s nutritional status requires data on biochemical, clinical, and anthropometric measures.

<sup>2</sup>The AI for infants is based on the average intake of the nutrient from human milk for infants at the midpoint of the age range, and the corresponding average composition of the nutrient from analyses of human milk obtained during the same stage of lactation. It should be used as a guide for infants, but actual intake and needs may vary depending on growth rate, etc.

<sup>3</sup>Requires statistically valid approximation of distribution of usual intakes.

Source: The Institute of Medicine, Food and Nutrition Board [7, 11, 16].

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**Fig. 1.** Conceptual model of dietary reference intakes (DRIs). The DRI model relating nutrient risk of inadequacy and excess includes four DRI categories. The estimated average requirement (EAR) can be used to assess adequacy of population intakes if assumptions are met and is the basis for the recommended dietary allowance (RDA). The adequate intake (AI) lies somewhere in the area depicted in the diagram, in that it is not directly related to the EAR, but may be an observed intake that appears adequate for all in the population. Its relationship to the EAR and thus the RDA is not known as it is only provided when it is not possible to determine an EAR from the available data. The goal in setting the tolerable upper intake level (UL) is that it is as high as possible without increasing the potential for adverse effects due to excess intake. It may actually be less than indicated in the conceptual model, if a great deal of uncertainty exists in the available data used to set the UL.
at the EAR, half will not. In order to estimate a recommended intake that will provide almost all healthy individuals in the group with enough to meet their needs, the EAR is increased by two standard deviations to obtain the RDA for the nutrient (fig. 2).

**Adequate for What?**

A key question is the determination of the criterion or criteria of adequacy. Which functional outcome, surrogate marker for disease, or biochemical or

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1The definition of the EAR is that of a median, while use of the word ‘average’ indicates a mean. The decision to call this DRI ‘EAR’ was made to follow precedent set by the UK [6], and because if the distribution of requirements is symmetrical, then the mean and median are the same.

2For some nutrients whose requirements are not symmetrically distributed such as iron, other statistical methods are used to establish both an average requirement (EAR) and RDA (amount that would be adequate for 97.5% of individuals in the group).
physiological indicator best reflects adequacy for a nutrient is not a trivial matter. The DRI reports outline the possible candidates, and describe in detail choices made for establishing adequacy, explicitly recognizing that if other criteria were chosen, the average requirement and the related RDA might well be significantly different. It is at this step, choosing the indicator, that geographic and policy-based decisions may direct different choices.

When Dose-Response Data Are Not Available

For well-studied nutrients, response data from individuals fed varying levels of intake are available to develop EARs and, from that RDAs. For many nutrients, however, available human data may only be at markedly deficient levels of intake or at amounts known to be more than adequate, with no information on intermediate levels needed to construct a dose response. For this situation, or where there are conflicting data regarding the appropriate criterion, or where responses are not uniform, an additional reference value, the AI, is established as a recommended intake for individuals [8].

Determination of the Coefficient of Variation of Requirements

While the average requirement is important in order to establish the EAR and thus the RDA, so too is the variation in requirements. In order to determine a reference value that will meet the needs of almost all in the population, the distribution of requirements must be estimated. In most cases where there were adequate data points to establish an EAR, there was not enough information to estimate the standard deviation (SD\text{EAR}) of the average requirement for the group; errors in estimating the distribution of requirements were considered sizable enough to not attempt to estimate it [8]. If cases where data on the variability of requirements for a nutrient was insufficient to calculate an SD\text{EAR}, then the coefficient of variation (CV) for the EAR is assumed to be 10% [8].

The use of 10% as a default CV comes from variation in measured basal metabolism of similar individuals estimated to be 10% [9], and on the distribution of protein requirements estimated to be 12.5% [9]. Seventeen nutrients have EARs; for six of them, the CV applied differs from the default CV of 10%: 15% for copper, molybdenum, niacin, and carbohydrate [10–12], and 20% for iodine and vitamin A [12]. For iron and protein [11, 12], where non-normal distributions of requirements were identified, statistical modeling was used to establish the EAR and the RDA.

Establishing the Tolerable Upper Intake Level

With the growing availability of nutrients at high levels in the diet compared to amounts obtained from typical natural food-based sources, the need to ascertain a level of intake that would not pose an increased risk of adverse effects due to overconsumption was needed. The traditional model for risk
assessment was adapted for nutrients, giving rise to the fourth category of DRIs, the UL (table 2).

Establishing upper levels of nutrient intake that do not increase the risk of adverse effects is often hampered by the following: (1) dose-response data at high levels of nutrient intake are usually lacking, thus requiring animal data review; (2) there are few chronic human or animal studies available in the literature, as those published typically determine the toxicity of acute levels of intake; (3) few surveillance studies are available in which high intakes are estimated to establish a ‘no observed adverse effect level’ (NOAEL); (4) intakes in the few studies available usually only include supplement intake rather than total intake, thus not capturing intakes from foods, which may also be fortified, and (5) estimates of bioavailability often differ due to the nutrient source.

**Steps in Risk Assessment**

Risk is defined as the probability of an adverse effect occurring at some specified level of exposure. The risk assessment model is described in each of the DRI reports on nutrients, and is comprised of four steps, following traditional toxicological risk assessment methodology: (1) hazard identification to find adverse effects resulting from ingestion of a nutrient on a chronic basis; (2) dose-response assessment, using quantitative data relating the chosen critical adverse effect to nutrient intake to identify a NOAEL, a LOAEL (lowest observed adverse effect level), and an uncertainty factor, which varies based on the strength of the data and seriousness of the adverse effect; (3) exposure assessment, which estimates the percent of population subgroups exposed at intakes above the UL, and (4) risk characterization, which determines the proportion of each subgroup in the population who may be at risk for the critical adverse effect associated with the UL. Since the UL is established taking into account sensitive individuals in the population, it is not expected that all or even many of those whose usual or chronic intake exceeds the UL will demonstrate the adverse effect. The term ‘tolerable’, however, was chosen to point out that since no health benefits of intakes by the general population above the RDA or AI have been adequately documented, the ULs should not be considered recommended intakes or desirable levels to attain.

**Extrapolation**

Given that the data on adverse effects of overconsumption of nutrients are minimal in most cases, age and gender groups are combined in establishing ULs. Adult values based on available data are extrapolated to children, elderly, or during pregnancy and lactation, based on body size or based on differences in route of ingestion, absorption, distribution, metabolism, or excretion. For vitamin E, boron, molybdenum, nickel, and vanadium, the ULs are based on animal studies, and thus the uncertainty factor applied to each takes into account extrapolating animal data to humans [12, 13].
Application of the Model of Nutrient Risk Assessment to Macronutrients

As part of the DRI process, the risk assessment model was applied to all nutrients reviewed, including macronutrients. Much of the evidence reviewed regarding the intake of fat and carbohydrate relates to their long-term effects on chronic disease [11].

For fat and other dietary lipid components, a NOAEL could not be established as, at the lowest levels of intake, there appeared to be continued benefit in further decreasing intake to decrease the risk of cardiovascular disease. Thus, rather than provide a UL for a level at which there would be an expected and quantifiable risk, the recommendation is to decrease intake of these dietary fats as low as possible while consuming a nutritionally adequate diet [11].

In the case of added sugars which were also evaluated, no UL was established as there was ‘no clear and consistent association between increased intake of added sugars and body mass index’ [11], although there was a trend toward dietary inadequacy with higher intakes of added sugars. In place of a UL, the following statement was provided: ‘A maximal intake of 25% of energy from added sugars is suggested . . . based on ensuring sufficient intakes of essential micronutrients that are for the most part present in relatively low amounts in food and beverages that are major sources of added sugars in North American diets’ [11].

Distribution of Energy-Yielding Macronutrients

The dual roles that fat, carbohydrate, and protein play in normal growth and in metabolism are recognized in the DRI provision of both recommended intakes (either AIs or RDAs) based on their independent roles in health as well as their use as a source of energy. The acceptable macronutrient distribution range (AMDR) was created to describe this second role: as a percentage of total energy consumed to provide guidance to individuals and to assess population group intakes (table 2).

Chronic intake above the upper end of the range can be viewed as potentially putting an individual at risk of overconsumption, in part because it could result in under-consumption of another macronutrient resulting in an increased risk of it being inadequate for its specific role in metabolism. The lower level of the range can be considered as the minimum amount required. The lower level of the protein range approximates the RDA; intake beyond the upper end of the range may result in under-consumption of fat or carbohydrate [11].

Approaches to Recommended Intakes for Infants

The AI was initially created for infants, where it would be unethical to intentionally feed infants varying levels of intake known to be deficient and evaluate
changes in body weight, growth, or other nutritional status indicators over time. Also of concern was the tendency seen with past reference standards for inaccurate comparisons to be made between recommended intakes and human milk composition. Human milk was frequently cited as inadequate for a number of nutrients. To eliminate this misinterpretation, AIs based on the nutrient content of human milk are provided for infants for nutrients for which there is no evidence indicating that breast-fed infants should have supplementary amounts above that provided in human milk [8].

The AIs for infants are calculated by estimating an average volume of intake by healthy, full-term, exclusively breast-fed infants midway through the first 6 months or the second 6 months of life. The amount of a nutrient in that volume is estimated from analysis of human milk samples taken during the same time period of infant feeding (2–6 or 7–12 months of lactation). During the second 6 months of life, the estimated contribution of complementary foods is added to the average amount of the nutrient provided by human milk. The values should be used in context; the DRI reports point out that there will be variation in both the amount consumed and its composition during normal infancy, and thus the computed values represent average values, noting that it is expected that infants will consume increased volumes of human milk as they grow.

While separate recommendations for infants fed formula are not made, if specific issues relative to bioavailability or the source of a nutrient are relevant to developing an optimal formula, the issue is discussed and data provided for modifying the recommended intake. Because of the reliance on human milk composition, the AI is less than previous recommended intakes for infants in the US [3] or Canada [14].

Of the nutrients reviewed as part of the DRI process, two nutrients were considered inadequate in the diets of infants beyond their 6th month of life when fed exclusively human milk: iron and zinc [12]. Using a factorial method to estimate average requirements that includes amounts for growth, EARs were developed for these two nutrients for infants 7–12 months of age, resulting in the only RDAs provided for this age group.

Because of organ immaturity, no ULs were established for infants, with the statement that infants should obtain nutrients from food (including human milk) or formula only.

**Approaches to Values for Children**

**Age Groups**

Since the age groups used in recent US RDAs [3] differed from those used in the Canadian Recommended Nutrient Intakes [14], a number of experts were initially queried on appropriate age cutoffs. New data on the onset of menarche indicated a need to revise female grouping. The new age categories now take into account the age at which young children enter institutional
feeding settings (pre-kindergarten) in Canada and the United States, potentially affecting energy requirements, as well as the change in onset of adolescent growth spurts [8].

Extrapolations due to Data Gaps

In spite of the significant progress in research related to human nutritional needs, data were not usually available with multiple levels of nutrient intake to directly determine nutrient requirements for each gender and life-stage group, including children. Thus available data from other subgroups were extrapolated to develop EARs, AIs, and ULs for each subgroup (each DRI report discusses extrapolation methodologies employed for nutrients included in the report). Nutrients involved in energy metabolism were extrapolated on the basis of metabolic body weight (B.Wt.3/4). Extrapolation based directly on body weight was used for nutrients involved in bone maintenance and growth. The size of compartment or tissue weight was used as the basis for extrapolation for nutrients primarily distributed in the water space or other specific tissues.

Energy and Physical Activity

The DRIs include estimated energy expenditure at four levels of physical activity. Previous energy allowances were based on estimated time spent in various activities in addition to measured or predicted basal metabolic rates [3]. Rather than provide an RDA (a level of energy intake that would be adequate for almost all the population), an estimated energy requirement (EER) is predicted from regression equations derived from doubly labeled water data based on gender, age, weight, height, and four levels of physical activity (sedentary, low active, active, very active) [11].

The DRI process also recommended levels of activity to both decrease the risk of chronic disease and maintain body weight below a body mass index of 25 [11]. The level of total activity recommended is >1.6 physical activity level (PAL, the ratio of total energy expenditure to basal energy expenditure), and is the equivalent of 60 min of moderate intensity activity on a daily basis above sedentary levels (moderate activity equivalent to walking at 4.8–6.4 km/h).

Conclusions

While an important part of the DRI process and conceptual framework is to incorporate the growing body of evidence on the role of nutrients and food components in decreasing the risk of chronic as well as deficiency diseases in order to maintain and enhance the quality of life through diet-related
benefits, there has been less evidence available to associate intakes of nutrients in childhood or infancy with long-term outcomes [15]. Future efforts to incorporate concepts of risk factor reduction in quantifying nutrient requirements and recommendations will continue to increase, focusing on nutrient intake during early life and its impact on future health.

Acknowledgements

To date, the DRI process has involved over 200 scientists in Canada and the United States over the last decade or more, funded by US and Canadian federal agencies, non-profit foundations, and corporate sponsors. The Institute of Medicine and the chairs, members, consultants, and staff of the Food and Nutrition Board, all of whom worked on aspects of this continuing project over the last decade, have been essential to its development. In particular, the contributions of the late Vernon R. Young, first Chair of the DRI Committee, who, through the grace of his wit and intellect, gave his full measure to the activity as he strove to imbed scientific validity in the process, must not be forgotten.

References

Discussion

Dr. Butte: I have been involved in evaluating the diets of toddlers from the second year of life. I was personally surprised that some of the nutrient intakes, when we compared them against the recommended daily allowances (RDAs) and the upper limits, were approaching the upper limits, specifically zinc, niacin and vitamin A. So when the upper limit committee was meeting, was one of their criteria to look at where they set the upper limit and then examine dietary intake from various age groups? We all acknowledge that it is not ideal to extrapolate from adults to toddlers, but that is all we have. I was just wondering if those committees did check to see if these were consistent with what observed intakes are?

Dr. Yates: Yes and no. They did do a check to see where the nutrient was coming from, and if they found it was coming from a heavily fortified food source then it made them less comfortable; although in fact it was acceptable, recognizing that what they were establishing was a no observed effect level (NOAEL). In the case of zinc the adverse effect was determined to be a decrease in copper absorption. The issue was are these individuals who are getting higher levels of zinc, primarily from breakfast cereal, also getting a lot of copper because it was being added to the breakfast cereals, and this is not the case. As there was documented copper deficiency resulting from the overconsumption of zinc (I believe it was in infants) their feeling was that by setting the upper limit as they did for the 1- to 3-year-old group, that was where the problem lay. In the US companies were fortifying their cereal products with the adult RDA which was probably an inappropriate level. Now the upper level is not the same as an average requirement. The agencies involved in regulating how much can be added to various food products asked for a safe level, but we didn’t want to use the term ‘safe’. So in a way it is a level at which one feels comfortable, that even going over it for a while is no problem. So it is much more of an average intake but it is on the other side of the slope of the curve. If you look at the data, the issue about where zinc is coming from, whether people have been using it over the last 5 or 10 years or companies have been putting it in a product, is a little different than if it has been part of the natural diet over the last 50 years and there is no apparent adverse effect. So I think part of it is derivation. But I think it is getting at “where are those nutrients coming from?” and it could be the extrapolation method.

Dr. Cong Khanh Nguyen: I would like to ask two questions. Regarding the dietary reference intakes, should they be based on the local bioavailability of food? The problem of food bioavailability is quite considerable in a critical period like pregnancy and lactation. In Viet Nam we did some studies on food contamination, particularly in fish because in some areas fish is contaminated with heavy metal. What is the upper limit for fish consumption in children? When we look at the level recommended by the Ministry of Public of Health the total intake is still lower than what is recommended as a toxicology issue. Do you think that we can recommend that reference intake from a food safety aspect?

Dr. Yates: The first question was about pregnancy and lactation with regard to bioavailability. The assumption is that you could determine requirements, and there
probably is very little difference (in requirements) depending on what geographic area
you are in or what your food supply is. When you want to set the recommended
allowance you are going to have to take into account bioavailability and, taking iron as
an example and depending on the iron source, there is a different average requirement
if the primary iron source is animal or vegetable. So yes, certainly you have to take
bioavailability into account for the average requirement. That is why we say these RDAs
are really for Canada and the US, given our food supply. How well they would apply to
other areas, I don’t know. I assume that other countries are doing their own RDAs based
on their food supply and the typical bioavailability of nutrients that they are interested
in. Your other question was how do to deal with food such as fish which may have a lot
of mercury contamination; the big question here is ‘are you below what you think is the
allowable exposure to something like mercury, which is really a concern over time?’ You
have to decide if fish is a really important staple for maintaining an individual in a state
of health, and if there is no alternative to providing fish, then you will likely cause more
problems than the potential mercury contamination. Actually there is a report from the
National Academy of Sciences about 2 years ago looking at dioxin in the food supply and
what should be the public health message. Because of it being in fat and certainly fish,
what should they tell pregnant women? They essentially said if you follow our typical
dietary guidelines which are low fat diets you will be decreasing your exposure signifi-
cantly, and that is probably the best public health message. But it is a problem, certainly
in the US, where people are really interested in n-3 fatty acid intake and increasing it by
fish consumption, but at the same time they try to avoid types of fish that have heavy
metal contamination. It is a public health problem that nobody has solved yet.

Dr. Koletzko: I would like to come back to the question from Dr. Butte as to how
do you extrapolate values for children, particularly for young children. I think it is
quite important which method to use because the younger the child, the more differ-
ent the results are. In 2003 the Scientific Committee on Food of the European
Commission critically looked back at what it has been doing and pointed out that the
approach it used for extrapolating upper levels or safe levels has really severe limita-
tions. They pointed out that if you extrapolate the upper level values for children from
adult values on body weight or body surface basis, in a number of cases you come up
with upper levels that are lower than the known nutrient requirements. So clearly
there are some severe limitations. If one looks around the world at reference nutrient
intake values it is quite remarkable how big the differences in values are for the same
nutrients for the children observed. I think that this can partly be explained by the
lack of scientific knowledge and data, but also I think it has to do with the very differ-
ent concepts, approaches and definitions that different people use. In that regard I
was wondering why the Dietary Reference Intake Committee chose as a default value
a metabolic body mass with the exponent of 0.75? Looking at the recent literature
there is still a hot controversy regarding the right exponent, and some people are
favouring the exponent of 0.66. As you know the younger the child, the bigger the dif-
ference. If I compare extrapolations based on body surface area and body weight area
then at 10 years it is only a difference of 25%, and in 1 year it is a difference of 60%; in
the infant between newborn age and half a year there is a difference of 100%. So this
is really an important question. The second question I have is my interpretation is that
the US DRI recommendations for upper levels in children were based on body weight,
except for sodium.

Dr. Yates: I am sorry, I didn’t differentiate that. But you are right, the upper levels
except for the B vitamins.

Dr. Koletzko: And sodium, based on body weight and not on metabolic body
weight. So the reference nutrient intake and upper levels for the same nutrient were
calculated on a different basis. I am wondering why this choice was made, because
again for young children this would lead to a proportionally much lower upper level.

Dr. Yates: This is a 10-year process, and what you start out with changes as you go
along; certainly there is new science and there are new people and approaches. There
were quite difficult scientific discussions to get toxicologists away from uncertainty fac-
tors of 10 and 100, depending on whether there were animal data, species extrapola-
tion, and so on. Thinking in uncertainty factors of less than 5 was a major accomplish-
ment. The big reason that the Food and Nutrition Board wanted to look at the upper level
model and try to use risk assessment was that in 1992 the Environmental Protection
Agency in the United States came out with a report saying that the reference dose for
zinc for children was 5 mg, I think, and at the time the RDA from 1989 for zinc for chil-
dren was 7 or 8 mg. But again the Environmental Protection Agency used the traditional
toxicity model. So when we started we were fairly careful to try to wrench away
uncertainty factors to find something that seemed reasonable. But I guess one of the
major issues is how do you extrapolate for children. I don't think that has been solved,
and I think it does make a difference whether you are looking at adequacy or upper lev-
els. As you probably know the upper levels are not nearly as specific in terms of group-
ings. So there is an adult upper level and then there is a child upper level and then
potentially there is pregnancy and lactation, but they are not broken up by age. They are
just very general numbers at which there is assumed to be no risk of consuming that
level. Beyond that there is a potential for risk but there is not a definable risk. So it is not
a well-cut criterion on and I think it is because it is probably 20 years behind where we are
with recommended reference intakes, and we just have to get the science to catch up.

Dr. Cong Khanh Nguyen: In Viet Nam we have a program for iron fortification in
food. We did efficacy studies and published 2 studies; one in the American Journal of
Clinical Nutrition [1] and the other in the Journal of Nutrition [2]. However, in imple-
menting the program we used upper limits because excess iron is quite dangerous.
But it is not easy as in the same family the women and men share the same food. So
upper limit here means for men or for women. Is it better for men or for women?

Dr. Yates: The data were so limited; trying to come up with the NOAEL or the low-
est observed adverse effect level (LOAEL), there might be a database of 30 subjects or
cases, often mixed with both men and women. So the data are too sparse to say that
for women it is 1,000 and for men it is 1,200 for iodine. This is one of the reasons that
the DRI reports are so large because they list all the studies that are available, and why
there are so many studies to use. So you look at all the data and for the situation estab-
lish a NOAEL or LOAEL, and that would be one way of establishing whether you are
giving too much fortification.

Dr. Rigo: When we look at your conceptual model there is a relatively large gap
between adequate intake and the upper level. How do you interpret this difference?

Dr. Yates: The adequate intake is an intake that is a recommended intake to con-
sume, and in most cases it is based on the average intake of a population that does not
appear to be inadequate for that nutrient. So it is definitely going to be more than most
people need. Now your question is why is the adequate level so far from the upper level?

Dr. Rigo: No, it is not why it is so far because it is calculated as such in the model.
But I think that when we look at the upper level and the intake in the population, we
don't know exactly if a large part of the population receives more than the adequate
intake, and it is difficult to study the consequences of this relatively high level.

Dr. Yates: The only way you are going to be able to study the consequence of a
high level of intake is obviously to have some examples or studies of specifically how
much is too much.

Dr. Rigo: Take protein intake during infancy as an example. The upper level is dif-
ficult to define and we have the adequate intake level; so what is the difference in the
long-term effect if we look at the higher level?
Dr. Yates: With proteins we didn’t establish upper levels because we could not come up with any real adverse effects. We have this range of caloric intake, and 30 or 35% is pretty high, but it is not set on the same basis. We don’t have an upper level for arsenic even though we know that arsenic is deadly; but there is no study of long exposure to chronic doses and then evaluation of adverse effects, and that is really what you have to have in order to establish an upper level.

Dr. Giovannini: When you spoke about carbohydrate, why didn’t you speak about the low or high glycemic index or about rapid or slow absorption? With the intake of carbohydrate it is very important to consider the glycemic index. It depends not only of the quality but also on the way something is cooked. I think a very important problem in nutrition is quality control. In every country it is different, but quality control is of central importance for nutrition.

Dr. Yates: David Jenkins was a member of the committee and he is certainly interested in the glycemic index. There is a carbohydrate recommendation related to total carbohydrate. The consensus of the committee was that the glycemic index was potentially very useful for diabetic individuals or people with pre-diabetes, but in terms of the normal healthy population there wasn’t enough information with a strong scientific basis to indicate that on a long-term basis glycemic index would maintain health. The other thing is this came out in 2002, but was finally printed in 2005. So we had the information available in 2002, but there are new data since then so that must be put into context too. Things have changed, so what is available now may well show that there is a need to look more closely at glycemic index and its role in health.

Dr. Giovannini: It may be useful to know the glycemic index because the most popular cereals sold in the world have the highest glycemic index, and every morning children receive milk and cereals. What Jenkins published is much higher in sucrose. For this reason it is very important to have nutritional education. In every part of the world it is important to know what kind of carbohydrate is being consumed because people think about eating fibers and do not realize that they are eating food with a high glycemic index.

Dr. Yates: Another interesting thing here is that at the request of the Food and Drug Administration in the US we came up with a definition of dietary fiber. Essentially fiber is endogenous in food. If it is an isolated fiber in terms of a chemical modification, then it has to have a demonstrated role in health to try and point people to the fact that it is the fiber in food and probably other things that are going to be of health benefit, rather than what one might put into a food from an external source.

References