Setting Dietary Reference Intakes for Micronutrients for Healthy North American Infants: A Process of Trials and Errors

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Introduction

From a purely biochemical and mechanistic viewpoint, normal growth and development of the infant depends upon a program that is orchestrated by the genome and initiated through transduction mechanisms by signals originating outside the cell. This response depends upon a sufficient level and appropriate balance of substrate and effector molecules, the primary sources of which are the nutrients provided via the diet. For this reason alone, it is critical to know the quantitative nutrient needs of infants during the early months of life, as well as at other stages in the life cycle and for different physiological states.

In December 1995, the US Food and Nutrition Board (FNB)/Institute of Medicine (IOM) established a Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI Committee) to develop a set of nutrient-based reference values (DRIs) for the North American population. These were intended to replace and expand upon the US 1989 Recommended Dietary Allowances (RDAs) [1] and the 1990 Canadian Recommended Nutrient Intakes (RNIs) [2]. The DRI committee was also charged with developing guidelines for the appropriate uses and applications of the DRIs. To date, six reports have been published, covering minerals, vitamins and trace elements [2–6], a model to establish upper levels for nutrients [7] and applications of DRIs in dietary assessment [8]. There is also available at the time of writing this chapter a prepublication report on recommendations for
Background, Purpose and Framework

As described in more detail elsewhere [3, appendix A], the Food and Nutrition Board/Institute of Medicine in 1995 appointed a Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI Committee) to oversee and conduct a review of the knowledge about quantitative needs for nutrients in human nutrition, to propose appropriate DRI values and to provide guidance as to their applications and uses. The DRI Committee has been intellectually supported, since that time, through the work of five expert, nutrient-related, group panels and two overarching subcommittees (Subcommittee on Upper Reference Levels of Nutrients; Subcommittee on Interpretation and Uses of Dietary Reference Intakes). In addition to this author, four other participants (L. Allen, J. Beard, K. West, S. Zlotkin) in this 52nd Nestlé Nutrition Workshop played significant roles as experts in the development of the new DRIs.

There are four primary uses of the DRIs, namely, for assessing nutrient intakes of an individual or a population group and, similarly, for the planning of intakes for an individual or a population group [8]. In the present case the individuals or population groups of major concern are those in the early months of life. First, however, it is useful to outline the general framework that has been used for setting the DRIs, before focusing more specific attention on the younger infant.
Thus, the nutrient specific expert panels received charges that included:
(a) a critical review of the scientific literature related to current knowledge of the relevant nutrient requirements for each stage of the life span, and
(b) development of DRIs for the nutrients for each stage of the life span, including people older than 50 years. The panels were asked to give particular attention to the criterion of nutritional adequacy that might be used in estimating the quantitative requirement. Hence, for each nutrient, various possible criteria were considered and a rationale given in each report for the choice made in finally setting the requirement estimates. Obviously, different criteria might give rise to different requirement estimates for a nutrient. Thus, as shown in figure 1 using iron as an example, the criterion would not only affect the requirement value but it would also influence the interpretation of the adequacy of a given intake of the nutrient. There are potential advantages to be gained in setting multiple requirement levels; by using different criteria, this would provide the user with the opportunity to plan for a particular or desired level of nutritional status – in the case of iron this might be the amount of dietary iron required to prevent anemia or that higher amount needed to sustain a give size of body iron store. On the other hand, the disadvantage of proposing a multiple requirement DRI for a given nutrient is that it might introduce confusion and certainly it would require a more careful consideration of the requirement value by the user, who would have to give thought about specific nutritional goals. In the final analysis, a single requirement estimate for each nutrient was presented, giving attention to the criterion on which the specific requirement value was based.

Fig. 1. An illustration of the effect of a different criterion of iron adequacy on the probability that a specified intake would be inadequate in a population of menstruating women. Kindly provided by G. Beaton, University of Toronto, Canada.
In addition to the issue of the criterion of nutritional adequacy, where the data were sufficient the panels were asked to establish (a) an estimate of the mean requirement value for a population group, and (b) the variance around this value. They were also asked to consider the issue of nutrient bioavailability and, where appropriate, develop a paradigm to arrive at a suitable ‘correction’ for transforming the physiological requirement value to a dietary intake level. This latter factor is of particular importance, while introducing complexity, in the present context when it is necessary to extrapolate requirement values from one age group (i.e. adults) to another (i.e. infants), especially because of the general lack of sufficient ‘bioavailability’ data for different age groups. Finally, panels were asked to consider the intakes of the nutrient in the US and Canadian populations and also to develop and apply a model to establish, wherever possible, the maximum level of a nutrient that would pose a low risk of adverse effects. This latter charge represented a new and important addition to that given by earlier committees whose purpose was to update DRI, that focused essentially on the RDAs which were aimed at preventing nutrient deficiencies rather than protecting against possible excesses.

Before final publication, the preliminary reports generated by each expert panel or subcommittee received extensive review, both internally within the FNB and externally following established National Research Council procedures. I will present, later in this chapter, some of the recommendations to illustrate their basis and also their limitations.

**Definition of the DRIs**

A DRI is used as a collective term to accommodate various nutrient-based reference intake values, including the more familiar RDAs. These will be defined and described in this section but it is worth first defining what is meant by ‘the requirement’ as follows:

The requirement of a nutrient is the smallest amount of that nutrient that must be absorbed (or ingested if intended to be a ‘dietary requirement’) on a continuing basis (average of daily absorption or intake over a period of weeks or months) that is adequate to maintain a defined state of nutriture in a particular individual. There is a distribution of requirements among seemingly similar individuals.

It might be useful to note that (a) a requirement refers to an individual; (b) it incorporates the notion of time in that it refers to a continuing intake or absorption; (c) there is a distribution of requirements among apparently similar individuals, thus it is possible to identify the median or average requirement or any particular point in the distribution of requirements; (d) as defined, it is possible to estimate and described multiple levels of requirement, and (e) the definition takes into account other factors affecting requirement (e.g. ‘bioavailability’, level of physical activity, levels of ingestion of other nutrients).
The question might also be raised as to what is meant by a ‘nutrient’, but this was not formally defined in any of the IOM reports. Nevertheless, based on the increased understanding of the function and roles of dietary constituents in human nutrition and health, a definition of a nutrient might be offered, as I earlier proposed [10], as follows: a ‘nutrient’ is a chemically and fully characterized constituent of a diet, natural or designed, that serves either as (a) a significant energy yielding substrate, (b) a precursor for the synthesis of macromolecules and/or compounds needed for normal cell differentiation, growth, renewal, repair, defense and/or maintenance, (c) a required signaling molecule, co-factor and/or determinant of normal molecular structure/function, and/or (d) a promoter of cell and organ integrity.

In the six published reports four different DRIs are presented, as follows.

(a) The EAR: this is a derived estimate of the average (more correctly, median) of the distribution of requirements of individuals belonging to the specified life-stage and gender group. If the median requirement has been estimated then it would be expected that half the individuals have true requirements less than the median and half would have true requirements greater than the median. The same would hold for an average requirement if the distribution of the requirements were symmetrical about the mean. This DRI is the most useful for the planning and assessment of diet adequacy [8].

(b) The RDA: this is an intake sufficient to meet the daily needs of most individuals of a specific life-stage and gender group. It is set at a level that is at the top 2–3% of the requirement distribution. The RDA is intended to serve as a goal for daily intake by individuals.

The RDA is derived from the EAR by adding an allowance for the variation in requirements around the EAR. This variation is usually taken to be the equivalent of 2 standard deviations of the mean. Because of the lack of good information about the variance in requirements for most nutrients an assumed coefficient of variation of 10 or 15% of the average has been used in setting the new RDAs for specific nutrients.

(c) The AI: this is an observed or experimentally derived mean intake by a group of individuals that, in the opinion of the DRI committee, would meet or exceed the needs to maintain a defined nutritional state in essentially all members of the specific, healthy population. The AI is set when data are considered to be insufficient or inadequate to establish an EAR on which to base a RDA. The AI represents a value that has similar application purposes as the RDA, but its derivation is different from an RDA and it acts as a surrogate RDA but with greater uncertainty. An AI (other than in breast-fed infants) is likely to be higher than an RDA equivalent but because of its derivation much care must be taken in its use. Thus, it serves as one, but limited, basis for planning and assessment of diets for populations.

(d) The UL: this is defined as the maximum level of continuing intake, expressed as a daily rate of intake that is unlikely to pose a risk of adverse health effects to the randomly selected individual in the specified life-stage
gender group. The UL refers to an explicitly defined marker of health risk and to an implicit distribution of susceptibilities among individuals, although the nature and extent of this distribution is usually not known. As such the UL represents the lower tail of the putative distribution of susceptibility. The ULs were set using a risk assessment model which has been described in detail separately [7], as well as in each of the nutrient group DRI reports [3–6].

In addition to these four DRIs, the recent prepublication (uncorrected proof) version of the macronutrient report [9] introduced two further DRIs, namely the estimated energy requirement and an acceptable macronutrient distribution range, which is the range of intakes of a particular energy source for an individual that is thought to be associated with the reduced risk of chronic disease while providing adequate intakes of essential nutrients. These additional DRIs will not be discussed further here since they apply to the energy yielding macronutrients.

In summary, the DRIs may be seen as identifying nutrient intakes that encompass a safe or adequate intake range (fig. 2) with the risk of inadequacy or excess increasing as intakes fall below and above these DRIs, respectively.

**Approaches Taken to Estimate Requirements, Especially in Infants**

In the DRI reports data from human studies were used to arrive at the DRIs, especially the EAR and UL. In the case of the EAR, metabolic balance experiments, biochemical indices of adequacy from analyses of blood and urine, growth and body composition studies and kinetic aspects of nutrient utilization and metabolism formed either singly or sometimes jointly the basis...
for deriving the requirement value. For the micronutrients, dietary intake data from population surveys either provided support for the derived EAR or were used to arrive at an AI where data on direct estimates of requirements for that nutrient were insufficient to establish an EAR. This latter approach is particularly necessary for arriving at a DRI for infants during the early months of life, because of the lack of direct experimental data on the actual physiological needs for micronutrients in this age group.

For this reason, the DRI for infants aged 0–6 months was the AI. This was derived from an estimate of the mean intake of human milk for healthy, exclusively breast-fed infants, taken to be 0.78 liters/day, and from the best estimates of the mean concentration of the specific nutrient in mature milk. Thus, 0.78 liters/day × the mean concentration of the nutrient = AI for 0–6-month-old infants. This AI is higher than the requirements for this age group, a reasoning for which, at least in reference to protein but in principle for the micronutrients, has been presented by Beaton and Chery [11].

In setting the DRI (AI or EAR) for infants 7–12 months of age four possible methods were considered: (a) extrapolation up from the AI for younger infants; (b) extrapolation down from the AI for adults (manganese, niacin, vitamin B₆); (c) mean intake by older breast-fed infants plus mean intake of nutrient from other foods (AI, e.g. for chromium, copper, vitamin C, selenium), and (d) by factorial estimation of an EAR (e.g. Fe, Zn). For some nutrients, such as for B₆ and riboflavin, for example, two types of extrapolation were used and the results combined.

The extrapolation from young infants involved the following calculation:

\[
\text{AI for 7–12-month-old infant} = \text{AI for 0–6-month-old infant} \times F,
\]

where, \( F = (\text{weight}_{7–12 \text{ months}}/\text{weight}_{0–6 \text{ months}})^{0.75} \).

For the extrapolation from adults, down to infants 7–12 months of age, the procedure was follows:

If maintenance needs expressed in relation to metabolic body weight (Wt⁰.⁷⁵, in kg) were thought to be the same in adults and children, then the extrapolation was based on Wt⁰.⁷⁵, according to the equation:

\[
\text{EAR}_{\text{child}} = \text{EAR}_{\text{adult}} \times F,
\]

where \( F = (\text{weight}_{\text{child}}/\text{weight}_{\text{adult}})^{0.75} \times (1 + \text{growth factor}) \).

If there was a lack of correlation between requirement (effectively, utilization of the nutrient) and metabolic rate, then the extrapolation was made in direct proportion to total body weight.

The growth factor was taken to be proportional to the increase in the protein requirement for growth, as summarized in table 1, based on values given by FAO/WHO/UNU [12].

Scaling micronutrient intakes based on different functions of body weight, such as absolute mass or body mass to the 3/4 power, is clearly an arbitrary and highly approximate procedure, especially given the fact that micronutrients
participate in many different processes, with multi-site controls. This point has been discussed with reference to the allometric behavior of energy turnover and the fact that there is no single power-law relation between metabolic rate and body size [13–15]. The need to make crude body weight-related extrapolations from one age group to another is dictated by the absence of data and this is an unsatisfactory situation. Nevertheless, in most cases the extrapolated values appear to have provided intake values that were not obviously inconsistent when more than one method of extrapolation was used and the intakes compared.

Finally the UL for infants was either based on case studies in this age group or it was derived via a downward extrapolation of the UL for adults, using the reference body weights given in the reports.

In essence, therefore, the micronutrient DRIs for young infants during the early months of life are, in large part, estimates of population group mean intakes that are consistent with the maintenance of a healthy population. They are not physiological requirements, that would be expected to be lower, unless there was a high correlation between intake and requirement, which presumably is the case for energy and perhaps also, but maybe to a lesser extent, for protein. For iron, perhaps the AI (see below) would not be adequate to meet the needs of almost all individual infants and so the DRI should be used ‘with extreme care’ [6, p 317].

Some Examples of DRIs for Infants

The DRIs of the specific micronutrients for infants during the first year of life are set out in detail in the various IOM/FNB reports [4–6]. Therefore, a selection is made here of three micronutrients to illustrate, in somewhat greater detail, the scientific basis and the ‘thinking’ behind some of the specific DRIs. I have chosen vitamin A, iron and zinc for this purpose, in view of their public health significance, especially in developing regions and as underscored elsewhere in this volume.

### DRIs for Infants

<table>
<thead>
<tr>
<th>Age group</th>
<th>Factor¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 months to 3 years</td>
<td>0.3</td>
</tr>
<tr>
<td>4–8 years</td>
<td>0.15</td>
</tr>
<tr>
<td>9–13 years</td>
<td>0.15</td>
</tr>
<tr>
<td>14–18 years</td>
<td>0.15</td>
</tr>
<tr>
<td>Males</td>
<td>0.15</td>
</tr>
<tr>
<td>Females</td>
<td>0</td>
</tr>
</tbody>
</table>

¹ Based on proportional increase in protein requirement for growth [12].

Table 1. The factor used for growth in extrapolation of an adult estimated average requirement (EAR) down to infants, 7–12 months of age
Vitamin A

For infants 0–6 months of age, an AI was derived from the average volume of milk intake (0.78 liters/day) and the average concentration of vitamin A in human milk, taken to be 1.70 μmol/l (485 μg/l) during the first 6 months of lactation. Hence, the AI was set at 400 μg retinol activity equivalents (RAE)/day. The contribution of carotenoids in milk was not considered since the bioconversion of milk carotenoids in infants is not known.

In the IOM/FNB [6] report, the RAE ratios for the various provitamin A carotenoids differed substantially from those in the 1989 report [1]. The new ratios are summarized in figure 3. These equivalency factors are important in the considerations of RAE intakes in children 1 year old and above where an EAR was derived as a downward extrapolation EAR value.

The AI for vitamin A for 7- to 12-month-old infants was based (a) on the extrapolation of the AI from young infants, based on a metabolic body size adjustment, giving an AI of 483 μg RAE/day, and (b) on the intake provided by human milk for this age group (0.6 liters/day) together with that from complimentary foods, estimated to be 244 μg/day from dietary survey data. Thus, in this case the total vitamin A intake was estimated to be 535 μg RAE/day (244 + 291 μg from milk). The rounded average of these two estimates gave an AI for 7- to 12-month-old infants of 500 μg RAE/day. Again, it is worth emphasizing that these AIs exceed requirements for all healthy infants during the first year of life.

For young children an EAR for vitamin A was established via extrapolation from adults using a metabolic body weight (kg0.75) adjustment, as described above. The adult EAR was determined from the amount of dietary vitamin A

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### Fig. 3.
The absorption and bioconversion of ingested provitamin A carotenoids to retinol based on the new retinol activity equivalent ratios proposed by IOM/FNB [6].

### Vitamin A

<table>
<thead>
<tr>
<th>Consumed</th>
<th>Absorbed</th>
<th>Bioconverted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary or supplemental vitamin A (1 μg)</td>
<td>Retinol</td>
<td>Retinol (1 μg)</td>
</tr>
<tr>
<td>Supplemental β-carotene (2 μg)</td>
<td>β-Carotene</td>
<td>Retinol (1 μg)</td>
</tr>
<tr>
<td>Dietary β-carotene (12 μg)</td>
<td>β-Carotene</td>
<td>Retinol (1 μg)</td>
</tr>
<tr>
<td>Dietary α-carotene or β-cryptoxanthin (24 μg)</td>
<td>α-Carotene or β-cryptoxanthin</td>
<td>Retinol (1 μg)</td>
</tr>
</tbody>
</table>

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[DRIs for Infants]

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required to maintain a minimal acceptable liver reserve of 20 µg/g and from the efficiency of storage of ingested vitamin A. For adult men and women the EAR was 625 and 500 µg RAE/day, respectively. Hence, if the average weight of 1- to 3-year-old children is taken to be 13 kg and that of adult men taken to be 76 kg, the EAR, based on a metabolic body size extrapolation, for this younger age group would be 210 µg RAE/day. The RDA would be 300 µg RAE/day, taking a coefficient of variation of 20%, based on the calculated half-life values for liver vitamin A. Hence, the AI of 500 µg RAE/day for 7- to 12-month-old infants, as stated above, is consistent with the EAR in young children, as derived via extrapolation from the adult EAR.

With respect to a UL for preformed vitamin A, four case reports of hyper-vitaminosis A in infants were used to identify a lowest observed adverse effect level (LOAEL) of 6,000 µg/day (rounded value). An uncertainty factor of 10 was selected to account for the uncertainty of extrapolating a LOAEL to a no observed adverse effect level (NOAEL), for the nonsevere and reversible adverse effect of a bulging fontanel. Thus, a UL of 600 µg of preformed vitamin A was set for infants, aged 0–12 months. This value was also accepted for 1- to 3-year-old children, based on a simple body weight extrapolation down from an adult UL of 3,000 µg preformed vitamin A. In the case of the adult, the UL was determined on the basis of hepatotoxicity as the adverse criterion.

Iron

For infants 0–6 months old an AI was set, as described earlier for this age group, at 0.27 mg iron/day. For older infants an EAR was determined using a factorial model in which the following major components of iron need are: (a) obligatory fecal, urinary and dermal losses (basal losses); (b) increase in hemoglobin mass (increase in blood volume and increase in hemoglobin concentration); (c) increase in tissue (nonstorage) iron, and (d) increase in storage iron.

The magnitude of these various components, respectively, was estimated to be (a) 0.26 ± 0.03 (SD), (b) 0.37, (c) 0.009, and (d) 0.51 mg/day. Hence, the median iron deposition for infants 7–12 months of age is estimated to be 0.43 mg/day (0.37 + 0.009 + 0.051) and, with a basal loss of 0.26 ± 0.03 mg/day, the median total requirement of absorbed iron is 0.69 ± 0.145 mg/day.

Thus, a moderate bioavailability of 10% was used to set an EAR of 6.9 mg/day for 7- to 12-month-old infants. The RDA was similarly set by modeling the components of iron requirements, estimating the requirement of absorbed iron at the 95 percentile, with use of an upper limit of 10% iron absorption and rounding, giving an RDA of 11 mg/day iron.

The iron UL for infants was derived from several studies in infants and young children which, in the aggregate, suggested a NOAEL by 40 mg/day of supplemental non-heme iron, based on the absence of adverse gastrointestinal effects at this intake. An uncertainty factor of 1 was specified, giving a UL of 40 mg iron/day.
Zinc

The AI for 0- to 6-month-old infants was set at 2 mg zinc/day, derived as described above. For 7- to 12-month-old infants a factorial method was used to estimate an EAR. This approach was based on (a) an estimate of endogenous zinc losses (intestinal, urinary, integumental) by extrapolation from measured values in either adults or young infants, (b) estimates of tissue zinc accretion, and (c) corrections for the fractional absorption of dietary zinc, taken to be 0.5 for human milk [16] and 0.3 for complimentary foods [17, 18]. Thus, an EAR of 2.6 mg/day for older infants would be obtained from a downward extrapolation of the adult male EAR value, based on metabolic body size.

The zinc UL for infants was derived from a NOAEL of 5.8 mg zinc/l or 4.5 mg/day for 0- to 6-month-old infants. With an uncertainty factor of 1 the UL for 0–6 months was set at 4 (after rounding down) and 5 mg/day for 7- to 12-month-old infants.

These UL values for young and older infants have been questioned, particularly with respect to their being too low [19]. A Life Sciences Research Office report [20] advises a maximum zinc content of 1 mg/100 kcal in infant formulas. Thus, if the mean intake of infants 6–12 month old approximates 600 kcal/day or more this would result in zinc intakes above the ULs proposed by IOM/FNB, as stated above. Hence, it would be desirable to revisit the question of a zinc UL for infants.

The Other Micronutrients

It is not possible, within the space available, nor is it necessary, to provide a detailed account of the derivation of DRI values for the other micronutrients. In table 2 a summary of the DRIs for selected micronutrients is given, indicating the criterion used and the values derived.

Relatively little detailed consideration was given by the expert panels as to how these DRIs compared with the composition of infant formulas that serve as the sole source of nutrition for term infants throughout the first year of life. A summary statement is given in table 3 to illustrate the general tone of the comments made in this context for many of the micronutrients.

General Applicability of the North American DRIs to Other Settings

Although the DRIs have been generated for application in healthy North American infants, as well as other age groups, it is to be recognized that they are widely consulted and used by various user groups throughout the world, either directly or with some modification. It is legitimate, therefore, to ask whether these DRIs are useful in consideration of meeting the macronutrient needs of infants during the early months of life in less well-developed regions of the world and in underprivileged, resource poor, populations.
DRIs for Infants

Table 2. Summary of DRIs for some micronutrients for the early months of life

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Age months</th>
<th>Criterion</th>
<th>AI per day</th>
<th>EAR per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>0–6</td>
<td>Intake from human milk</td>
<td>400 µg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–12</td>
<td>Extrapolation from 0–6 months (E0–6)</td>
<td>500 µg</td>
<td></td>
</tr>
<tr>
<td>Vitamin K</td>
<td>0–6</td>
<td>Intake from human milk</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–12</td>
<td>E0–6</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>0–6</td>
<td>Intake from human milk</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–12</td>
<td>Intake from milk and foods</td>
<td></td>
<td>220</td>
</tr>
<tr>
<td>Iodine</td>
<td>0–6</td>
<td>Intake from human milk</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–12</td>
<td>E0–6</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>0–6</td>
<td>IHM</td>
<td>0.27 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–12</td>
<td>Factorial modeling</td>
<td></td>
<td>6.9 mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>0–6</td>
<td>Intake from human milk</td>
<td>2 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–12</td>
<td>Factorial analysis</td>
<td></td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>0–6</td>
<td>Intake from human milk</td>
<td>0.3 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–12</td>
<td>Extrapolation from adults (E_A)</td>
<td></td>
<td>0.4 mg</td>
</tr>
<tr>
<td>Niacin</td>
<td>0–6</td>
<td>Intake from human milk</td>
<td>2 mg (preformed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–12</td>
<td>E_A</td>
<td>4 mg NE</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Comments made in reports about micronutrients and formulae and the AIs or EARs for the young

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1, B2 niacin, panthothenate and biotin</td>
<td>No comment</td>
</tr>
<tr>
<td>B6</td>
<td>Infant formulae higher levels than human milk</td>
</tr>
<tr>
<td>Folate</td>
<td>No data found to support need to adjust intake of folate on the basis of formula type</td>
</tr>
<tr>
<td>B12</td>
<td>Infants of vegan mothers should be supplemented at AI level</td>
</tr>
<tr>
<td>Choline</td>
<td>Significance of differences in choline-containing compounds and formula not known</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Some isomerization of trans- to cis-retinal</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>No information on K bioavailability in formula</td>
</tr>
<tr>
<td>Copper</td>
<td>Bioavailability lower in cow's milk-based formula</td>
</tr>
<tr>
<td>Iodine</td>
<td>Bioavailability comparison between human/cow's milk: no data</td>
</tr>
<tr>
<td>Zinc</td>
<td>Bioavailability less for cow's milk and soy-based formula</td>
</tr>
</tbody>
</table>

It is known that various factors influence nutrient utilization, requirements and nutritional status. Some of these are set out in a general summary in table 4. It is known, for example, that intestinal parasites and infection result in malabsorption and increased losses of nutrients. Such examples are the reduced absorption of iron with hookworm infestation [6] and increased urinary
output of vitamin A in systemic infection [21, 22]. However, the quantitative impact of these factors on nutrient utilization and needs is generally unknown. For this reason it is difficult to assess with confidence the worldwide relevance of the US/Canadian DRIs. Clearly, they should be suitable for healthy infants wherever their geographic situation. However, it is now important to conduct research aimed at determining the impact of chronic immunostimulation on quantitative aspects of nutrient utilization and needs. A major challenge is how best to determine the EAR for specific nutrients in an ethical way. Related to this is the additional important challenge to better estimate and define micronutrient status and its functional significance. In part, this will require that we explore new lines of investigation for determination of requirements for micronutrients. It seems to me that we might even consider moving away from use of simple single indicators (markers) of adequacy/deficiency and begin to explore more comprehensive indices of functional significance and include a more global approach (apoptosis, signaling pathways, membrane activities) in real time, with quantitative metabolic kinetics during different states (fasting, prandial, postprandial). This paradigm may seem unrealistic, when in reality it is not, given the teamwork and inter-institutional collaboration that is beginning to emerge in this post-genome era.

**Conclusion**

Despite their many limitations and the discouraging lack of experimental data, the US/Canadian DRIs should serve as a reasonable basis for the planning
and assessment of nutrient needs and adequacy in healthy infants. It is clear that there are large gaps in our knowledge about many aspects of micronutrient utilization and requirements in the early months of life. This is an area for further critical research; vigorous and exciting collaboration between north, south, east and west is a potential way to reduce this gap. Whatever the detailed nature of the evolution of the science of micronutrient nutrition in infants during the early months of life, the exercise undertaken by the IOM/FNB has been fascinating and informing. It represents, perhaps, a worthwhile but still small advance in our attempt to put the nutrition of the young on a sounder, quantitative, scientific footing.

References

Discussion

Dr. Beard: I would like you to address a concern about how reasonable it is to scale nutrient requirements from adults down to infants. If you answer that first, then I will ask the second question if I may.

Dr. Young: I think that is a nice question and it implies some sort of criticism. However, we don’t really have an alternative at the moment and, for example, when we did extrapolate down with respect to the iron requirement the value obtained for the estimated average requirement (EAR) was consistent with what a 6-month-old child would be consuming. One of the issues that we faced was whether or not we should use metabolic body size (kg 0.75) for some of the nutrients that seemed to be the appropriate body weight characteristic on which to make this downward extrapolation; this would be so, for example, for thiamine which is involved in carbohydrate metabolism and therefore related to energy metabolism. It was an approach that we were forced to use for lack of data, but I think it has limitations and can be criticized.

Dr. Beard: I am not really trying to be critical of the approach, I am just trying to highlight for the audience the lack of knowledge, if you will, on how nutrient requirements truly do change with age and stages of growth. I think one of your last slides points to a really critical issue which is whether or not there are going to be some techniques, imaging techniques or other things, that will allow us to have a much better grasp of how nutrient metabolism changes and requirements change during those very rapid periods of growth and development. The amount of apoptosis and cell differentiation can be influenced. I think over the next 2 days we will talk about some of those things, but if zinc and vitamin A and iodine and iron and other micronutrients are really going to have tremendous effects, it is going to be on cell differentiation, organogenesis, and apoptosis events, and that is where we need to have a focus.

Dr. Young: Yes, I agree with what you are saying. What we need to do now is to perhaps step back and forget about trying to estimate a requirement. What we really need to do is to understand what the nature of the dose-response intake relationship is, and to generate a body of knowledge that incorporates many of the new biological techniques and cellular processes that have been elaborated recently. In that context I feel that it is time that we apply ‘big science’ to this particular issue and develop the sorts of collaborations among those who are technological experts in particular areas, and so combine our various resources to actually achieve this particular goal. Ultimately, we will then be able to understand better what the consequence of a particular level of intake are for the functioning of the young infant. Also, nanotechnology is available to us now, and instead of measuring plasma retinol and perhaps β-carotene levels, we can measure 300 other metabolites simultaneously in small blood samples; we can generate huge data bases and then undertake an intelligent data mining approach. Eventually we are going to move nutrition into the 21st century and, hopefully, as a consequence improve the nutritional status of those vulnerable individuals that we are concerned with at this workshop.

Dr. Zlotkin: Congratulations on taking 8 years of work and putting it into 20 min. Since the topic of the symposium is micronutrient deficiencies in the first months of
life, my question is related to the first months of life. If I were the Minister of Health of Dubai or Saudi Arabia or the Gambia, I would feel confident in using the adequate intake values that the dietary reference intake report came up with in my individual country. Is it fair to say that the average amount of breast milk ingested by infants around the world is 780 ml/day? Are the mean values of the concentrations of micronutrients in breast milk collected from mothers in Canada or the US transferable to the rest of the world?

Dr. Young: I knew you would ask a difficult question. First of all, an adequate intake is a level of intake of a nutrient that exceeds the nutrient needs of all healthy infants. So from that point of view it is in excess of requirements. The big problem is the use that the Health Minister of Dubai faces: the difficult challenge of determining whether chronic immune stimulation in your population is sufficient to have increased the requirement level to the point at which this adequate intake is actually no longer in excess of the requirements but perhaps meets or fails to meet the requirements for this particular population whose health status is very different. I think unless there is a substantial basis for thinking otherwise, it would seem to me that these adequate intake levels would provide a very useful, at least, initial basis on which to plan diets that are meant to meet the needs of a particular population group. But I am hesitating. I don't know whether I can fully answer your question. This is all there is Mr. Minister, use the information intelligently. What would you do?

Dr. Zlotkin: I am not going to answer that but let me ask you another question. Is there anything in the report that would suggest that exclusive breast-feeding in the first 6 months of life was inadequate for any population of infants around the world?

Dr. Young: I can’t answer that question because I don’t recall whether or not a specific indication was made in any of the reports along those lines. Do you remember? It was recognized in these reports that factors such as those indicated on one of the slides could alter the requirements and, therefore, the capacity of breast milk to exclusively meet them.

Dr. Zlotkin: I wonder whether the only exception might be vitamin D in those populations who aren’t exposed to sunshine either because of where they live or how the infants are clothed.

Dr. Young: I don’t honestly recall. I am going to have to go back and try to answer that question, and I will try to do it before the end of the workshop.

Dr. Sazawal: Dr. Zlotkin started the question that I was going to ask and I wanted to make it a little more practical because I understand the complexities and lack of knowledge in the area, and I think the committee has done a wonderful job with the knowledge that is available. The problem that usually arises is how those values are interpreted. Specifically the kind of problem I have with some of the recommendations that were drawn is that we talk of the availability of a nutrient in breast milk and then people extrapolate to the quantity of a nutrient, and we know the bioavailability of certain nutrients from the breast milk is totally different. For example, a 6-month-old child is to be weaned to food and you are experimenting from a 6-month breast milk zinc level: we know that zinc is seven times more bioavailable in breast milk, and there is a regulatory body which says that a certain amount is required and should not be exceeded, so this then becomes a therapeutic level for a nutrient in a supplement or a fortified food. That is one area of concern that I have and I would like to ask you to comment. Has mention been made anywhere about the amount of intake and how this translates into this much bioavailable intake, because truly the concept is what is the fraction absorption and what is the total absorbed nutrient from that amount of intake. The second question, which is commonly ignored, is the morbidity patterns between the US population and a various populations around the world: the loss of these elements, I mean in an acute phase reaction, the loss of zinc for example, of a very
high magnitude. Now if you are talking about a population where there is one episode
of diarrhea per child a year versus a population, for example, in India where 10% of
the time there is diarrhea and multiple infection episodes, and what does this do? So
it is dynamic and globally added, there is infection and nutrient intake and the two are
compared. This is less understood, and has some mention been made to that in the
revised report?

Dr. Young: You raised terribly important questions because in the final analysis it is
the application of these data, the intelligent application of these recommendations, that
really matters. The issue of bioavailability is addressed in all of these reports and it is
recognized beyond the breast-feeding stage that the bioavailability of a specific nutrient
is affected by various factors. The extent to which they influence, to a quantitative
extent, the absorption of a particular nutrient and its availability to meet its functions
can vary from India or the US and so on. But these issues are addressed in the reports
I referred to in my paper. Incidentally there are two reports, one that is near completion
and one that has been completed, that deal in considerable detail with the way in which
these particular reference values are intended or should be used. I think one of the most
exciting outcomes of this particular initiative was actually these reports on the uses of
the dietary reference intakes. I think, they break new ground in terms of assisting those
who are the intended users, whether they are policy makers or dieticians or aid workers
and so on. These two reports go into considerable detail as to how to use, what to use,
when not to use and so on. But the issue of bioavailability is handled; the reference
values that were generated in these reports of course are specifically intended for the
North American population whose dietary history and characteristics can be very
different from those of the Indian population, as you indicated. And that needs to be
recognized, but you can’t necessarily immediately apply, without some further
consideration, the values that were generated in these reports to other populations.
This is another topic that I have been particularly interested in; I want to see a so-called
harmonization effort developed so that we can establish the concepts and framework
for generating these estimates worldwide and then for each specific national situation
to include in its framework concerns for these other factors that further influence these
requirement estimates. In this way it would be possible to arrive at a requirement
estimate that is appropriate for that new population, but it is based on the same global
framework and concepts. So harmonization is very important. The issue of these
modulating factors will be raised, I am sure, from time to time during this workshop;
the quantitative effect of disease conditions and so on, on nutrient utilization and
requirements. It is recognized as being fundamentally important to generate
appropriate quantitative data, that is all I can say. I have been interested for years in
estimating the requirements for specific amino acids in health and disease states but to
generate these data for specific disease conditions has not been successful.

Dr. Al Frayh: The task of this committee was to replace the existing recommendation
for dietary intake. The question is, were there any clinical studies which made the
authorities decide to change the recommendation as there were, for example, certain
health risk factors as a result of the existing recommendation? Were there any
longitudinal studies done which indicate that the current recommendation for healthy
infants in North America is possibly leading to say cardiovascular diseases, congenital
anomalies of infants due to certain micronutrient deficiencies, or were there any other
reasons behind looking at the existing recommendation and trying to replace it by a new
recommendation?

Dr. Young: That is a very good question. It was recognized that there is growing
evidence to indicate that intakes of nutrients above those that are just sufficient to
prevent the development of clinical nutritional inadequacy might have a long-term
health benefit, and in this case it relates for example to the intake of the antioxidant
nutrients and the implications that this has with respect to reducing the risk of cardiovascular disease and so on. The committee has looked at the epidemiological evidence and recognized that there are indications that intakes, lets say, of vitamin C, well above those that are necessary to prevent the development of scurvy might have a benefit with respect to reducing the risk of various chronic disease conditions of one kind or another. That recognition, I think, played a role in the vitamin C recommendation, although you can’t use epidemiological data to generate requirement estimates. As I indicated I think it did influence the panels’ decision to use leukocyte near-saturation of vitamin C as the criterion for estimating the vitamin C requirement of individuals. So the panels did recognize that nutrient function goes well beyond preventing classical clinical nutritionally deficient disease, but the evidence was insufficient in the epidemiological context to use that for the purpose of estimating quantitative requirements. For example, let’s take folic acid in relation to the folic acid-homocysteine interrelationship and so on. The implication that this has for increasing or decreasing cardiovascular risk was well recognized by the panel charged with developing the folate recommendation, but in the final analysis they did not use plasma homocysteine, an independent risk factor for cardiovascular disease, as the criterion. The panel recognized that more evidence was required in order to use it as a basis for generating the requirement estimate. They actually ended up using erythrocyte folate levels, the traditional criterion of folate adequacy. So our reports recognize the significance of levels of nutrient intake in relation to the development of chronic disease but the epidemiological associations could not be used to arrive at quantitative estimates of requirements. Does that answer your question? Many of the criteria used in setting the new requirement figures were based on the traditional sort of criteria. This then goes back to Dr. Bates’ presentation, linking a plasma level with a function is the real challenge. The trouble is that this whole area of nutrient requirement estimations is considered to be somewhat dull by many investigators and it hasn’t attracted major input of resources and intellect. I think it is fascinating, especially with the opportunity to now use these new techniques and look at the issue more globally, but it has not attracted the minds that it should have done.

Dr. Pettifor: Although you did mention that there are problems related to the generality of the dietary reference intakes to other areas, and that they are related to the Northern American continent, to Caucasians as well, what concerns me has been the estimation of calcium recommendations in the older age groups and the interpretation of those calcium requirements by other communities elsewhere. What concerns me more is that perhaps we are trying to address a problem of lifestyle and changes in economic status and many other factors by changing nutrient intakes. If you look at calcium intakes in many developing countries they are very much lower, and yet fractures are very much lower. Although people are suggesting this may be genetic, it is difficult to believe that this is a genetic effect and there may be lifestyle factors unrelated to nutrition which may be playing a much more important role in the prevalence of fractures in the postmenopausal period than for instance a change in nutrient intake such as calcium. Are we not hiding behind nutrients to try and deal with the other problems?

Dr. Young: I don’t know whether we are hiding behind nutrients but I am not surprised you brought up the calcium issue. I think in one way that was actually the first nutrient that our panel was asked to address and it is probably the most complex nutrient. I think it is a shame we chose to look at calcium before we looked at many of these others which were easier to handle and, Dr. Allen will agree with me on this point, you can’t imagine what discussions and arguments we had with respect to ultimately arriving at the calcium recommendation. I wanted just to say, as I have said in public before, I have questions about the appropriateness of the calcium

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recommendations that were made. But I was only the chairman of the parent committee and I wasn't one of the experts on the calcium panel. One of the experts told me that I 'don't know anything about calcium, so you listen to us or you set the values yourself'. I think of all the nutrients there is a very good indication that the calcium needs of different populations are different, whereas I don't believe that is the case for any other nutrient. Calcium is very special in this sense. I am aware of Prentice's [1] work in the Gambia and the indication that bone health is achieved at much lower levels of calcium intakes than seems to be the situation in North America. The reasons for that are not certain, and whether or not there is long-term adaptation and so on are questions that still need resolution. I also understand and I am aware of the fact that in China fewer fractures occur in spite of the much lower levels of calcium intake than is the case of the US population. Dr. Heaney told me one reason for this is that Chinese fall differently, and this contributes to a difference in the extent to which fractures occur. So there are differences and some of these lifestyle factors that you allude to presumably have an important bearing in this context. I think calcium is a particularly difficult nutrient to address in this context.

**Dr. West:** A question about the estimated average requirement (EAR). Just briefly, would you believe that the concept of the EAR, which divides a population between deficient and sufficient, at that median, is relevant and valid even if we don't have the functional indicators that we would like to have in an age group and especially in young infants? Secondly, can we expect the EAR to be valid across all populations?

**Dr. Young:** If you change the criteria and if you change the health status, the needs are going to differ. So I think the concept of an EAR is good. We recognize that among apparently similar individuals there is a variation that presumably has, at its fundamental basis, complex genetic mechanisms. Hence there is going to be variation around the mean requirement but for a given status of health, body size and age and condition, and so on. It seems to me as though a median or an average is an extremely useful parameter to have available to us.

**Dr. Mousa:** I am an endocrinologist and a geneticist. So I am faced with a lot of cases of vitamin D deficiency, genetic diseases and nutritional diseases, and unfortunately in most of them it is more nutritional than genetic diseases. In answer to the question of Prof. Zlotkin, yes, we have a lot of young mothers with exclusively breast-fed babies, and all of them unfortunately have severe neonatal vitamin D deficiency. It is a disaster, it is a big problem for us.

**Dr. Young:** So you are saying that you see vitamin D deficiency to a significant extent?

**Dr. Mousa:** Yes, neonatal.

**Dr. Young:** And you think this is nutritional?

**Dr. Mousa:** I am sure about it because we are tracing the mothers in the neonatal period and we treat them. After that the next pregnancy will improve. So it is mainly a nutritional problem of the mothers, who are usually young or have had multiple pregnancies, more than 5 pregnancies.

**Dr. Young:** I will talk to you afterwards. At the moment we have done our best, I suppose, but this is in no way the last word, that is for sure. I think we are going to have a marvelous time for the rest of this meeting addressing many of these issues and I really look forward to everything that follows and I will relax now. Thanks very much.

**Reference**