Contribution made by biomarkers of status to an FP6 Network of Excellence, EURepean micronutrient RECommendations Aligned (EURRECA)\(^1\)–\(^5\)

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ABSTRACT
Dietary reference values for micronutrients vary considerably among countries, and harmonization is needed to facilitate nutrition policy and public health strategies at the European and global levels. The EURepean micronutrient RECommendations Aligned (EURRECA) Network of Excellence is developing generic instruments for systematically deriving and updating micronutrient reference values and dietary recommendations. These include best practice guidelines, interlinked web pages, online databases, and decision trees. Journal supplements have been published on micronutrient intakes and status, and an ongoing activity of EURRECA is the completion of systematic reviews on associations between intakes, status, and various health outcomes for priority micronutrients (ie, iron, zinc, folate, vitamin B-12, and iodine), which were selected by using a triage technique. Future activities include meta-analyses to identify dose-response relations and the variability, factorial estimates of requirements, bioavailability from whole diets, effects of genotype, and modeling techniques for addressing dietary recommendations for combinations of nutrients with common health endpoints. \textit{Am J Clin Nutr} 2011;94(suppl):651S–4S.

INTRODUCTION
Nutritional status is measured by a range of biochemical and other indexes of short- and long-term exposures to a micronutrient and direct or surrogate biomarkers of the functional consequences of different levels of intake. These measurements are essential for deriving dietary reference values, which is a generic term used to describe recommended levels of nutrient intakes for populations and individuals that are usually presented as average requirements with lower and upper limits that minimize risk of deficiency or toxicity, respectively.

DIETARY REFERENCE VALUES
In the process of deriving micronutrient recommendations, biomarkers are essential for deriving the average requirement and for identifying and anticipating adverse effects of too low or too high an intake of a micronutrient.

A database has been compiled by the EURepean micronutrient RECommendations Aligned network (EURRECA; \url{http://www.eurreca.org}) that includes all available information on dietary reference values. These values vary considerably among countries, and harmonization is needed to facilitate nutrition policy and public health strategies within Europe and around the world (1). Expert bodies use different terminologies, often to describe the same value, as illustrated in Figure 1. The European Food Safety Authority (2) uses the term Population Reference Intake (PRI), which is equivalent to the Recommended Dietary Allowance (RDA) of the Institute of Medicine (3), to define the quantity of a nutrient that will meet the needs of 97.5% of the population, but when assessing the nutritional adequacy of an individual, the PRI is the appropriate benchmark value. In 2007, an expert group convened by the United Nations University, in collaboration with the Food and Agriculture Organization, World Health Organization, and United Nations Children’s Fund, proposed a new term, nutrient intake values, which was judged to be neutral and more flexible (4). Nutrient intake values include just 2 values, the average nutrient requirement (from which the individual nutrient level for \(x\)% of the population can be calculated) and the upper nutrient level.

BIOMARKERS OF MICRONUTRIENT STATUS
EURRECA is developing generic instruments for deriving and updating micronutrient reference values. Workshops were held with international experts, and a series of systematic reviews were undertaken to identify the best methods for measuring micronutrient intakes (5, 6) and the most appropriate biomarkers of status. A web-based resource (best practice guidelines) that identifies the most useful biomarkers of status for 20 micronutrients (calcium, chromium, copper, iodine, iron, magnesium, etc.) and provides a decision tree for selecting the most appropriate biomarker for any given task.

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\(^2\) Presented at the conference “Biomarkers of Nutrition for Development: Building a Consensus,” held in Vienna, Austria, 8–10 February 2010.

\(^3\) This article does not necessarily reflect the views of the Commission of the European Communities nor its future policy.

\(^4\) Supported by EURRECA (\url{http://www.eurreca.org}), which is financially supported by the Commission of the European Communities, specific Research, Technology, and Development Programme Quality of Life and Management of Living Resources, within the Sixth Framework Programme (contract 036196).

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cutoff values that were collated from all available published sources for iron, zinc, selenium, folate, vitamin B-12, and iodine is also available on the website.

SYSTEM FOR PRIORITIZING MICRONUTRIENTS
During the first couple of years of the EURRECA project, systematic reviews on biomarkers of status and intake methodologies used a significant proportion of the resource available to the network, and therefore, the research activity in EURRECA for the next 3 y was focused on a few key nutrients. A transparent and systematic triage system was designed to select priority micronutrients (11) in which micronutrients were scored according to several criteria (Table 2), and from the list populated, 5 micronutrients were selected (ie, iron, zinc, folate, vitamin B-12, and iodine). Systematic reviews are currently underway to explore the associations between intakes, status, and selected health outcomes.

PERSONALIZED NUTRITION
A wiki-based website (http://www.eurreca.org/everyone/1431) has been established to provide information on micronutrients in collaboration with members of NuGO (http://www.nugo.org/everyone). Modeling techniques are being developed for groups of biomarkers that are related to one of 3 health endpoints (ie, inflammation, oxidative stress, and metabolic stress) to explore

<table>
<thead>
<tr>
<th>Vitamin B-12²</th>
<th>Star rating¹</th>
<th>Research or field use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum/plasma total vitamin B-12</td>
<td>** F</td>
<td></td>
</tr>
<tr>
<td>Serum/plasma MMA</td>
<td>** F</td>
<td></td>
</tr>
</tbody>
</table>

³ F, field (survey) use; R, research only; MMA, methylmalonic acid.
² Evaluation of vitamin B-12 biomarkers and associated ratings are based on the opinions of the EURRECA Biomarkers of Status Working Party (7) and include supporting evidence from the recent systematic review of biomarkers of vitamin B-12 status (9). A member of the working party also published an eminence-based review of methods to assess vitamin B-12 status (10).

³ Star (quality) rating was assessed as follows: excellent (***) , good (**), limited use (*), and not useful (—).
the “health space” (12), and metabolomic data are being generated from stored samples from dietary intervention studies that involve multiple micronutrient doses and in which subjects were well characterized and significant changes in biomarkers of status reported.

FUTURE ACTIVITIES

Meta-analyses are being undertaken on data collected from published randomized controlled trials, cohort studies, and some cross-sectional studies to examine intake-status-health dose-response relations for priority micronutrients. Modeling techniques will be applied to derive figures for micronutrient requirements by using a combination of data extracted for the systematic reviews, factorial calculations, and bioavailability estimates. The database will also be used to derive information on individual variability for biomarkers of status. Systematic reviews are currently underway to examine absorption data from meals and whole diets for priority micronutrients that are not efficiently absorbed (ie, iron, zinc, selenium, folate, and vitamin B-12 in the elderly) (13) and to examine the effects of genotype on absorption.

A generic scheme is being developed (shown in Figure 2) that will be tailored for individual micronutrients and take into account the needs of different stakeholders, and from the missing information, research requirements will be identified for priority micronutrients. Steps 3–6 are central to the interests of the Biomarkers of Nutrition for Development (BOND) group. Step 8 is beyond the remit of EURRECA but is essential for public health policy both nationally through government departments and globally (eg, the World Health Organization). Sustainability plans for EURRECA are underway to identify curators for databases and, where appropriate, tools developed by the Network of Excellence. It is anticipated that the Biomarkers of Nutrition for Development (BOND) group will have a central role in the use of many of EURRECA resources and outputs.

![Figure 2](image-url)
The author’s employer, the University of East Anglia, is a partner of the EURRECA Network of Excellence. The author is a member of the European Food Safety Authority Dietetic Products, Nutrition and Allergies Panel and PRI Working Group.

REFERENCES