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ORIGINAL ARTICLE

Prioritizing micronutrients for the purpose of reviewing their requirements: a protocol developed by EURRECA

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Background: The EURRECA (EURopean micronutrient RECommendations Aligned) Network of Excellence (http://www.eurreca.org) is working towards the development of aligned recommendations. A protocol was required to assign resources to those micronutrients for which recommendations are most in need of alignment.
Methods: Three important '*a priori*' criteria were the basis for ranking micronutrients: (A) the amount of new scientific evidence, particularly from randomized controlled trials; (B) the public health relevance of micronutrients; (C) variations in current micronutrient recommendations. A total of 28 micronutrients were included in the protocol, which was initially undertaken centrally by one person for each of the different population groups defined in EURRECA: infants, children and adolescents, adults, elderly, pregnant and lactating women, and low income and immigrant populations. The results were then reviewed and refined by EURRECA's population group experts. The rankings of the different population groups were combined to give an overall average ranking of micronutrients.
Results: The 10 highest ranked micronutrients were vitamin D, iron, folate, vitamin B12, zinc, calcium, vitamin C, selenium, iodine and copper.
Conclusions: Micronutrient recommendations should be regularly updated to reflect new scientific nutrition and public health evidence. The strategy of priority setting described in this paper will be a helpful procedure for policy makers and scientific advisory bodies.
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Keywords: micronutrients; recommendations; reference values; setting priorities; revision; EURRECA

Background

Need for evidence-based policy development

National and international scientific nutrition advisory bodies function as an interface between policy makers and the scientific community as they are charged with providing, interpreting and advising governments on the evidence base for policy decisions. However, there is often limited clarity on how nutrition-related requests are framed and selected by policy decision makers to submit to these advisory bodies. Moreover, the development of modern health policies relies on evidence-based recommendations to (i) make policies more efficient and reasonable and (ii) ensure greater accountability for decisions. As advisory bodies are bound by practical constraints such as limited resources, predefined

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prioritization tools would be helpful to guide policy makers in making evidence-based, transparent requests to advisory bodies.

Revision of nutrient recommendations

One of the requests made by governments to policy advisory bodies such as the European Food Safety Authority or other (inter)national nutrient recommendation setting bodies is the updating of micronutrient intake reference values, including the Average Nutrient Requirement (ANR) and the Individual Nutrient Level ($INL_{97,5}$), otherwise known as 'recommendations', or population reference intakes or dietary reference intakes (Dhonukshe-Rutten *et al*., 2010). The revision of reference intake values on the basis of the best and most recent available evidence is a costly process for advisory bodies in terms of expert time and money. Therefore, a systematic prioritization process may need to be applied to decide those micronutrients on which to focus.

Many advisory bodies responsible for setting recommendations acknowledge that (changes in) public health consequences and new scientific evidence are important indicators for prioritizing micronutrients for revision, but they do not use transparent '*a priori*' criteria. The need to incorporate transparent '*a priori*' criteria into strategies for future reviews of micronutrient recommendations has recently been highlighted by several international groups of researchers (Lambert and Ashwell, 2010; Yetley *et al*., 2009).

This paper addresses the development and use of a protocol for identifying priority micronutrients for the purpose of reviewing dietary recommendations.

This work was undertaken within the context of the EURRECA (EURopean micronutrient RECommendations Aligned) Network of Excellence (http://www.eurreca.org). EURRECA is funded by the EU 6th Framework Programme, to address the disparity in micronutrient recommendations between countries.

Methods

*Derivation of '*a priori *'criteria used for priority setting*

The most important trigger for reviewing and revising micronutrient recommendations for any organization involved in, or responsible for, setting recommendations is the availability of new scientific evidence on intake–status–health indicator/outcome associations published since the previous sets of values were established (Taylor, 2008; Yetley *et al*., 2009). A second trigger relevant for policy makers is (a change in) the public health burden of a particular micronutrient. An additional trigger for EURRECA, in the European context, was the need to align the scientific basis for micronutrient recommendations across different countries.

These triggers were translated into the following criteria:

(a) amount of relevant, new scientific evidence available for a particular micronutrient for different life-stage population groups;
(b) public health relevance of the micronutrient for the different population groups, including vulnerable groups such as low income and immigrant population:
(c) heterogeneity defined as variations in current micronutrient recommendations in different European countries.

These three theoretical criteria were translated into quantifiable indicators (see Figure 1 for schematic presentation). Once translated, the indicators were combined into an assessment matrix as shown in Figure 2. The multidimensional matrix was transformed into a priority pyramid that includes the four cells of the matrix with the highest attributed priority. Highest priority was given to micronutrients for which the amount of new evidence was substantial (A), were most relevant for public health (B) and for which variations in current recommendations were relatively large (C).

Translation of three theoretical criteria into quantifiable indicators

The quantification of these three criteria was applied to 28 micronutrients reviewed previously by the US Institute of Medicine (IOM) (Taylor, 2008), namely, vitamins A, D, E, K, C, thiamin (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), cobalamin (B12), folic acid (B11), biotin, choline, calcium, chromium, copper, fluoride iron, iodine, magnesium, manganese, molybdenum, pantothenic acid, phosphorus potassium, selenium, sodium and zinc.

Amount of new evidence

New evidence was quantified as the number of publications in PubMed from 2003 onwards using two standardized search strategies. To focus on recent evidence, searches were limited to the period from 1 January 2003 to 15 July 2008. This point in time was chosen because the micronutrient reference values that were most recently published worldwide, including all micronutrients, namely, those from Australia/New Zealand (Ministry of Health, 2005), included scientific evidence up to the end of 2002.[1]

The first standard search strategy performed on text words in title[ti] and abstract[ab] was as follows: (*Micronutrient* intake [ti, ab] OR *Best Status marker* [ti, ab]) AND *Health indicator* [ti, ab] (for example, balance, health, growth, factorial) AND NOT (patient [ti] OR patients [ti]) AND for pregnancy and lactation only additional terms for example,

[1]Please note that this applied at the beginning of 2008 when we started this study. Some countries, such as The Netherlands (http://www.gezondheidsraad.nl/en/publications/healthy-nutrition) and Belgium (https://portal.health.fgov.be/pls/portal/docs/PAGE/INTERNET_PG/HOMEPAGE_MENU/ABOUTUS1_MENU/INSTITUTIONSAPPARENTEES1_MENU/HOGEGEZONDHEIDSRAAD1_MENU/ADVIEZENENAANBEVELINGEN1_MENU/ADVIEZENENAANBEVELINGEN1_DOCS/HGR_8309_NL.PDF), published new recommendations for all micronutrients, or for a specific micronutrient, after 2005.

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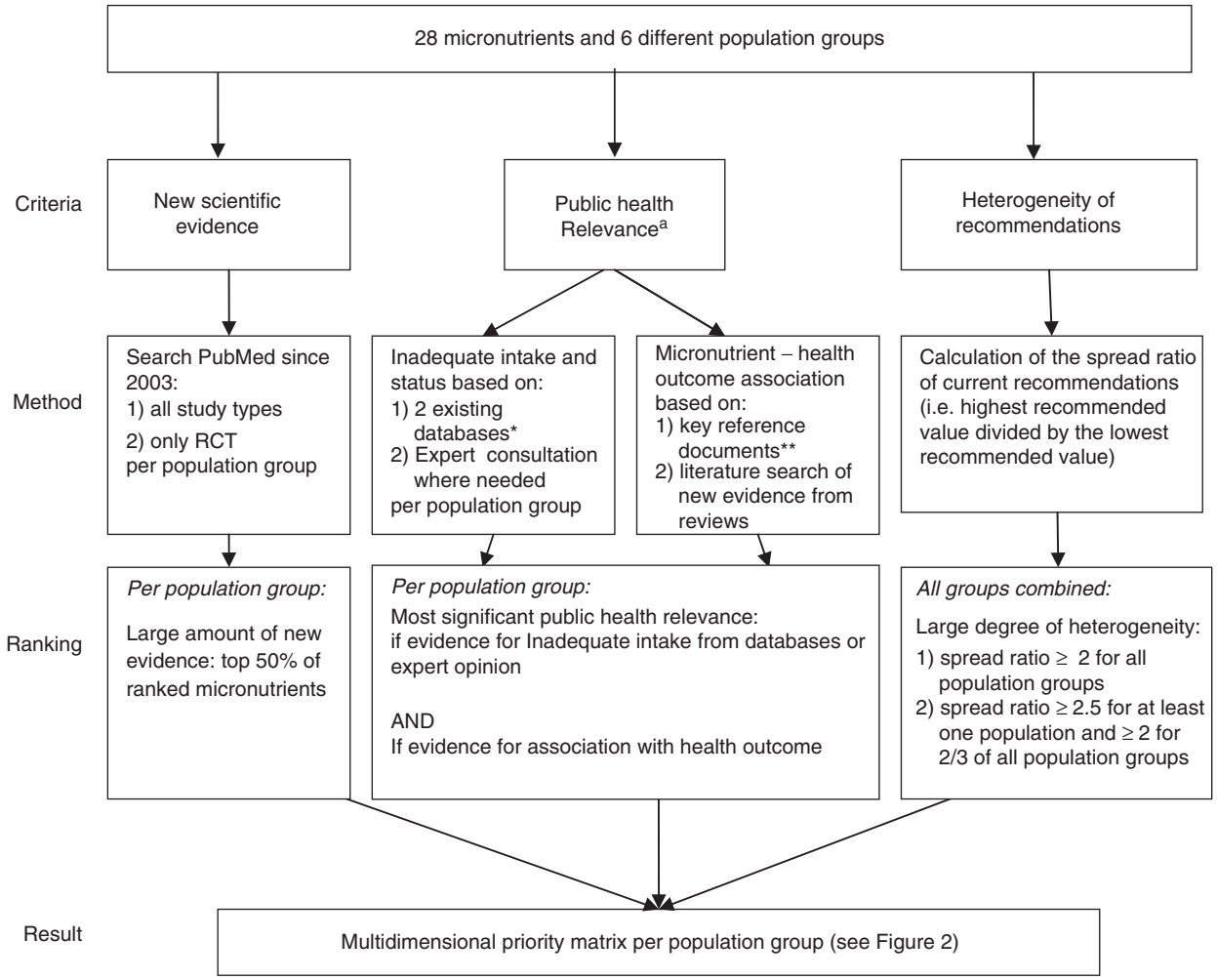

Figure 1 Schematic presentation of EURRECA's protocol to prioritize the selection of micronutrients. [a]Not measured for micronutrients for which the amount of new evidence (first criteria) was considered small for all population groups. **Database 1*: Contained crude dietary intake data from national surveys made available by ILSI Europe: Anonymous, 1998; Gregory *et al.*, 2000; Serra-Majem and Aranceta, 2001–2006; Irish Universities Nutrition Alliance, 2001; Turrini *et al.*, 2001; Henderson *et al.*, 2002; Mensink *et al.*, 2002; Hulshof *et al.*, 2004; Männistö *et al.*, 2003; Szponar *et al.*, 2003; Lyhne *et al.*, 2005; Irish Universities Nutrition Alliance, 2006; Ocké *et al.*, 2008. *Database 2*: Held data from a EURRECA literature review previously undertaken by Tabacchi *et al*, (2009). **Food and Nutrition Board, 1997–2003; World Health Organization, 2003; Ministry of Health 2005; World Cancer Research Fund and American Institute for Cancer Research, 2007.

pregnan* [ti, ab] or lactat* [ti, ab] OR limitation to age group of concern. The second search strategy was identical to the first one, with the exception that this search was limited to randomized controlled trials. This approach was chosen to give more weight to the more robust scientific evidence provided by such trials.

In the context of EURRECA, various micronutrient status markers used to assess intake/exposure to and/or body levels of each micronutrient were evaluated (Fairweather-Tait, 2008). A list of potential markers were collated in a table and assigned a star rating by seeking the consensus of a group of international micronutrient experts. Biomarkers were rated as excellent (***), good (**), limited use (*) or unacceptable (no star), and were also categorized according to their usefulness either 'in the field' or in a research setting. Biomarkers used or considered by the IOM (Food and Nutrition Board, 1997–2003; Institute of Medicine, 2007; Taylor, 2008) for setting recommendations for the United States/Canada were included in the table, together with others identified by Gibson (2006) and by international experts.

The amount of new scientific evidence for all 28 micronutrients was assessed separately for the five population groups defined within the network, namely, (i) infants, 0- to 1-year olds; (ii) children and adolescents, 1- to 18-year olds; (iii) pregnant and lactating women; (iv) adults, 18- to 64-year olds; and (v) the elderly, 65 years or older. For each population group, the 14 micronutrients (50%) with the highest ranking based on the number of hits of the two searches were micronutrients for which the amount of new

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	A New evidence ↑ B Public health relevance ↑	A New evidence ↑ b Public health relevance ↓	A New evidence ↓ B Public health relevance ↑	A New evidence ↓ b Public health relevance ↓
C Heterogeneity ↑	1: ABC	3. AbC	aBC	abC
c Heterogeneity ↓	2: ABc	4: Abc	aBc	abc

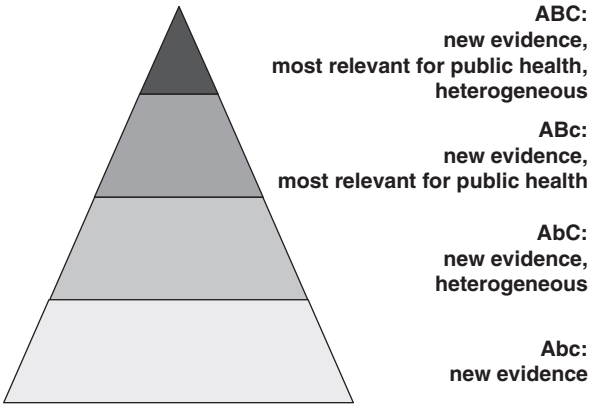

Figure 2 Schematic presentation of the matrix and priority pyramid used for scientific triage.

evidence was considered 'large' as defined by the protocol criteria.

For low income and immigrant populations, no specific searches were carried out, as physiological requirements are not expected to differ from the general population, and studies on intake–status–health relationships are commonly not focused specifically on these groups. Therefore, for this population group, the ranking of micronutrients was based on the total number of hits of all other (life stage) populations. As a quality check, the titles of the publications identified using the first search strategy for each micronutrient were screened for contributions of irrelevant publications, for example, relating to treatment of chronically ill populations.

Public health relevance

Public health relevance for a particular micronutrient was assessed using measures of dietary inadequacy and disease burden, such as

(1) evidence from national representative or large population samples for inadequacy of intake or poor status of a micronutrient in five or more European countries;
(2) evidence (from meta-analyses or reviews) for an association between the micronutrient and a severe health problem, or an association between the micronutrient and a mild health problem with high incidence in the population. This was defined as nutrition-related health outcomes causing the largest burden of diseases in Europe as expressed in disability adjusted life years.

Public health concerns were considered the most relevant if both criteria were applicable. However, micronutrients for which limited data were available to assess inadequacy of intake and status, but fulfilled only the second criterion, were also accepted.

Public health relevance was not assessed for those micronutrients for which only limited new evidence was available for all population groups as described in the previous section (that is, micronutrients with low priority, allocated to the 'a' column of the matrix shown in Figure 2).

Assessment of inadequacy of intake and poor status. Two databases were created and used to assess inadequacy of dietary intake:

Database 1: It contained crude dietary intake data from national surveys. Data were available for 13 micronutrients (calcium, copper, folate, iodine, selenium, zinc, vitamin A, vitamin D, vitamin E, magnesium, niacin (B3), phosphorus, pyridoxine (B6)) and for 9 countries for population groups aged 4–10, 11–17 and 18+ years (Anonymous, 1998; Gregory *et al*., 2000; Irish Universities Nutrition Alliance, 2001, 2006; Turrini *et al*., 2001; Serra-Majem and Aranceta, 2001–2006; Henderson *et al*., 2002; Mensink *et al*., 2002; Männistö *et al*., 2003; Szponar *et al*., 2003; Hulshof *et al*., 2004; Lyhne *et al*., 2005; ILSI Europe, 2008; Ocké *et al*., 2008).

Database 2: It held data from a EURRECA literature review previously undertaken by Tabacchi *et al*. (2009). This review included observational studies and methodological papers

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on dietary intake and adequacy measurements for 20 micronutrients, published between 1990 and 2008.

These two databases were used to evaluate the existence of inadequacy for all available population groups. The Nordic Nutrient Intake Values were used as reference values to evaluate adequacy of intake, as they are the most recently published European recommendations (Nordic Council of Ministers, 2004).

The available intake data from the two databases (1: intake of the 5th and 50th percentile; 2: mean/median intakes) and the published reference values ($INL_{97,5}$, which is the ANR plus 2 times the standard deviation, or Adequate Intake) precluded the use of best practice methods to assess inadequate intake as described by Roman-Viòas *et al*. (2009) for all population groups. Therefore, a simplified method was used. Some evidence for inadequacy was accepted:

- if the mean or median intake was less than 75% of the $INL_{97,5}$, otherwise known as recommended dietary allowance[2] or
- if the intake of the fifth percentile was less than 50% of the $INL_{97,5}$ for five or more European countries.

On using these databases, adequacy and intake data for some population groups and micronutrients were limited; therefore, additional scientific input was required. This involved an eminence-based judgement on inadequacy of intake by a panel of EURRECA experts, all co-authors of this paper, on nutritional requirements in each population group. Moreover, the experts were asked to assess the inadequacy of the micronutrient status for their population group and to (re)classify micronutrient inadequacies on the basis of additional evidence from literature. No specific guidelines were provided to the expert panel.

Evidence for association with health outcomes causing the largest burden of disease. Nutrient-related health outcomes causing the greatest burden of disease in Europe, as expressed in disability adjusted life years, are cardiovascular, respiratory and neuropsychological diseases, cancer, osteoporosis, diabetes and, indirectly, suboptimal growth and development during the entire lifespan (World Health Organization, 2001, 2003, 2004b). Three different sources were consulted for evidence of associations between each micronutrient and one or more health outcomes:

(1) Micronutrient reports from the United States/Canada and Australia/New Zealand: these reports provided an overview of chronic diseases that may be associated with micronutrients (Food and Nutrition Board, 1997–2003; Ministry of Health, 2005).
(2) Recent reports of international organizations; such as the World Health Organization and the World Cancer Research Foundation, were screened for their conclusions on the evidence base for these associations (World Health Organization, 2003; World Cancer Research Fund and American Institute for Cancer Research, 2007).
(3) Reviews and meta-analysis identified from the PubMed database since 1 January 2003 for the different micronutrients.

We judged that there was 'evidence' for an association if the authors of the reports (source 1 and 2) concluded that there was convincing or probable evidence for an association, or if the authors reported the possibility of an association that was supported by one or more recent reviews and/or meta-analysis (not necessarily consistent over all available publications) from the PubMed database.

Heterogeneity

Information on variations in current recommendations was available from a previous EURRECA research activity and published by Doets *et al*. (2008). Variations were quantified by 'spread ratio per micronutrient', that is, the highest recommended value divided by the lowest recommended value. Ratios were calculated for specifically defined ages (3 and 9 months, 5, 10, 15, 25, 50 and 70 years), males and females, as well as for pregnant and lactating women. Comparison of the recommendations was restricted to European countries, and organizations that defined recommendations themselves or in collaboration with other countries '*de novo*', that is, using teams of experts who weighed the scientific evidence (Panel on DRVs of the Committee on Medical Aspects of Food Policy, 1991; Food and Nutrition Council, 1992; Commission of the European Communities, 1993; German Nutrition Society *et al*., 2000; Latvian Food Center, 2001; Guéguen, 2001; Health Council of the Netherlands, 2000, 2003; Nordic Council of Ministers, 2004; World Health Organization and Food and Agriculture Organization, 2004a; Doets *et al*., 2008). As recommendations usually consist of values, ranges and multiple values that apply to one population group (for example, values for different activity levels), standardization procedures were defined to enable a comparison of the recommendations as described elsewhere (Doets *et al*., 2008).

Heterogeneity was defined for the total population, and not per population group, as it should indicate general misalignment. Heterogeneity was considered large when (1) the spread ratio was $\geqslant 2$ for all populations groups, or (2) the spread ratio value was $\geqslant 2.5$ for at least one population group and $\geqslant 2$ for two out of three of all populations groups. These cutoff points were defined after reviewing the range of spread ratios.

Priority matrix

The scientific triage methodology developed was undertaken centrally by the first author to produce matrices (see Figure 2) that were completed for each EURRECA population group (infants, children and adolescents, adults, elderly, pregnant

[2]75% was chosen, as on an average the ANR (published together with the $INL_{97,5}$ for adults and for a selection of micronutrients only) was 75% of the $INL_{97,5}$.

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and lactating women, low income and immigrant populations). Subsequently, each matrix was reviewed, and refined by EURRECA's population group experts, on the basis of their extensive knowledge of the specific published literature for that group. Finally, these matrices were combined to produce an overall ranking of micronutrients. Micronutrients were given a score of 1 if they were allocated to cell ABC of the matrix, 2 for cell ABc, 3 for cell AbC, 4 for cell Abc and 5 if they were assigned to other cells (Figure 2). The final ranking order was based on the total score of the micronutrient, allocating an equal rank to micronutrients with an equal score.

Results

Amount of new evidence

Micronutrients for which the amount of new evidence was large for all of the five population groups were calcium, folate, iodine, iron, selenium, zinc, vitamin D and choline (ranked in the top 14). Evidence for sodium, vitamin A, vitamin B12, vitamin E, vitamin C and copper was large for four out of five population groups, and evidence for magnesium, vitamin K, thiamine and fluoride was large in one out of five population groups. For all other micronutrients, the evidence was small in all population groups.

Screening of the titles of papers showed that sodium publications were mainly related to risks of high intake rather than to evidence to estimate minimal physiological needs for optimal health. As upper limits are not within the scope of EURRECA, sodium was excluded from the list of micronutrients for which the amount of evidence was considered as 'large'.

Public health relevance

Evidence for inadequate micronutrient intake or status. On the basis of databases 1 and 2, we found some evidence for inadequacy for one or more life-stage population groups for calcium (children and adolescents, elderly), folate (children and adolescents, adults, elderly, pregnant and lactating women), iron (children and adolescents, adults, elderly, pregnant and lactating women), zinc (infants, children and adolescents, adults), vitamin D (children and adolescents, adults), vitamin E (adults) and copper (adults). From the expert consultation, we concluded that there was additional evidence on inadequacy in the elderly population group for vitamin D and vitamin B12 (inadequate status) (Holick, 2007; McLean *et al*., 2008), and for infants for vitamin D and iron (inadequate status) (Brunvand and Brunvatne, 2001; Pal and Shaw, 2001; Scientific Committee on Food, 2003; WHO global database on anaemia, 2008a). Moreover, for low income and immigrant populations, additional evidence for inadequate intake was available for iodine, vitamin C, vitamin A, vitamin E and magnesium (James *et al*, 1997; DeLange *et al*., 2000; Brussaard *et al*., 2001; McNeill *et al*., 2002; Pavlović *et al*., 2005; Andrieu *et al*., 2006; Nelson *et al*., 2007; World Health Organization and UNICEF 2007; Rasmussen *et al*., 2008; Zimmermann, 2009).

Evidence for association with health outcomes causing the largest burden of disease. Table 1 provides an overview of available information on the association between each micronutrient and nutritionally related health problems most relevant in Europe from the three different sources of information/references. For most micronutrients, we concluded that there was evidence available for an association with one or more relevant micronutrient-related diseases in Europe. No evidence was found for choline, copper, phosphorus and thiamine.

Public health relevance, which was considered important if both criteria described above applied, was overall highly relevant for vitamin D and iron (all population groups), followed by zinc and folate (five out of six population groups), and calcium (four out of six population groups).

Heterogeneity

'Spread ratios' to quantify heterogeneity were calculated for 27 out of 28 micronutrients. Ratios for choline could not be defined as none of the reports included recommendations for this micronutrient. Heterogeneity was large for vitamin D, vitamin C, sodium, folate, selenium, copper, iron, zinc, phosphorus, vitamin B12, fluoride, biotin, chromium and molybdenum. Figures 3a and b show the 'spread ratios' for females and males, respectively, for the micronutrients for which heterogeneity (C) and the amount of new evidence were considered to be large (A). Because of the 'zero' recommendation for various age and population groups in the United Kingdom for dietary vitamin D intake, the ratios for vitamin D were often infinity and thus could not be included in the graph.

Overall ranking of micronutrients

Table 2 shows the completed priority matrix for the different population groups. Collating and summarizing information for all population groups resulted in an overall ranking of micronutrients. The top 10 micronutrients were vitamin D, iron, folate, vitamin B12, zinc, calcium, vitamin C, selenium, iodine and copper.

Discussion

Scientific triage tool for prioritizing micronutrients

We have described the development and use of a transparent scientific triage protocol for establishing priority micronutrients for reviewing dietary requirements. Three key criteria were derived '*a priori*' from triggers relevant for bodies responsible for setting nutrient recommendations, as well as from EURRECA's guiding principles. The key criterion

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Table 1 Overview of evidence that supports an association between micronutrients and diseases causing the largest burden in health in Europe

Micronutrient[a]	*DRI reports of USA, Canada/Australia, New Zealand*	*WHO, 2003*	*WCRF/AICR, 2007*	*Reviews and meta-analysis published since January 2003*[b]	*Evidence*[c] *of association*
Calcium	Osteoporosis, bone health, colon cancer, hypertension, inflammatory and autoimmune disease, for example, diabetes mellitus	Convincing: osteoporosis, osteoporotic fractures in elderly Possible: cancer	Convincing: colorectal cancer	Osteoporosis, hypertension, diabetes mellitus/optimal glucose metabolism, colorectal cancer	Osteoporosis, cancer, diabetes
Folate	Neural tube defects, leukaemia children, cardiovascular disease, dementia, mental function	Probable: cardiovascular disease Possible: cancer	Probable: pancreas cancer	Neural tube defects, stroke, depression	Cancer, cardiovascular disease, neurological disease
Iodine	Impaired mental and physical development	Convincing: impaired mental and physical development		Intelligence deficit	Growth, neurological diseases
Choline	Cancer, cardiovascular disease, cognitive function and memory at all ages, dementia, fatty liver syndrome			Memory	
Iron	Anaemia, decreased physical work capacity, delayed psychomotor development in infants, impaired cognitive function, impaired immunity and adverse pregnancy outcomes			Mental development	Growth, neurological diseases
Selenium	Keshan disease, cancer	Possible: cancer	Convincing: prostate cancer, Probable: lung cancer, colorectal cancer (food)	Cardiovascular disease, prostate cancer, gastrointestinal cancer, colorectal cancer	Cancer
Zinc	Growth, depression, suboptimal pregnancy outcomes and impaired immune response	Possible: cancer		Preterm birth, respiratory diseases (?)	Growth, respiratory diseases
Vitamin D	Osteoporosis, bone health, cancer, hypertension, inflammatory and autoimmune disease, for example, diabetes mellitus	Convincing evidence: Osteoporosis, osteoporotic fractures in elderly Possible: cancer		Diabetes mellitus, optimal glucose metabolism, active tuberculosis, total mortality, colorectal cancer, osteoporosis in elderly	Osteoporosis, diabetes mellitus
Vitamin A (retinol), incl carotenoids, beta-carotene	Immune function, mortality, cancer, cardiovascular disease, macular degeneration, cataracts		Probable: skin cancer, oesophagus cancer, lung cancer	Skin cancer	Cancer
Vitamin B12		Possible: cancer		Cognitive function	Neurological disease
Vitamin E	Cardiovascular disease, diabetes mellitus, cancer, impaired, immune function, cataracts, central nervous system disorders	Possible: cancer	Probable: prostate cancer	Parkinson disease	Cancer, neurological diseases
Vitamin C	Cardiovascular disease, cancer, cataracts, asthma, common cold, cognitive function and memory	Possible: cancer	Probable: oesophagus cancer (foods)	Cardiovascular disease	Cardiovascular disease, cancer
Copper	—			NA	
Magnesium	Cardiovascular disease, osteoporosis, optimal glucose metabolism, hypertension			Diabetes mellitus	Diabetes mellitus

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Table 1 *Continued*

Micronutrient[a]	*DRI reports of USA, Canada/Australia, New Zealand*	*WHO, 2003*	*WCRF/AICR, 2007*	*Reviews and meta-analysis published since January 2003*[b]	*Evidence*[c] *of association*
Potassium		Convincing evidence: cardiovascular disease			Cardiovascular disease
Phosphorus					
Vitamin K	Osteoporosis, atherosclerosis,			Bone loss in elderly	Osteoporosis
Vitamin B6	cognitive function, depression	Possible: cancer			Neurological disease
Thiamin					
Fluoride	Cancer, cataracts, dental caries	Convincing evidence: dental caries		Fracture risk	
Riboflavin		Possible: cancer		NA	Growth

Abbreviation: NA, no relevant reviews or meta-analyses available.
[a]Public health relevance was not measured for those micronutrients for which the amount of new evidence was considered small for all population groups.
[b]Conclusions of reviews and meta-analysis on same relationship were often not consistent.
[c]We judged that there was 'evidence' for an association if the authors of the reports (source 1 and 2) concluded that their was convincing or probable evidence for an association, or if the authors reported the possibility of an association which was supported by one or more recent reviews and meta-analysis (not necessarily consistent over all available publications) from the PubMed database.

'new evidence' is also recognized by other experts involved in priority setting for reviewing nutrient intake values (Yetley *et al*., 2009), whereas the concept of 'burden of the disease' is a criterion often included in tools for priority setting for health-care research and policy (Global Forum for Health research, 2000; World Health Organization, 2008b). We defined the three criteria such that they were easily measurable and reproducible in a short time frame. However, despite striving to develop an objective method, the involvement of eminence-based expert opinion was still required to compensate for the lack of a comprehensive overview of micronutrient inadequacy in different population groups in Europe. This means that our current method is based on both evidence and eminence.

It could be suggested that the qualitative to quantitative translation of criteria in the current protocol is not sufficiently well founded. Alternatively, a more thorough process could be set up to evaluate the amount of new evidence, similar to the one described by Yetley *et al*. (2009) who used 'new evidence' as a criterion to justify the review of vitamin D requirements. Further, the method of accepting evidence could be improved using, for example, guidelines published by the Scottish Intercollegiate Guidelines Network (http://www.sign.ac.uk/methodology/index.html). However, the criteria used, and the extent to which sophisticated measures are needed to measure them, will largely depend on the context of priority setting and will vary depending on the key question to be addressed. For EURRECA, the central question was which micronutrients were most important to be critically reviewed at this point in time, rather than justify whether a review was needed. Given this central question, the use of more sophisticated measures would not have resulted in a different ranking order of micronutrients. This is supported by the fact that the high priority given by IOM to vitamin D (Chung *et al*., 2009) is in line with the high ranking that we also obtained for this micronutrient.

Having completed the process, we do acknowledge that the quality of our 'simple' measures could be improved, for example, by extending the key terms in the search when identifying the amount of new evidence (such as bioavailability). Moreover, consideration might be given to consulting more experts to identify relevant additional data sources/evidence.

Use of overall ranking of micronutrients

We used the resulting overall ranking of micronutrients to assign resources to micronutrients for which recommendations are most in need of alignment. Currently, EURRECA systematic reviews relevant for estimating requirements on intake–status–health indicator associations are being undertaken for a subset of micronutrients (iron, zinc, folate, vitamin B12, selenium and iodine). This subset of micronutrients was driven by the priority ranking of micronutrients, as well as by other factors such as (i) avoidance of duplication of work already started by other organizations

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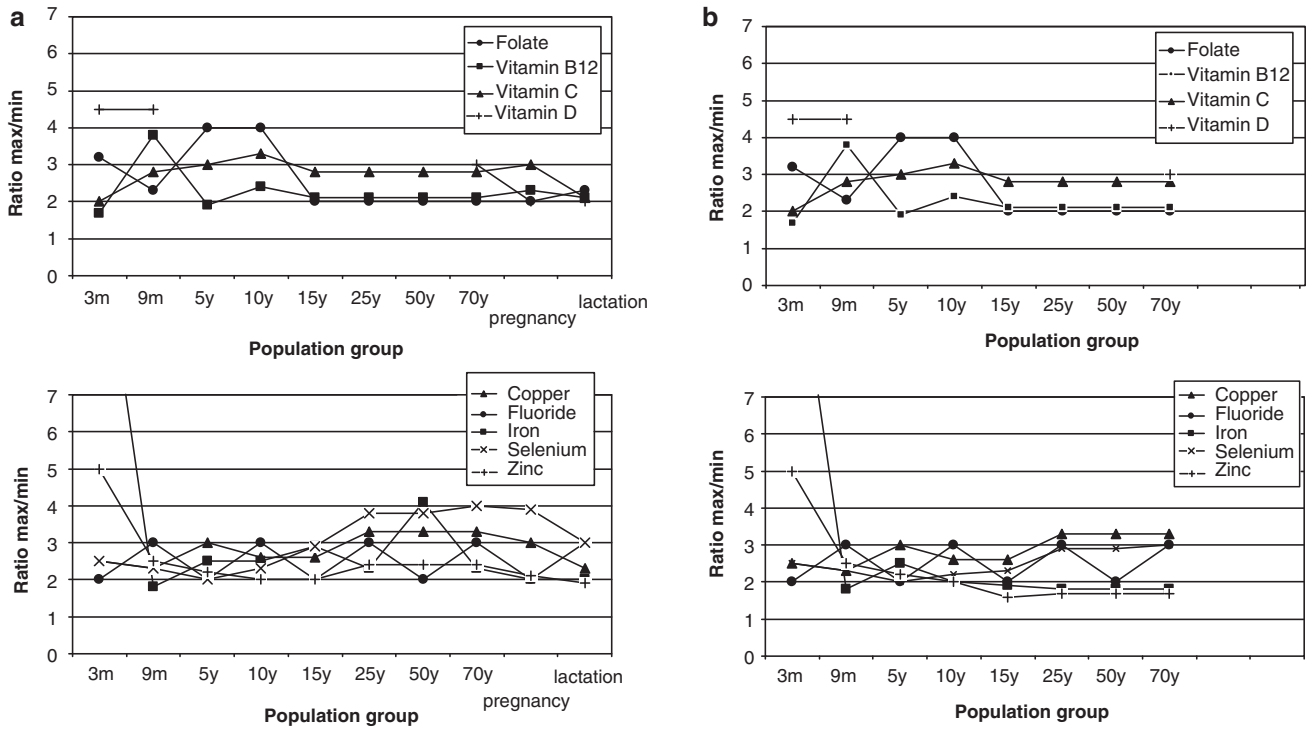

Figure 3 'Spread ratios': highest recommended value divided by the lowest recommended value for (**a**) females and (**b**) males for micronutrients for which the amount of evidence and heterogeneity was considered large (Because of the 'zero' recommendation for various age and population groups in the United Kingdom for dietary vitamin D intake, the ratios for vitamin D were often infinity and thus could not be included in the graph.).

Table 2 Priority matrices completed for the different population groups

Priority	*Infants*	*Children and adolescent*	*Adults*	*Pregnancy and lactation*	*Elderly*	*Low income immigrants*
ABC	Vitamin D, iron, zinc	Vitamin D, folate, iron, zinc	Vitamin D, folate, iron, zinc	Vitamin D, folate, iron, zinc	Vitamin D, folate, iron, vitamin B12	Vitamin D, folate, iron, zinc, vitamin C, vitamin B12
ABc		Calcium		Calcium	Calcium	Calcium, iodine, vitamin A, vitamin E, magnesium
AbC	Selenium, folate, vitamin B12, copper	Selenium, vitamin C	Selenium, vitamin B12, vitamin C, copper	Selenium, vitamin C, vitamin B12, copper	Selenium, zinc, vitamin C	Selenium, copper
Abc	Iodine, calcium, vitamin A, vitamin E, vitamin B6, fluoride, choline	Iodine, vitamin A, potassium, vitamin K, thiamin, riboflavin, choline	Calcium, iodine, vitamin A, vitamin E, magnesium, choline	Iodine, vitamin E, vitamin A, choline	Iodine, vitamin E, vitamin K, magnesium, choline	Choline
aBC abC aBc abc	Vitamin C, vitamin K, potassium, magnesium, thiamin, riboflavin	Vitamin B12, copper, vitamin E, vitamin B6, magnesium, fluoride	Fluoride, vitamin K, vitamin B6, riboflavin, thiamin, potassium	Fluoride, vitamin K, vitamin B6, riboflavin, thiamin, potassium, magnesium	Fluoride, vitamin K, vitamin B6, riboflavin, vitamin A, thiamin, potassium, copper	Fluoride, vitamin K, vitamin B6, riboflavin, thiamin, potassium
		Biotin, chromium, manganese, molybdenum, niacin, phosphorus, sodium, pantothenic acid[a]				

ABC: new evidence, most relevant for public health, heterogeneous.
ABc: new evidence, most relevant for public health.
AbC: new evidence, heterogeneous.
Abc: new evidence.
[a]Micronutrients that are allocated to the lowest prioritized groups for all population groups.

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(for example, vitamin D and calcium reviews have been initiated by IOM (Chung *et al*., 2009)), and (ii) micronutrient expertise and (iii) available resources within the EURRECA network (for these reasons, iodine and selenium were chosen in preference to vitamin C).

Health indicators relevant to the selected micronutrients have been identified and prioritized using public health reports (Institute of Medicine, 2007; Ministry of Health, 2005) and scientific literature (current evidence of a relationship, including the number of hits).

Translation to other projects

Priority setting is a frequently needed procedure for allocating resources for health-related research and health care, and yet several theoretical priority setting models in this area have been developed, published, used, evaluated and compared (Global Forum for Health Research, 2000; World Health Organization, 2008b).

To our knowledge, this is the first tool developed to explicitly address priority setting related to reviewing micronutrient requirements, using clearly defined criteria and translating qualitative into quantitative measures. It may therefore be a useful example for scientific advisory bodies responsible for reviewing micronutrient requirements and subsequently setting recommendations. Moreover, the newly developed protocol could be used as a model when developing a strategy to prioritize other policy-related questions for national and international scientific bodies addressing nutrition and its relation to health. Although the exact protocol will need modification, the main principle with regard to the derivation of transparent measurable criteria should remain.

Conclusion

Micronutrient recommendations must be regularly updated to reflect new scientific evidence. However, resources are often limited and an evidence-based transparent system is needed for prioritization. The strategy of priority setting described in this paper will provide a useful model for policy makers and scientific advisory bodies.

Conflict of interest

SJ Fairweather-Tait has received consulting fees from FSA SACN Working Group and EFSA NDA Panel and has received grant support from Kellogg's HarvestPlus, and BBsrc. The remaining authors have declared no financial interests.

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