ORIGINAL ARTICLE

Developing micronutrient reference values: prioritization of tool development by the EURRECA Network of Excellence

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Objectives: The EURRECA Network of Excellence is developing standardized methods that will guide the alignment of micronutrient reference values (RVs) across Europe. A consultation process to identify and prioritize the best practice, 'tools' or guidance for EURRECA was undertaken.

Subjects/Methods: A questionnaire was sent to 90 individuals with experience of setting or using RVs. Respondents were asked to rank the usefulness of each type of possible guidance.

Results: In all, 52% of individuals returned completed questionnaires. For the planning process, the most needed guidance was on the best way to assess the '*status quo*' of RVs; what to cover, setting priorities, how to take into consideration the diverse needs of the users; and making the whole process transparent. The most needed guidance for the active stage of development was how to obtain valid and robust data on intakes and status to use as a base for RVs; how to account for food-related factors; how to incorporate results of systematic reviews; how to identify unbiased and independent reviews and make decisions if evidence is conflicting; methods to 'weight' the evidence; and formats or concepts to convert scientific requirements into RVs. Users of RVs required guidance on communication, codes of practice to raise professional and public awareness, making them easy to use in the intended way.

Conclusions: The questionnaire responses provided views from a wide range of experts on the most needed 'tools' and standardized methodologies for the process of reviewing micronutrient RVs. This will help the EURRECA Network of Excellence to prioritize resources.

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Introduction

The EURRECA Network of Excellence (http://www.eurreca.org) is working towards the alignment of micronutrient reference values (RVs) (also known by terms such as dietary RVs, nutrient intake values, recommended daily allowances and so on) across Europe (Ashwell *et al.*, 2008). In this context, alignment refers to the alignment of principles used in developing RVs and not necessarily their values, although alignment of principles should result in greater harmonization of values.

Fundamental to this alignment is the standardization of methodologies by EURRECA. These are needed at the start for setting up panels of relevant experts and reviewing currently published global recommendation/RVs right through to communicating and facilitating correct usage of new values once published. Between these two extremes, standardization of methods to evaluate the available science and reach a consensus on micronutrient requirements for different population groups is essential.

From this standardization, EURRECA will be able to produce guidance on best practice, or 'tools', as aids for use in the derivation of micronutrient RVs for use by organizations such as the European Food Safety Authority (EFSA) and scientific panels within Member States (MS). Tools will also be produced for users of RVs such as developers of food-based dietary guidelines (FBDG), educationalists, health professionals and the food industry.

This paper reports the results of a consultation process to help identify and prioritize useful and practical 'tools' to be produced within the EURRECA framework. A questionnaire was designed to ascertain what guidance (and in what

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format) would have been helpful, had it been available, for developing RVs in the past and would, therefore, be helpful for similar future tasks.

Methods

A questionnaire was developed by the authors after initial consultation with a number of experts who had key roles in setting recommendations in the United States of America and Canada, Australasia and the European Union and its MS. It was refined after it had been piloted among the members of the EURRECA steering committee.

The questionnaire (available on the EURRECA website, http://www.eurrreca.org) had an introductory section (Part A) on the respondent's involvement in developing RVs, what they considered to be the biggest barriers to their development and whether they already had experience of useful tools. This was followed by four sections, with questions

Table 1 Numbers of respondents and their scoring, on a scale of 1–5, of types of guidance needed for planning the process for developing/updating micronutrient reference values and weighted average scores

Type of guidance	Score[a]					Average scores
	5	4	3	2	1	
Process: where to start, what to cover, setting priorities (which nutrients, which population groups) and how to take into consideration the diverse needs of the users.	26	10	5	1	1	4.4
The best way to assess the 'status quo' in terms of nutrient recommendations/reference values (for example, searchable database of those currently used in Europe/rest of the world, information on how they were derived).	20	14	6	2	0	4.2
Making the whole process transparent.	17	14	4	5	1	4.0
Personnel to involve within the project (for example, scientific experts, consumers, small and medium enterprises, industry, health professionals, teachers, policy makers and so on) and how.	11	17	10	4	0	3.8
Estimating costs and timescales.	8	11	18	4	1	3.5

[a]5 = extremely useful; 4 = very useful; 3 = moderately useful; 2 = slightly useful; 1 = not at all useful.

Table 2 Numbers of respondents and their scoring, on a scale of 1–5, of types of guidance needed for the active stage of developing micronutrient reference values and weighted average scores

Type of guidance	Score[a]					Average scores
	5	4	3	2	1	
How to get valid data on micronutrient intakes and assess whether data is robust enough to use as a base for recommendations/reference values.	28	10	5	2	0	4.4
How to get enough data on micronutrient status (and information on good biomarkers) and to assess whether it is robust enough to use as a base for recommendations/reference values.	28	11	5	2	0	4.4
How to account for food related factors; for example, bioavailability that affect requirements and recommendations/reference values.	21	12	7	2	0	4.2
How to produce or incorporate results of systematic reviews, how to identify unbiased and independent reviews; how to eliminate bias and so on.	19	16	4	3	2	4.1
Methods to 'weight' the evidence. Guidance on how to make decisions if evidence is conflicting.	18	16	8	1	1	4.1
Use of formats or concepts to convert scientific requirements into recommendations/reference values (for example, averages, ranges and so on).	20	14	4	4	1	4.1
How to avoid unnecessary extrapolation of data, such as for age groups with limited evidence (for example, statistical techniques).	16	13	13	1	1	4.0
How to account for host-related factors (environmental, genomic), which affect inter-individual variation and requirements.	16	12	13	3	1	3.9
How to deal with adaptation to low/high nutrient intake over time.	13	14	10	4	0	3.9
How to deal with knowledge gaps (no data, no experts and so on).	15	15	9	3	1	3.7

[a]5 = extremely useful; 4 = very useful; 3 = moderately useful; 2 = slightly useful; 1 = not at all useful.

Table 3 Numbers of respondents and their scoring, on a scale of 1–5, of types of guidance needed after micronutrient reference values have been published and weighted average scores

Type of guidance	Score[a]					Average scores
	5	4	3	2	1	
A system that allows you to continuously update the recommendations/reference values.	16	15	7	4	2	3.9
A system that allows you to continuously update the evidence.	16	13	11	3	2	3.8
A 'trigger' system that allows you to revisit special problem areas without complete updates.	12	13	11	5	2	3.7

[a]5 = extremely useful; 4 = very useful; 3 = moderately useful; 2 = slightly useful; 1 = not at all useful.

Table 4 Numbers of respondents and their scoring, on a scale of 1–5, of types of guidance needed to help others to use micronutrient reference values and weighted average scores

Type of guidance	Score[a]					Average scores
	5	4	3	2	1	
Communicating the recommendations/reference values, and accompanying codes of practice in order to raise professional and public awareness.	20	13	7	4	0	4.1
Making the recommendations/reference values and Codes of Practice easy to use in the intended way.	24	12	7	1	0	4.3
Producing more practical tools from micronutrient recommendations/reference values (for example, food-based dietary guidelines) to help end users.	16	19	5	0	2	4.1

[a]5 = extremely useful; 4 = very useful; 3 = moderately useful; 2 = slightly useful; 1 = not at all useful.

relating to the guidance required at each stage of setting and using micronutrient RVs:

Part B, planning the process for developing or updating RVs (Table 1).

Part C, the active stage of developing RVs (Table 2).

Part D, actions after RVs have been published (Table 3).

Part E, actions to help others use RVs (Table 4).

Respondents were asked to score each type of guidance on a scale of 1 (not at all useful) to 5 (extremely useful) and to add further clarification or make suggestions for the format of any guidance or tool, and propose any other forms of guidance that they considered to be helpful.

The questionnaire was sent to individuals who had been, or are currently, involved in setting country nutrient RVs, either in the process of setting up, running or chairing expert panels or by sitting on panels as experts. In addition, the questionnaire was also sent to some individuals whose interest is mainly in the use of RVs once they have been agreed.

The questionnaire was sent electronically during the summer of 2008, with a covering explanatory letter, to 90 people identified from the following groups:

- The EURRECA steering committee and individuals recommended by them.
- The EURRECA Scientific and Users Advisory Groups.
- Those identified by a previous EURRECA questionnaire (Doets *et al.*, 2008) to investigate stakeholder involvement.

Questionnaires were sent to individuals from the entire European Union and some candidate countries, Norway, Switzerland, the United States, Canada, Singapore, Australia and New Zealand. After 2, 3 and 4 months, reminders were sent to those who had not responded. The final date for responses was set for the end of December 2008.

Results

Response rate to survey

A total of 47 people responded to the questionnaire, resulting in a 52% response rate. Some respondents did not answer all the questions, concentrating on those that were relevant to their experience. Over half (30) had been, or were currently, involved in setting their own national nutritional recommendations in a number of ways: as the scientific secretariat, coordinator or member of the steering committee, the chair or vice-chair of a panel, as a panel member, an invited expert on micronutrient(s)/member of a working group or as an invited expert on specific population groups. Twelve experts had also been involved in setting recommendations at the European or international level. Other respondents had a variety of experience that included micronutrient requirement research, implementing RVs in areas such as nutrition policy and the development of food-based dietary guidelines, menus and recipes, or their use in assessing nutritional

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adequacy, clinical nutrition, dietetics, food supplements, fortification and product development.

Responses to the question: What are the barriers to developing RVs?

The main barrier mentioned by respondents was limited scientific evidence for determining the average micronutrient requirements of population groups on which RVs are based because of a lack of good-quality physiological, clinical and epidemiological data. The points specifically mentioned were the small size of most depletion–repletion studies; the lack of standardized methodologies; an absence of robust biomarkers to assess status and few surveys in which status is assessed alongside micronutrient intakes; a lack of precision on factors affecting bioavailability; limited data on inter-individual variation; and insufficient information with regard to adaptation and in which nutrients have more than one physiological effect. It was thought that these issues are more problematic for certain micronutrients and vulnerable population groups such as young children, females of reproductive age and the elderly.

In addition, some countries have no reliable surveys of food and micronutrient intakes and many dietary surveys have limitations. Food composition data may be limited or unreliable, surveys may not properly account for fortified foods and food supplements and national surveys may not identify target population groups.

Other barriers mentioned were lack of resources, difficulties in collecting and assessing all available evidence and the lack of knowledgeable experts willing to devote time to a science-based process. There can be disagreement on what to base estimates of requirements on, key criteria and critical cutoff points for the definition of adequate intakes and definitions to use when deriving RVs. Knowledge is lacking on statistical interpretation of experimental data and use of statistical techniques and models for producing RVs. One request was for guidance on precision of data, with advice needed on when to round up or down.

Practical and political issues were mentioned, such as obtaining international consensus on the process of deriving RVs and the actual values, conflicting advice by different medical specialities and political pressure affecting the adoption of values.

Responses to the question: What tools are already available for development of RVs?

Publications are already available on the underlying principles used by committees such as those of the Institute of Medicine (IOM) when producing their Dietary Reference Intakes (DRIs) (Institute of Medicine, 2003, 2006), as well as the reports of more recent workshops on updating RVs (Sheffer and Taylor, 2007) and the United Nations University (UNU) Food and Nutrition Bulletin publications (King and Garza, 2007; King et al., 2007).

The Australia and New Zealand review (National Health and Medical Research Council, 2006) used a streamlined process built on extensive work carried out for the US and Canadian DRIs. This involved the use of a proforma structured questionnaire for each nutrient in which expert reviewers listed the source of any new or emerging data relevant to specific topics that were not available when the IOM DRIs were set.

Responses relating to the question: What tools are still needed for RVs during the planning process?

Most respondents rated the guidance on the best way to assess the 'status quo' as extremely or very useful (Table 1). Comments were that collecting this type of data can be very time-consuming; it could be useful to analyse why different groups of experts have, in the past, arrived at different conclusions for apparently similar concepts and with similar data sets at their disposal; and that web-based, searchable databases of current recommendations would be most valuable. Transparency was said to be important for judging the quality of the data and making it easier for others to use the information.

Costs were thought to be important to the sponsors but difficult to estimate, as it depends on the quality of the work and methodologies used. It was considered irrelevant to most scientific experts, as they worked on a voluntary basis or as a part of their main job. Estimation of timescales was thought to be more helpful and a cost–benefit analysis could be worthwhile to the sponsors.

Other guidance suggested by questionnaire respondents included the following:

- Agreed definitions and methodology.
- A repository and links to other relevant projects and reports (such as other EU projects Food and Agricultural Organization (FAO, UNU, IOM and so on).
- How to tackle nonscientific issues such as policy issues, stakeholder influence and expert bias.
- How to make use of the potential commonality between nutrition and toxicology emerging in the assessment of safe and adequate exposures and in setting RVs.

Responses relating to the question: Tools still needed for RVs during the 'active stage'

The greatest perceived need was for obtaining valid data on micronutrient intakes and status and guidance on the assessment of the methods used to measure them (Table 2). Respondents stressed that without valid data from validated methodology, the reliability of the exercise is reduced, as methods used to generate data can vary widely and their limitations are not always apparent to the reviewer.

For food-related factors, nutrient-specific guidance was thought to be necessary, including a list of host-related factors affecting bioavailability.

Not all respondents were totally in favour of more guidance on producing systematic reviews with further data

interpretation. Alternative views were that this was more useful for nonscientists, and not so useful for scientists who should already be trained in this methodology. Others noted that sources of information vary so much that systematic reviews are really difficult to accomplish and, when it comes to incorporating the results, original primary publications are often preferable to the use of secondary data. It was suggested that a critique of existing methods for systematic reviews would be useful, including a minimum standard and an outline of the optimal approach, and that ideally a common database should be created.

Guidance on weighting evidence was generally thought to be useful for determining the quality of studies, and it was suggested that using real and simulated examples based on micronutrients would be most beneficial. However, there was some sceptism with a comment that expert judgement, on a case-by-case basis, considering the totality of the evidence, remains the best feasible approach.

As some countries have to set RVs despite knowledge gaps, some guidance was considered to be helpful, including some on the limitations of extrapolation and the need for transparency when arbitrary decisions are reached. An alternative view was that, as little could be done about the gaps, providing guidance should not be high priority.

Some concern was expressed that guidance on host-related factors could be so varied that it would be essential to focus on specific aspects and be micronutrient specific. Other views were that a list of host-related factors affecting bioavailability should be provided, ethnic differences should be considered for some nutrients and that genetic profiling could have an important role in the future.

The general view was that extrapolation of data is scientifically unsatisfactory, but suggestions to avoid this were made, for example, by starting work on one age/gender group and developing ideas on whether extrapolations should be made on the basis of metabolic activity, surface area, body mass, energy turnover or protein turnover according to the nutrient function.

Other useful guidance suggested by respondents included the following:

- How to deal with strong personal opinions within the working groups.
- A list of all the key steps that are required to derive RVs.
- The pros and cons of 'intermediate end points', related to future disease risk, to relate nutrient intakes (or more complex dietary patterns) to disease outcomes, especially for chronic disease in old age.
- How to extend the approach used in evidence-based medicine, already being used for other nutrition issues, for RVs.
- How to decide whether data from European studies only or studies from all industrialized countries, or indeed whether all global data, should be included.
- Which papers, journals and review literature are suitable for being considered as a basis of RVs (study design, validity, representativeness and so on).

A general point was made that any guidance is only useful if there is international consensus.

Responses relating to the question: Tools required after micronutrient RVs have been published

Respondents were less certain about the need for triggers and systems to update evidence and RVs (Table 3). A low rating was given by individuals who thought that continuous updating of the evidence was not feasible or who believed that it did not relate to them, as updates would be carried out by international organizations specifically charged with this task. Other views were that too frequent updates might confuse users such as health professionals, and that existing RVs should be reevaluated after a specified time period, for example, every 5 years.

An additional suggestion was for a tool to estimate or evaluate the impact of the implementation of the whole process, for example, on the global burden of disease (Global Forum for Health Research, 2004).

Responses relating to the question: Tools still needed for communicating RVs

The survey respondents were very keen for EURRECA to produce practical 'tools' and guidance on making RVs and codes of practice easy to use (Table 4). It was suggested that efforts should be concentrated on raising public awareness about nutrients with suboptimal intakes that could be country specific. Developing clear principles for using nutrient RVs as a basis for FBDG and for how consumers should use nutritional information was considered to be very important. For some, however, guidance on setting RVs was considered to be of higher priority than communicating them to users.

Further suggestions for guidance were the following:

- Training programmes on RVs and their use.
- Transforming RVs into 'newspaper'-unbiased language to limit misinterpretations.
- A 'Wikipedia' or glossary of phrases relating to nutritional assessment.
- Special advice for patient groups in whom RVs for the general population may be contraindicated, for example, vitamin K intakes in patients taking vitamin K antagonists (warfarin and so on) and folate intakes in cancer patients treated with antifolate drugs.
- Basic tools that concentrate on adapting science to the local context.

Discussion

Response rate and scores

The responses to the questionnaire not only gave a quantitative indication of the likely importance of each of the possible tools but also, from the extensive comments

from some of the most experienced respondents, a more detailed qualitative insight into the types of tools required, sources of help for producing the tools and potentially useful additional guidance.

The response rate to the questionnaire was just over 50%. Most of the tools were rated between 3 (moderately useful) and 5 (extremely useful) by most of the respondents, and the overall scores were quite close, ranging from 3.5 to 4.4; hence, additional respondents are unlikely to have had major effects on the overall outcome. Although detailed information was not available on nonrespondents, it is known that, similar to respondents, they included those who had experience in setting recommendation and those who were mainly users.

The range of scores indicated that all tools covered in the questionnaire were rated as useful to some degree because of the initial consultation that had already identified useful tools. The questionnaire results served to confirm that others had similar views to those initially consulted. Its main role was to prioritize the development of tools to ensure that the best uses were made of the limited EURRECA resources.

Main barriers

Not surprisingly, the lack of good data on which to base estimates of requirements was seen as the main barrier to the development of RVs. EURRECA is not positioned to conduct the original research needed to fill the data gaps; however, through a systematic review process of current literature, it will be able to synthesize current knowledge and highlight areas that are most lacking and in urgent need of attention.

Tools to be developed

A number of tools are being developed using the results from EURRECA's research and integrating activities. Publications from the United States (Institute of Medicine, 2003, 2006; Sheffer and Taylor, 2007), the United Nations University (King and Garza, 2007; King et al., 2007) and Australia (National Health and Medical Research Council, 2006), highlighted by respondents, as well as more recent ones from the United States and Canada (Taylor, 2008) and EFSA (European Food Safety Authority, 2008b), will also be used as starting points for developing guidance for Europe. Furthermore, the principles of the Scottish Intercollegiate Guidelines Network (Scottish Intercollegiate Guidelines Network, 2008) system of grading, used for medical guidelines in clinical practice, could be extended to nutrient RVs.

Process tools

One of the first tasks of the EURRECA network was to collect current micronutrient recommendations from across Europe and from other parts of the world, where recommendations have been developed, to look for similarities and divergences (Doets et al., 2008). These have now been put into a searchable database, a one-stop tool for those wanting to look up current micronutrient recommendations (Cavelaars and Kadvan et al., 2010).

Another tool that has been developed is a scientific triage process to prioritize nutrients for systematic reviewing of intake–status–health relationships, as resources can be wasted revisiting nutrients on which there is already good international agreement or for which little new data exist (Cavelaars and Doets et al., 2010). Another early task was to examine consumer and stakeholder involvement in setting micronutrient recommendations across Europe, an area in which a divergence of views is apparent (Timotijevic et al., 2010). In Australia and New Zealand, food industry and end-user representatives sat in the steering committee alongside scientists to encourage buy-in when the RVs were published.

Other tools planned as a result of questionnaire responses are a glossary of terms, a database of other relevant reports and projects, and models to help identify points in the process of decision making, highlighting those driven by science and those by policy. The need for the latter has been confirmed by a review of the process undertaken in Australasia (Thuraisingam et al., 2009).

Active stage tools

Valid data are essential for the development of RVs. The first stage of EURRECA included the collection of valid and robust data on micronutrient intake and status measures (Fairweather-Tait and Harvey, 2008; Ashton et al., 2009; Harvey et al., 2009; Lowe et al., 2009; Ristic-Medic et al., 2009; Seamans and Cashman, 2009; Serra-Majem et al., 2009; Hoey et al., 2009a, b). High scores for the questions relating to these two aspects confirm their importance, and best practice guidelines on the use of intake and status data in setting recommendations are being developed.

Systematic reviews have many purposes in nutrition (World Cancer Research Fund and American Institute for Cancer Research, 2007) and publications already exist that deal with methodology (Moher and Tricco, 2008). EURRECA partners have identified a need for a systematic review methodology to be adapted for use to assess micronutrient adequacy (Hooper et al., 2009). Following this adaptation, a template for selecting papers using best intake and biomarker methodology has been produced and, once validated, will be developed into a decision tree. As highlighted by survey respondents, a searchable database of all original papers satisfying the EURRECA quality/inclusion criteria will be built that will avoid duplication by others working on RVs in the future. Respondents emphasized the need for international consensus on any tools on methodology alignment that will help ensure different expert groups come to similar conclusions using available data.

RVs currently focus mainly on representative average groups of people, hence it will be a challenge to consider host-related factors and build individual variation into them. EURRECA will begin to consider whether micronutrient

recommendations should be given according to an individual's nutritional phenotype, by considering relationships between status and a wide range of metabolites. Adaptation to high or low intakes over time is also potentially important, but although there is need for guidance on how to deal with it, there is uncertainty with regard to the manner in which such data could be used.

EURRECA will produce tools where possible to help support the science base of micronutrient RVs. However, the best ways of achieving logical conclusions in which evidence is incomplete or conflicting will still need to be found and expert (eminent) judgement may still be needed.

Post-publication tools

Updating, either between major updates or continuously, is an issue that some organizations have been trying to resolve (National Health and Medical Research Council, 2006; Sheffer and Taylor, 2007). What would trigger an update, what method should be used and how will it be funded? Some of the EURRECA tools could be adapted to help with the decision and review processes; for example, the scientific triage used to prioritize micronutrients for review (Cavelaars et al.). If the database of quality papers can be sustained by keeping it updated with the latest key original publications and reviews that relate to RVs worldwide, it will help with prioritization and reduce workload once a review of a micronutrient has been agreed upon.

Tools for communicating RVs

It may seem obvious to communicate RVs to users to ensure that they are aware of their existence and use them corrrectly. However, rarely are sufficient budgets available for this purpose at the time that values are published. IOM published their revised micronutrient values between 1997 and 2004, but Application in Dietary Assessment (Institute of Medicine, 2000) and Health Canada's manual for health professionals (Dietitians of Canada, 2001) were published some time after the first sets. Europe should learn from this and include some kind of guidance at an earlier stage in the process of RV reviews. With the publication of the EU Health Claims (European Parliament and Council, 2007) and Addition of Nutrient Regulations (European Parliament and Council, 2006), a specific tool on the use of RVs for small and medium enterprises specializing in food production will be very timely. Tools already under development are a Wikipedia of software available for calculating nutrient intakes in Europe (http://www.eurrecawiki.com), food fortification models using the EURRECA database of RVs and guidance on food analytical methods.

It will be important to develop clear principles for using micronutrient RVs as a basis for FBDGs and for how consumers should use nutritional information. For FBDG, any guidance can be built on those of FAO and EFSA (World Health Organization, 1998; European Food Safety Authority, 2008a).

Conclusions

The responses to the questionnaire have provided the views of a wide range of experts, who have been involved in setting and using RVs, on the types of practical tools and standardized methodologies most needed during the process of reviewing micronutrient RVs. This has been extremely useful for helping the EURRECA Network of Excellence to prioritize its resources. It is important that the EURRECA concept becomes sustainable so that any tools developed are kept updated and refined and additional tools are developed in the future.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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