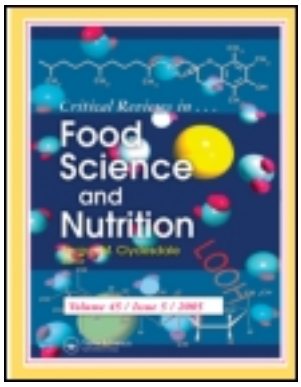

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EURRECA—Principles and Future for Deriving Micronutrient Recommendations

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EURRECA—Principles and Future for Deriving Micronutrient Recommendations

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The EURopean micronutrient RECommendations Aligned (EURRECA) Network of Excellence (NoE) explored an approach for setting micronutrient recommendations, which would address the variation in recommendations across Europe. Therefore, a framework for deriving and using micronutrient Dietary Reference Values (DRVs) has been developed. This framework comprises four stages (defining the problem—monitoring and evaluating—deriving dietary reference values—using dietary reference values in policy making). The aim of the present paper is to use this framework to identify specific research gaps and needs related to (1) knowledge available on specific micronutrients (folate, iodine, iron, selenium, vitamin B12, vitamin D, and zinc) and (2) the methodology presented in the framework. Furthermore, the paper describes the different outputs that support the process like protocols, guidelines, systematic review databases, and peer-reviewed publications, as well as the principal routes of dissemination of these outputs to ensure their optimal uptake in policy, practice, and research collaborations. The importance of ensuring transparency in risk assessment and risk management, systematic searching the literature, and taking into account policy options is highlighted.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Critical Reviews in Food Science and Nutrition* for the following free supplemental files: Additional tables.]

Keywords EURRECA, research gaps, dietary reference values, framework

INTRODUCTION

Currently, the approach by which Dietary Reference Values (DRVs) for micronutrients are derived, as well as the reference values themselves, varies considerably across countries. In order to harmonize and align nutrition policy and public health strategies in Europe, the *EURopean micronutrients RECommendations Aligned* (EURRECA) Network of Excellence (NoE) was funded by the European Commission Framework Programme 6. EURRECA developed a series of activities to support the harmonization of methodologies for deriving European micronutrient reference values, which form the basis for nutrient recommendations. In this paper, we consider the average requirement (AR) and the AR plus two times its standard deviation (SD) as the key DRVs for micronutrients (see Fig. 3 in van't Veer et al., 2013a).

The present paper outlines EURRECA's final conclusions that originate from the EURRECA NoE outcomes as described in the current issue of Critical Reviews of Food Science and Nutrition. This current issue represents the EURRECA final report reaching a total of 10 papers that concentrate on the evidence and methodology for deriving micronutrients requirements and DRVs for micronutrients. As part of this EURRECA final

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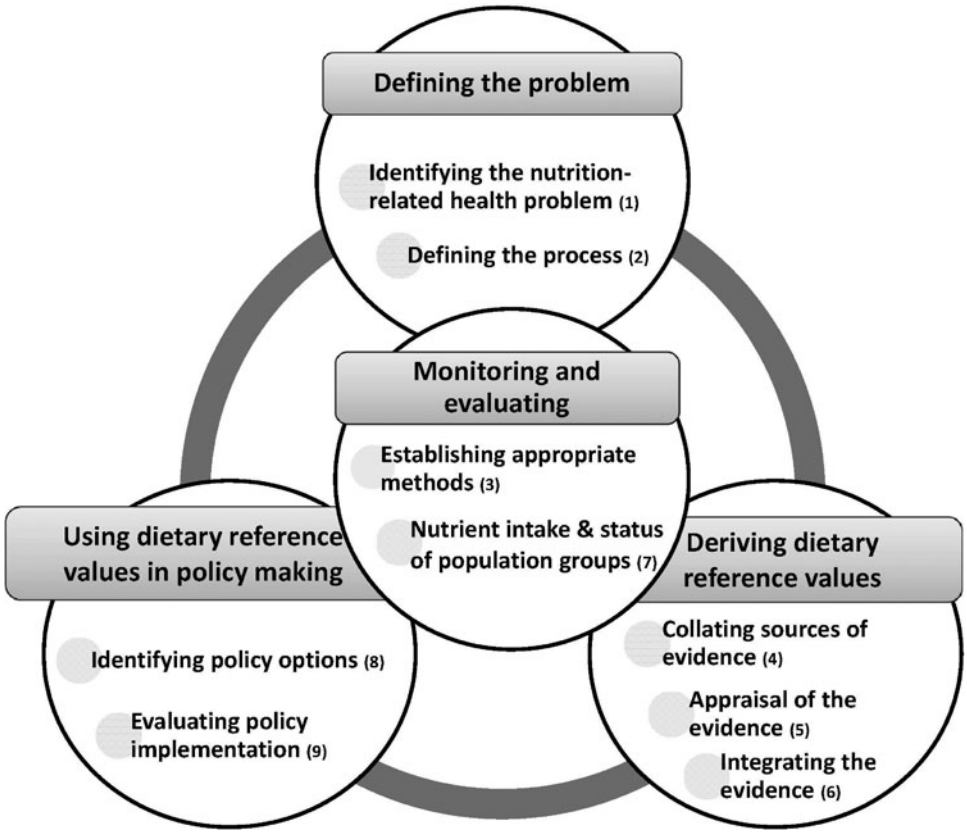

Figure 1 EURRECA framework that can be used for deriving and using micronutrient Dietary Reference Values (DRVs). The framework consists of nine activities clustered in four different stages.

report, the introductory part, which corresponds to the paper entitled "EURRECA—Framework for aligning micronutrient recommendations," provides the background and purpose of the EURRECA NoE. The second part, which is described in the paper "EURRECA—Evidence-based methodology for deriving micronutrient recommendations," focuses on the methodological description of the process for setting micronutrient DRVs as identified by the EURRECA NoE. To apply this methodology, the third part of the EURRECA final report covers the estimation of individual micronutrient DRVs for deriving recommendations for six case studies: folate, iodine, iron, selenium, vitamin D, and zinc. In addition, a paper on developing public health nutrition policy based on micronutrient DRVs develops a framework for considering the evidence. Finally, the present paper summarizes the concept and its key messages, then concentrates on the research needs/gaps and describes the final outputs, and the scientific dissemination and impact of EURRECA.

THE EURRECA FRAMEWORK FOR DERIVING AND USING MICRONUTRIENT REQUIREMENTS

The resulting EURRECA approach, which is transparent and systematic, can be summarized into its framework for deriving and using micronutrient DRVs (see Figure 1 for a visual representation).

This EURRECA framework combines the evidence base from scientific research and policy making with the process of setting micronutrient recommendations. This framework deals with nine activities summarized in a checklist that ideally could be used for deriving DRVs (Table 1). However, it is possible to use only the most relevant and urgent activities depending on the needs and resources available at a particular time and place. The nine activities of the framework can be clustered into four stages: (i) defining the problem, (ii) monitoring and evaluating, (iii) deriving DRVs, and (iv) using DRVs in policy making (described in brief hereunder).

An earlier representation of the process depicted the activities as sequential (Matthys et al., 2011), which was revised and extended to its current form (van't Veer et al., 2013a).

The main objective of EURRECA was to identify a process for deriving DRVs for micronutrients (activities 4, 5, and 6). This required the formulation of a clear definition of the micronutrient-related health problem(s) (activities 1 and 2), and the eventual purpose of reference values in policy development (activities 8 and 9). These three stages are underpinned by a central fourth stage "Monitoring and evaluating." This fourth stage comprises two closely related activities: (i) the assessment of micronutrient intake and status in etiological and monitoring

Table 1 Overview of the EURRECA stages, activities, and topics dealt with in each activity

Stage	Activities	Activity topics
Defining the problem	Identifying the nutrition-related health problem (1)	• Health outcomes • Population groups • Micronutrients
	Defining the process (2)	• Scientific Advisory Bodies • Risk assessment and risk management • Communicating findings to policy decision-makers
Monitoring and evaluating	Establishing appropriate methods (3)	• Assessment of dietary micronutrient intake • Assessment of micronutrient status
	Nutrient intake and status of population groups (7)	• Assessing dietary intake and nutritional status • Assessing health status reflecting the nutritional status • Identifying vulnerable groups • Determinants of micronutrient inadequacy
Deriving dietary reference values	Collating sources of evidence (4)	• Systematic data collection • Factorial approach and bioavailability • Dose–response approach • Inter-individual variability
	Appraisal of the evidence (5)	• Study design: observational studies and RCTs • Evaluation of heterogeneity • Overall quality of the evidence
	Integrating the evidence (6)	• Quantification • Expert consultation • Factorial and bioavailability approach • Dose–response model • Scaling of ARs to other population groups • Biological modeling for multiple micronutrients
Using dietary reference values in policy making	Identifying policy options (8)	• Identify policy goals • Evaluate evidence • Select appropriate policy action • Explicit and transparent process
	Evaluating policy implementation (9)	• Current policies in Europe • Policy evaluation measures • Barriers to policy implementation

studies (monitoring, activity 3) and (ii) the use of dietary intake data from monitoring studies to identify nutritional inadequacy (evaluating, activity 7). The circular nature of the diagram indicates that it is a continuous and interactive process in which all the stages are interlinked and have the potential to feed into each other. Furthermore, this representation allows taking into account any one stage of the process together with the option to use a reiterative process between the various activities for adaptation on a case-by-case basis. Having distinct activities ensures that the process is sufficiently transparent to allow applicability and reproducibility by various scientific advisory bodies. For methodological details of the description of the stages and activities, please see in this issue (Dhonukshe-Rutten et al., 2013) and for an application to various micronutrients, please consult also this issue (Cashman and Kiely, 2013; Harvey et al., 2013; Hoey et al., 2013; Hurst et al., 2013; Lowe et al., 2013; Ristic-Medic et al., 2013; Timotijevic et al., 2013).

KNOWLEDGE GAPS IN THE EVIDENCE ON SPECIFIC MICRONUTRIENTS

This section summarizes specific research gaps and needs that were identified through the application of the micronutrient requirement process framework to six micronutrients (folate, vitamin B12, iodine, iron, selenium, and zinc) for:

- the factorial approach (Cashman and Kiely, 2013; Harvey et al., 2013; Hoey et al., 2013; Hurst et al., 2013; Lowe et al., 2013; Ristic-Medic et al., 2013; Timotijevic et al., 2013), and
- the dose–response approach.

Both approaches are described in detail elsewhere in this issue (Dhonukshe-Rutten et al., 2013). Table 2 shows an overview of research gaps and needs for selected micronutrients, by study approach and includes population groups, bioavailability, intake, status-health, and health outcomes.

FACTORIAL APPROACH

For the factorial approach, the available evidence on micronutrient losses and needs for growth, pregnancy, and lactation tends to be very limited, especially for some vitamins such as vitamin B12 and folate, for which older studies lack recent methods for assessing plasma levels. Studies also included small population groups and often did not address all factors in the model; furthermore whole meals or food patterns (essential to

Table 2 Examples of research gaps and needs for selected micronutrients, by study approach

Micronutrient	Factorial approach	Dose–response approach
Folate	For all *population groups*, there are very limited data. *Bioavailability*: Interactions of other B-vitamins (B12, B6, riboflavin) and choline and bioavailability of folate.	*Intake*: Accurate data on folate intake, both natural food folate and folic acid (supplements, fortified foods). *Intake-health*: Standardization of health outcomes for CVD, cancer, and cognition would facilitate meta-analyses. *Status-health*: Data needed on folate status and health outcomes in infants, children, adolescents, pregnant and lactating women. *Health outcomes*: Adverse effects in addition to benefits, for example, in populations already with high folic acid intakes (fortified population, supplement users).
Vitamin B12	*Population groups*: There are no factorial data for children, adolescents, pregnant or lactating women. Reference values, where present, are currently based on scaling from adults and elderly.	*Intake-health*: Standardized measures for health outcomes are needed, particularly for cognitive outcomes and bone health. *Status-health*: Data needed on functional markers of vitamin B12 status (MMA and holoTC); relationship between B12 biomarkers and liver stores is not clear.
Iodine	*Population groups*: There are no factorial data for children, adolescents, pregnant or lactating women and elderly. *Bioavailability*: There was limited data of iodine absorption from whole diet.	*Intake*: Very limited data on iodine intake assessment. *Intake-health*: RCTs across all population groups and life stages with measuring relevant long-term health outcomes are needed to generate robust data. *Health outcomes*: Standardized measure of assessing cognitive function and reference ranges for thyroid function tests are needed.
Iron	*Population groups*: Effect of gender and menopausal status on obligatory losses and needs for lactation and in elderly are controversial. *Bioavailability*: Host-related factors that affect bioavailability and requirements are insufficiently studied, especially from whole diets.	*Intake-status*: Very few trials in the low-dose range. *Status markers*: Biomarkers of iron status need to be assessed in combination; the part of their variation due to infection/inflammation must be accounted for by measuring proper inflammatory markers. *Health outcomes*: Scarcely studied, little data on requirements for growth and development in the young.
Selenium	*Population groups*: Selenium demand for testes and prostate function during puberty and adolescence needs attention.	*Status-health:* The joint effect of selenium biomarkers, SNPs, and status/health outcomes needs attention; as does interaction with, for example, iodine and vitamin E.
Zinc	*Population groups*: There are little data on young children, pregnant or lactating women. *Bioavailability*: Phytate, calcium, and iron need attention because they may be potent modifiers.	*Status-health*: Need for reliable and sensitive marker for zinc status, and for better characterization of signs and symptoms of suboptimal intake.

calculate a dietary bioavailability factor) were not addressed; additional needs for growth, pregnancy, and lactation (folate) or related to ageing (vitamin B12) cannot be easily determined. Therefore, micronutrient balance is difficult to assess and this hampers the derivation of reference values.

For trace elements like iron and zinc analysis, methods are more widely available and the body of evidence is less restrictive. However, the chemical species of the trace elements still affect bioavailability, especially because they can be bound to factors in the food matrix (e.g., heme and non-heme iron; inorganic and organic species of selenium). Knowledge gaps in this area are mainly related to the availability of micronutrients from specific foods and the availability from whole diets. For both the vitamins and the trace elements, estimation of both losses and additional needs must be improved. This requires further research into both the nature of the micronutrient exposure from the food matrix and its relevance to functional biomarkers that critically depend on the micronutrient.

The majority of factorial estimates and bioavailability studies were conducted in population groups that may not be suitable for extrapolation to the general population. This hampers their generalization to other subgroups of the population, and the derivation of additional needs for growth, pregnancy, and lactation, or in old age.

DOSE–RESPONSE APPROACH

The dose–response approach builds on the rationale of the Institute of Medicine to separate out the sequential steps in the causal chain starting with micronutrient intake, via intermediary biomarkers to the eventual health outcome. To achieve this, EURRECA included randomized trials and cohort (nested case-control) studies to assess the associations between either (1) micronutrient intake and biomarkers of status (mainly randomized control trials (RCT)), or (2) micronutrient intake and health outcomes (mainly cohorts, some RCTs), and finally (3) between markers of micronutrient status and health outcomes (cohort studies). As compared to the factorial approach, the total body of evidence appeared much larger for dose–response studies, especially when the relation between dietary intake and markers of nutrient status was considered.

For studies on *health outcomes,* the body of evidence on micronutrient intake or biomarkers of nutrient status was

often limited to a handful of cohort studies that used different assessment methods (for intake and biomarkers), as well as different methods to assess the health outcome. Although these different study types partially reflect the advancement of research, their heterogeneity hampers quantitative summarizing of the associations by meta-analyses and their subsequent use in deriving DRVs. In addition, most associations with health outcomes tended to be weak, because of the multifactorial nature of most health outcomes and methodological constraints in dietary assessment. When biomarkers were used as proxies for exposure (e.g., for vitamin B12 and fracture risk), or where supplements were used (e.g., for iodine and thyroid-related outcomes), the associations tended to be stronger.

A substantial amount of evidence was available on the association between dietary intake and *biomarkers of intake*/*status*, mainly based on RCTs and cross-sectional analyses of baseline data in cohort studies. In EURRECA, associations reported from the RCTs were used in meta-analysis to predict the intermediary biomarker by the level of intake (dose) from RCTs. Because in RCTs the dose provided is known (rather than assessed by, for example, food frequency questionnaires (FFQs)) such an analysis is minimally affected by errors in the exposure (as compared to dietary assessment methods) and can be used to derive DRVs, when a cut point for the biomarker has been established. Although this approach, like the factorial approach, addresses intake and status, it is of interest that the available evidence for these dose–response associations was considerably larger than for the factorial approach.

METHODOLOGICAL ISSUES, GAPS, AND OPPORTUNITIES

The methodological issues and research needs that were identified while setting up the micronutrient requirement framework are summarized below. For an overview of the key methodological research gaps and needs, see Table 3 (Cashman and Kiely, 2013; Harvey et al., 2013; Hoey et al., 2013; Hurst et al., 2013; Lowe et al., 2013; Ristic-Medic et al., 2013; Timotijevic et al., 2013). Since the EURRECA NoE mainly focused on the methodology for deriving and setting micronutrient recommendations, this section does not cover the stage "Defining the problem."

Monitoring and Evaluating

The assessment of food and nutrient intakes is challenging and prone to reporting errors, especially among infants, children, and adolescents. While using appropriately validated methods for measuring food intake is essential, specific consideration should also be given to mineral and vitamin supplements and the time-period covered by the dietary assessment methodology in this population group. However, validation studies of FFQs are necessarily restricted to recovery biomarkers (e.g., urinary nitrogen, potassium) and/or the presence of correlated errors (e.g., between FFQs and 24 hour recalls). Reliability for micronutrients can therefore only be inferred from evaluation studies addressing protein, potassium, and a few other nutrients, in combination with expertise on micronutrient composition of foods and dietary habits of the study population. Thus, apart from innovative approaches to the validation of micronutrient intakes, transparent methods for appraisal of dietary assessment methods for micronutrients require appropriate scoring components. Furthermore, there is a well-established need to develop improved biomarkers of status for many micronutrients. It is essential to identify (potential) vulnerable groups (i.e., immigrants, Central and Eastern European (CEE) populations, and children, pregnant and lactating women) who are at risk of inadequate micronutrient intake and/or status. However, because of inherent limitations of dietary assessment, it should be kept in mind that this way of identifying risk groups usually requires subsequent in-depth surveys to confirm whether indeed nutritional status is inadequate in the population groups identified. Although EFSA is currently collecting data on nutrient intake from all over Europe (EFSA, 2009, 2012), harmonized pan-European nutrition surveillance has not yet been implemented. Such data would help with the identification of risk groups for micronutrients, the derivation of DRVs, and the formulation and evaluation of policies.

Table 3 Key methodological research gaps and needs

→ Standardization and calibration or appraisal of research methods, data analyses, reporting formats, to allow better exploitation of results.
→ Standard protocols and training for searching and data extraction. Meta-analysis and organizing common data sets allowing cumulative meta-analysis when new research data become available.
→ Public domain data sets allowing "individual patient data" rather than meta-analyses to summarize and integrate data. Shared data formats for data storage of individual studies.
→ Development of data synthesis methodologies, such as the stochastic Intake-Status-Health model to tri/multivariate models, allowing for other nutrients and covariates.
→ Development of systems biology approaches to improve understanding of micronutrient function in molecular and pathophysiological pathways relevant to intermediate health outcomes and clinical disease.
→ For the EURRECA top 10 micronutrients information on intake and status in children, pregnant and lactating women in Europe are lacking, and data for all stages of the life cycle in Central and Eastern Europe are insufficient.
→ Lack of scientific evidence on micronutrient intake/status associated with socioeconomic position (education, occupation, income, ethnicity, urban/rural area) for Central and Eastern European populations for all life stages.

Deriving Dietary Reference Values

Despite the initially large number of papers identified in the *systematic literature searches*, only a limited number of RCTs and observational studies with sufficient quality and usable data remained after screening titles, abstracts, and extracting data. The efficiency of this time-consuming process could be improved by more efficient searching technologies, possibly incorporating a priori expert knowledge, open-access micronutrient-specific databases standardized reporting formats for research, and standardized databases with study results, all preferably based on open-access databases of original research data. Currently, for the majority of micronutrients there is a paucity of data, particularly in relation to health outcomes. In many instances, there are poorly reported or low-quality studies with a number of factors potentially disturbing the dose–response relation between intake, status, and subsequent health outcomes. As a result, the evidence base is often heterogeneous in nature or contains gaps that limit their analysis and subsequent inference. Methods for appraisal of the evidence are in place, but they are tedious and require much expertise and judgmental issues; moreover, quantitative methods aiming to attribute the between-study variation of results by methodological and/or biological study-characteristics tended not to be very successful in explaining the heterogeneity. Standardization and calibration of dietary assessment methods, biomarkers and health outcomes, and development of shared and accumulating open-access databases with "individual patient data" can lead to improvements.

Many current DRVs are based on *estimates of losses, additional needs, and bioavailability*. These estimates are usually obtained from independent studies and their uncertainties, random and systematic errors carry over to estimates of DRVs. Little work has been done to estimate the extent of these errors. Similarly, the dose–response approach cannot directly lead to estimates of DRVs, as it requires at least additional information on the usual micronutrient intake and status of populations. In addition, both the factorial and dose–response approach to derive DRVs require a cut-off point for "normal" or "suboptimal" function or health outcome/disease risk. When intermediary or clinical health outcomes are used (e.g., pernicious anemia in vitamin B12 deficiency, or assuming minimal liver stores of B12), study groups may be afflicted with additional health issues affecting the results. The choice of intermediary markers and their presumed (or demonstrated) association to health outcomes (e.g., cancer, stroke, and fracture incidence) can strongly influence the assessment of DRVs. Moreover, the markers of status or health outcome necessarily contain random error and possibly systematic error as well. Such errors are usually ignored when deriving DRVs and in evaluation of micronutrient intake of individuals and populations. From a scientific point of view, insight into the implications of such errors in deriving and applying DRVs would be valuable. Thus, although deriving DRVs at first sight seems a purely scientific risk assessment task, the act of choosing cut-points for (functional and intermediary) health (outcomes) implicitly incorporates its implications for health and well-being of populations (i.e., the prevalence of inadequacies, disease risk), and therefore necessarily contains a policy component. Clearly, the central role of biomarkers in the dose–response approach and its potential to address health outcomes fits to the need to shift from preventing deficiencies to optimizing health in the current Western and non-Western setting. The least that is required is a widely accepted list of (bio)*markers with their cut-off values* as well as a clear view on the most important policy objectives (disease risk and prevalence).

In EURRECA, a *stochastic approach* was developed to enable utilization of dose–response data for deriving DRVs. For this method, both dose–response data and data on nutrient intake and status in populations must be available from cross-sectional studies, for example, nutritional surveillance data (activities 3 and 7). Although this method requires further development, it can possibly widen the incorporation of research data that have not been used before, and can result in estimates of DRVs such as the AR as well as recommendations for individual and population intake levels. The model can shed light on implications of errors in variables, and it can incorporate both meta-analysis and individual patient data, covariates and additional health outcomes. In addition, further opportunities such as biological modeling for multiple nutrients need to be explored into more detail before it can be applied to deriving DRVs and their subsequent application by Scientific Advisory Bodies (SABs) in either nutritional recommendations or in the evaluation of population intake distributions. For the time being, the stochastic approach is consistent with the relevant concepts of DRVs and with knowledge on errors in dietary assessment; moreover it enables researchers to incorporate a wider body of evidence into deriving ARs and to compare the consistency of results with factorial estimates.

Using Dietary Reference Values in Policy Making

The derivation and application of DRVs to support nutritional policies in Europe would benefit from evidence obtained from nutrition surveillance, including status biomarkers, thus supporting both policy development and evaluation. EURRECA's research suggests that regardless of the quantity and quality of science, institutions and their wider context play a key role in defining the potential for a policy option to be adopted and developed. *Uncertainties* in the evidence dilute the potential impact of the evidence, for example, because of imperfections in study methods, design and internal validity or because of uncertainties on behavioral aspects that underpin an individual's diet. In addition, the policy context can be framing decisions about what evidence to allow or what stakeholders to engage. Furthermore, it was noted that interpretations of what is meant by the term "health" vary widely and may differ when considering public

health nutrition policy (health as a "resource for living") or in deriving micronutrient reference values (biomedical indicators of nutrient status, health, and disease). Broadening or narrowing the definition of health may have a direct effect on the health policy or reference values chosen. More research is needed to better understand this relationship. At the national level, transparency in the remits of SABs can be improved by distinguishing between the task of setting DRVs (risk assessment) and the act of setting population micronutrient recommendations (risk management), thus ensuring greater transparency of the process and more open engagement with stakeholders. Where, within the context of risk assessment, judgments are being made on the basis of policy-making realities, these should be justified and made explicit. Further development of EURRECA's Public Health Nutrition Policy-making Framework could be used to support this. Moreover, the considerations and types of evidence used to inform policy decisions need to be clearly articulated. SABs in EU countries may adapt DRVs set by EFSA or others to their own countries population characteristics and health issues. The criteria and procedures used for such adaptation differ between countries and there is a need for sharing of best practice and alignment where appropriate. Finally, to achieve the former, it is relevant to better understand how the SABs are embedded in the institutional infrastructures and how they communicate with other bodies who might have related but different remits, for example, different government departments (Agriculture, Trade, Education), those responsible for food safety versus nutrition, clinical versus public health.

OUTPUT AND IMPACT OF EURRECA

EURRECA's Output

Over the course of the 5.5-year project, EURRECA generated different kinds of outputs, for example, best practice guidelines, protocols, and search strategies for systematic reviews, case studies, databases, internal reports, and peer-reviewed publications. The EURRECA outputs can be categorized as (1) network communication, (2) final output (EURRECA's final report), (3) publications/reports (including decision trees, guidelines and/or frameworks), (4) e-learning tools, which are important for the acquisition of knowledge, skills, and competencies, and (5) databases and software programs, which disclose information sources, relevant data, and knowledge, as shown in Table 4. The integrated platform of instruments will, in particular in CEE countries, contribute to future capacity building development in nutrition (Pavlovic et al., 2009).

Since EURRECA covered multiple micronutrients and different population groups, harmonized guidelines, and a general protocol for systematic reviews were prepared. From this, separate protocols, including the search strategy used, were developed for each systematic review to ensure that they were all done in a similar and aligned way. The main advantage of this way of working is that with these detailed protocols the existing systematic reviews can be easily updated not only by EURRECA partners but also by other scientists or stakeholders that are interested in further building on EURRECA's results. Guidelines and protocols that were developed in relation to the performed systematic reviews will be made publically available.

EURRECA's Impact

To ensure optimal uptake and use of EURRECA's outputs in policy, practice and research, collaborations were sought with key stakeholders, including other scientists to make sure that most, if not all, outputs can and will be used in future research. The principal routes of dissemination of EURRECA outputs, including how these may be used by authorities or institutions, that is, EURRECA's impact, are depicted in Figure 2 and described below.

EURRECA's Network Communication, Publications, E-Learning Tools, and Databases

All peer-reviewed publications resulting from the EURRECA NoE are listed on www.eurreca.org and will, copyrights allowing, be publicly available. Non-peer-reviewed reports are also available with the proviso that their development and review is only internal to the EURRECA consortium.

The Nutri-RecQuest database (see Table 4) is a user-friendly software tool that allows easy access of data on current recommendations for 28 different micronutrients from 37 European countries, eight key non-European countries/regions as well as recommendations set by the European Commission and World Health Organisation/Food and Agriculture Organisation. The database will be transferred to WHO Europe where it will be integrated into the WHO European Database on Nutrition, Obesity and Physical Activity (NOPA). The unique platform that was developed to easily access the data cannot, unfortunately, be taken over by WHO Europe. Micronutrient WIKI, the Nutritional Phenotype Database, and EURRECAWIKI are freely available on www.eurreca.org. NutPlan and the EURRECA tool for extracting data on nutritional adequacy and its determinants are for internal use only and will therefore not be publically available. The e-learning modules can be used as part of a course by any university upon request. In this regard, they are, for example, being used in the international advanced courses "Exposure Assessment in Nutrition Research" as well as in "Nutritional and Lifestyle Epidemiology" organized by the Division of Human Nutrition of Wageningen University in cooperation with the Graduate School VLAG (www.vlaggraduateschool.nl).

Sharing Systematic Review Protocols and Databases

Through use of standardized guidelines and search strategies, all systematic reviews are easily reproducible and

Table 4 Inventory of EURRECA outputs

Output category	Outputs	Short description
Network communication	Introductory film	A short film intended as an introduction to the EURRECA Network of Excellence – its mission, work streams, people, and progress
	Podcast	Interviews of EURRECA partners bringing specific aspect of the work performed by the consortium in the spotlight.
	Webinars	1. A 20-min slide show that aims at presenting EURRECA objectives and key outcomes to a large audience. 2. Webinars from the EURRECA/WHO Workshop "Deriving micronutrient recommendations: updating best practices." The webinar will comprise the following presentations: • Anja Brönstrup: EFSA – How are dietary reference values for micronutrient intakes set? (slide presentation only) • Luz Maria de Regil: WHO – What are the current issues in setting micronutrient intake recommendations? (slide presentation only) • Pieter van't Veer and Lisette de Groot: EURRECA flowchart: Theoretical background and practical application in the case of vitamin B12. (audio presentation with slides) • Laura Contor: Workshop's general conclusions. (audio presentation with slides)
Final output	EURRECA final report	The EURRECA final report presents a key outcome of the Network. The final EURRECA framework aspires to be used as a practical tool for defining the appropriate process for deriving DRVs. It brings together scientific research and evidence base with policy decision making to achieve a transparent and systematic approach to setting micronutrient recommendations. This report is collating most of the outcomes of EURRECA and comprises of five parts: 1. Introductory part: "EURRECA – Framework for aligning micronutrient recommendations" (van't Veer et al., 2013a) 2. Methodological part: "EURRECA – Evidence-based methodology for deriving micronutrient recommendations" (Dhonukshe-Rutten et al., 2013) 3. Case studies: Six papers that apply the EURRECA methodology on a specific micronutrient and one paper focusing on policy aspects (Cashman and Kiely, 2013; Harvey et al., 2013; Hoey et al., 2013; Hurst et al., 2013; Lowe et al., 2013; Ristic-Medic et al., 2013; Timotijevic et al., 2013) 4. Concluding part: EURRECA – Principles and future for deriving micronutrient recommendations (current manuscript) 5. Executive summary (Contor et al., 2013)
Publications/reports	Peer-reviewed papers (150)	EURRECA peer-reviewed papers (to date, 110 published since 2007) and presentations at key events and exhibitions (e.g., 65 in 2010).
	Non-peer-reviewed reports (32)	EURRECA unpublished deliverables: • Guidance documents (11) • Reports (18) • Protocols (3)
E-learning modules	Dietary assessment modules	To provide insights in the aims and principles of evaluation studies in the context of nutritional research.
	Nutrient requirements and recommendations module	To provide an insight into how nutritional reference values are derived and how they can be used in evaluating nutrient intake adequacy at both the group and the individual level.
	Study designs and assessment of validity module	To provide insight into the characteristics of epidemiological study designs and to critically evaluate the internal and external validity of these studies.
Databases and software programs	Nutri-RecQuest	A database holding all data collected for the recommendations, as well as additional data tables (e.g., with conversion factors for different units used). It contains recommendations for 29 micronutrients from 37 European countries and eight key non-European countries as well as general information about the source of these recommendations and scientific background information. The database contains information for different population groups: infants, children, and adolescents, adults, elderly, pregnant and lactating women (Cavelaars et al., 2010).
	Micronutrient WIKI (NuGO)	A freely accessible webpage describing the relationships of micronutrients status or intake and the relevant markers along with the accompanying references (http://www.nugowiki.org/index.php/Category:Micronutrients). Micronutrient WIKI does not present comprehensive reviews of available data but rather an expert-based opinion including relevant scientific references.
	Nutritional phenotype database (dbNP)	A freely accessible infrastructural project that is designed to facilitate storage of biological relevant, pre-processed "–omics" data, as well as study descriptive and study participant phenotype data. It enables integration and interrogation of data from multiple studies, different research groups, different countries and different "omics" levels (www.dbnp.org) (van Ommen et al., 2010).

Table 4 Inventory of EURRECA outputs *(Continued)*

Output category	Outputs	Short description
	EURRECA WIKI on nutrition software	An inventory of nutrition software used to assess the nutrient intake of an individual or a population group, including necessary information to help make an informed choice on nutrition software available in 13 countries. It was originally developed as Wikipedia-related nutrition software but is now frozen and therefore cannot be updated anymore. It is publically available on www.eurreca.org/everyone/8247/5/0/32.
	NutPlan	A user-friendly software program that can be used for individual and group nutrition planning, recipe calculation, creating food labels, diet planning, and nutrient intake assessment. NutPlan mainly focuses on Eastern European and West Balkan countries (Gurinovic et al., 2010) and is not publically available.
	EURRECA tool for extraction of data on nutritional adequacy and its determinants	A tool that can be used for the extraction of the data on micronutrient intake and status for all population groups; in addition it accommodates information on socioeconomic and cultural determinants associated with intake and/or status. Currently, it is a database of the extracted data and the software tool is accessible only with a username and password (http://www.serbianfood.info/eurreca_low/main_low.php), which can be obtained upon request.
	Systematic review databases (68)	A set of EndNote and Access databases including the search protocols used. The EndNote databases contain all selected references fulfilling the inclusion criteria. The same references were also extracted to a standardized Access databases to which additional relevant information, like methodological details, study groups, and population characteristics, was added (see supplementary Tables 1–7, available online).

updatable. The systematic research (SR) protocols and databases are being shared with EFSA's panel on Dietetic Products, Nutrition and Allergies (NDA) to input into the review and update of the reference values for nutrient and energy intakes established in 1993 by the Scientific Committee on Food (see http://www.efsa.europa.eu/en/topics/topic/drv.htm). The micronutrients prioritized by EFSA's NDA panel are vitamins A, C, D, folate, choline, potassium, iron, zinc, iodine, manganese, copper, and fluoride. Since the NDA panel aims to limit the overlap with activities of other authorities/networks as much as possible, they will take the outcomes of, for example, EURRECA's systematic reviews for common micronutrients into consideration.

The Biomarkers of Nutrition for Development (BOND) Program will use the literature search strategies developed by EURRECA and model its strategy after EURRECA. The BOND project was initiated in 2010 by the Eunice Kennedy Shriver National Institute of Child Health and Human

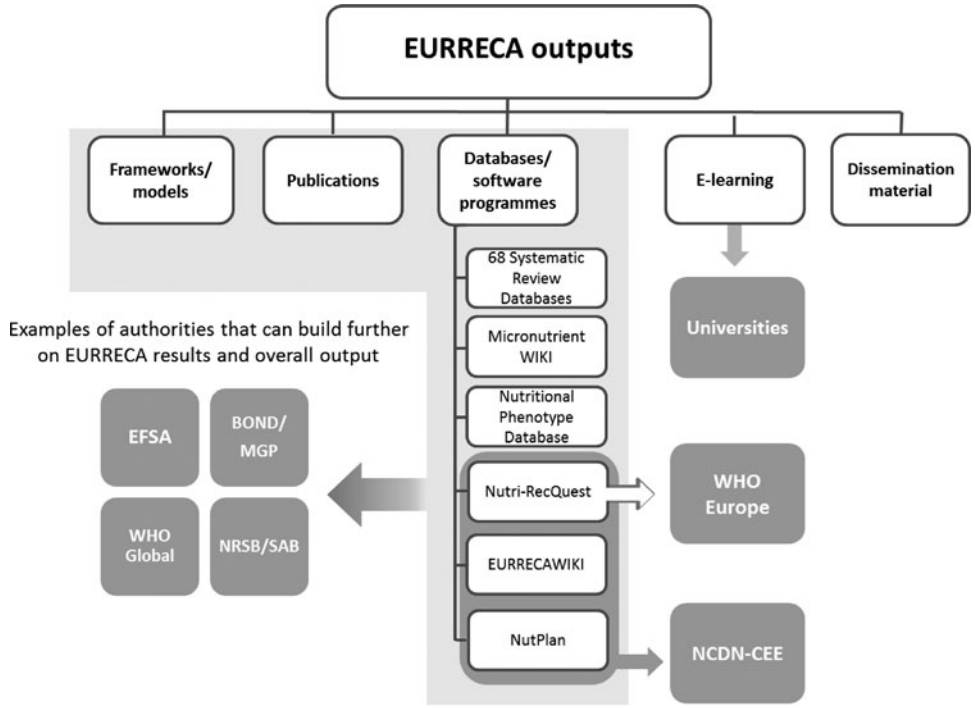

Figure 2 Dissemination and impact of EURRECA.

Development (NICHD) of the National Institutes of Health (NIH)/US Department of Health and Human Services (USDHHS), with support from a consortium of partners representing the global food and nutrition enterprise (see http://www.nichd.nih.gov/global_nutrition/programs/bond). The goals of BOND are to identify and address the need for discovery, development, and implementation of reliable and valid biomarkers.

EURRECA's SR databases have been made available to WHO's Department of Nutrition for Health and Development, based at WHO's headquarters, to, where applicable, make use of these in the WHO evidence-informed guideline development processes. WHO is currently tasked with updating or developing guidelines on, among others, iron supplementation, food fortification for vitamin A, iron, folic acid, iron and iodine; as well as considering indicators of vitamin and mineral status (e.g., for anemia, iron, vitamin A, and folate status). To do so, the WHO Guideline Steering Committee, WHO Nutrition Guidance Expert Advisory Group, and an External Experts and Stakeholders Panel were set up. As a result of the slight difference in the scope of the work to be done by WHO's Department of Nutrition for Health and Development compared to that of EURRECA, WHO's main interest is in the databases describing relevant papers and to a lesser extent in the developed protocols.

In addition to providing all SR protocols and databases directly to EFSA, BOND, and WHO Global, they will also be made publically available (www.eurreca.org) so that other organizations, like FAO, UNICEF, and UNSCN (United Nations System Standing Committee on Nutrition), can also use them. The same is true for the other EURRECA outputs that are publically available (see below).

Sustainability of EURRECA

Micronutrient Genome Project. The micronutrient genomics project (MGP) was established as a community-driven project to facilitate the development of systematic capture, storage, management, analyses, and dissemination of data and knowledge generated by biological studies focused on micronutrient–genome interactions. Specifically, the MGP creates a public portal and open-source bioinformatics toolbox for all "omics" information and evaluation of micronutrient and health studies (see http://www.micronutrientgenomics.org). The core of the project focuses on access to, and visualization of, genetic/genomic, transcriptomic, proteomic, and metabolomic information related to micronutrients (van Ommen et al., 2010). The knowledge gathered by the micronutrient genome project is fed into the genetic variation module of the nutritional phenotype database (dbNP, see Table 4), adding knowledge from new studies of micronutrient–genome interactions to the already existing data from publicly available databases. In addition to the above-mentioned activities of the MGP, a database with many published intervention studies on genetics and micronutrients has been created by EURRECA and will be made available in the genetic variation module of dbNP, which will be linked to the MGP portal.

Collaboration with UNU/SCN Network for Capacity Development in Nutrition in Central and Eastern Countries (NCD-NCEE) (www.agrowebcee.net/ncdn/). EURRECA and NCD-NCEE started to collaborate in 2007 by collecting the current micronutrient recommendations from CEE countries. One of the goals of this collaboration was to identify relevant gray literature on micronutrient intake and status from CEE nutritional data and to use it for the assessment of micronutrient inadequacy (Gurinovic et al., 2008). This revealed that gray literature is a good source for identifying open-access datasets in this population. Therefore, this source requires further attention in obtaining nutritional information from CEE. Introduction and testing of the EURRECA tools were discussed at several network meetings in 2009–2011 (Gurinovic et al., 2011).

Collaboration with the Early Nutrition Academy (ENA). EURRECA organized, in collaboration with The Early Nutrition Academy (ENA) in June 2011, a workshop on "Critical micronutrients in pregnancy, lactation and infancy." The aim of this workshop was to identify research gaps within the field of micronutrients during early human development. The question of whether, and under which circumstances, supplementation with vitamin D, folic acid, and iron would be advisable was addressed. It was concluded that public health strategies for improving supplementation with these micronutrients in pregnancy, lactation, and infancy are of utmost importance. Further research priorities should focus on adequately powered studies to obtain a stronger evidence base for the specific amounts of these micronutrients needed for optimal health effects. The results of this workshop are published in an e-supplement of the Annals of Nutrition and Metabolism (Hermoso et al., 2011).

Furthermore, an e-learning platform (The Early Nutrition e-Academy (ENeA), www.early-nutrition.org/ENeA) with systematic training in nutrition issues related to pregnant and breastfeeding women, and infants and children, is established in collaboration with the EU FP7 Project Early Nutrition and the Early Nutrition Academy. Knowledge and outcomes of EURRECA are incorporated into this platform. The key target groups addressed by the ENeA are health care professionals, nutritionists, dieticians, and researchers in the field of early human nutrition. All EURRECA partners were invited to collaborate in the development of new e-modules related to this particular population group (e.g., iron in pregnancy). On April 30, 2012, this ENeA platform has been launched for registration to users.

Research infrastructures: EURO-DISH. EURRECA has contributed to the building of a network that covers expertise on determinants of dietary habits (D), assessment of dietary intake (I), research into nutrient status (S), and biological function, and the health effects at the population level (H), the EURO-DISH project (2012–2014). The aim of EURO-DISH is to provide recommendations on the needs for food and health research infrastructures (RIs). EURO-DISH will first identify the needed RIs by means of a mapping approach of existing RIs, synthesize these into EU-wide RIs relevant to research, policy, and

industry, address the governance issues involved, and then develop a conceptual design and roadmap for implementing the most important RIs for Europe. To face the major challenges in promoting health and reducing the disease burden of age- and diet-related NCDs, it will include links with basic research, intervention and cohort studies relevant to nutrition, food, and lifestyle. The results of EURO-DISH will contribute to the development of EU-wide RIs by informing the European Strategy Forum on Research Infrastructure (ESFRI) Roadmap and future EU-funding programs and by supporting the Commission Recommendations on the Joint Programming Initiative "A Healthy Diet for a Healthy Life."

EURRECA has also contributed to the development of the INPROFOOD project (2011–2014; http://www.inprofood.eu) funded to promote bottom-up development of concepts (processes and structure) of societal engagement in food and health research. The project is investigating current processes and structures of public engagement in food and health research and its current role, and developing stakeholder engagement programs both at national and European levels. The project will stimulate the adoption of concrete initiatives of societal engagement in food and health research.

CONCLUSION

Taken together, deriving reference values in a transparent, systematic way is a scientific and logistical challenge. Therefore, the EURRECA network developed a methodology to prioritize micronutrients based on the availability of new scientific evidence, public health relevance, and heterogeneity of recommendations (Cavelaars et al., 2010) and prioritized eight micronutrients (iodine, folate, iron, riboflavin, selenium, zinc and the vitamins B12, and D). Furthermore, EURRECA developed a comprehensive framework (Figure 2) for deriving and using reference values that is unique and satisfies the following criteria:

- *Transparent*: providing the evidence and clarifying the assumptions and uncertainties, and distinguishing risk assessment and risk management issues.
- *Systematic*: developing systematic reviews addressing the factorial approach as well as dose–response associations on intake, status, and health outcomes (risk/benefit assessment).
- *Useful*: (i) comprising tools and methodologies helpful in deriving and/or adapting DRVs; (ii) shared through collaborations with key stakeholders, including other scientists, and used in policy, practice, and future research (van't Veer et al., 2013b); and (iii) identifying specific data needs and research gaps necessary for updating existing DRVs.
- *Complete*: including a Public Health Nutrition Policy-making Framework for identifying policy options.
- *Relevant for the future*: initializing tools for future applications in personalized nutrition.

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