Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

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Accepted author version posted online: 01 Aug 2013.

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Keywords: EURRECA, framework, dietary reference values, systematic review

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Abbreviations

A-1-ACT	alpha -1-antichymotrypsin
ACE	angiotensin-converting enzyme
AHRQ	Agency for Healthcare Research and Quality
AI	average intake
ANR	average nutrient requirement
ApoE	apolipoprotein E
AR	average requirement
b-car	beta-carotene
BMD	bone mineral density
BPG	best practice guidelines
CASP	critical appraisal skills programme;
CC	correlation coefficients
CD2, CD4, CD19	cluster of differentiation 2, 4 and 19;
CEE	Central and Eastern Europe
CHD	coronary heart disease
CRP	C-reactive protein
Cu	copper
CV	coefficient of variation

CVD	cardiovascular disease
DACH	German-speaking countries (Germany, Austria, Switzerland etc)
DFE	dietary folate equivalent
DR	dietary records
DRI	dietary reference intake
DRV	dietary reference value
EAR	estimated average requirement
EBP	evidence based policy
EC	European Commission
EFSA	European Food Safety Authority
ENA	Early Nutrition Academy
ENHR	European Nutrition Health Report
ENO	European Nutrigenomics Organisation
EU	European Union
EU27	The European Union (EU) is an economic and political union or confederation of 27 member states located primarily in Europe.
EURRECA	EURopean micronutrient RECommendations Aligned Network of Excellence
FAO	Food and Agriculture Organisation
FBDG	food-based dietary guidelines
FCDB	food composition database
Fe	iron

FFQ	food frequency questionnaire
FSA	Food Standards Agency UK
GDS	geriatric depression scale
GPx	glutathione peroxidase;
GST	glutathione S transferase
GSTM1	glutathione S-transferase Mu 1 gene;
GSTT1	glutathione S-transferase theta 1 gene;
HBS	household budget survey
HIV	human immunodeficiency virus;
i.m.	intramuscular
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
ID	iron deficiency
IDA	iron deficiency anaemia
IDD	iodine deficiency disorders
IDE	iron deficiency erythropoiesis
IL	interleukin
IL-1	interleukin-1;
ILSI	International Life Sciences Institute
IOM	North American Institute of Medicine
I-S-H	intake - status – health
IU	international unit
LBW	low birth weight

LRNI	lower reference nutrient intake
LTI	lower threshold intake
Mg	magnesium
MMSE	mini-mental state examination
MTHFR	methylenetetrahydrofolate reductase
MT1A	metallothionein 1A gene;
NHANES	National Health and Nutrition Examination Survey
NO	nitric oxide
NoE	Network of Excellence
NORDEN	Nordic Council of Ministers
NRSB	nutrient recommendation setting body
NTD	neural tube defect
NuGO	Nutrigenomics Organisation
NuGOwiki	European Nutrigenomics Organisation webpages link
PGE2	prostaglandin E2
PGF2a	prostaglandin F2a
PRI	population reference intake
PSS	perceived stress scale
PTH	parathyroid hormone
RAF	risk assessment framework
RCF	red cell folate
RCT	randomised controlled trial

RDA	recommended dietary allowance
RNI	reference nutrient intake
SAB	scientific advisory body
SAC	scientific advisory committee (or council)
SACN	UK Scientific Advisory Committee on Nutrition
SBP2	selenocysteine insertion sequence
Se	selenium
SEBR	systematic evidence-based review
SEEN	Spanish Society for Endocrinology and Nutrition
SelH, SelI SelK	selenoproteins H, I and K;
SEP15	15 kDa selenoprotein gene;
SEPP1	selenoprotein P gene;
SES	socioeconomic status
SF	serum ferritin
SNP	single nucleotide polymorphism
TNFα	tumour necrosis factor alpha
TNFαR2	tumour necrosis factor alpha receptor 2
TrxR1-3	thioredoxin reductases 1-3;
TSH	thyroid stimulating hormone
UIE	urinary iodine excretion
UL	tolerable upper intake level
UNICEF	United Nations Children's Fund

USI	universal salt idiosation
UVB	ultraviolet blue
VCAM	vascular cellular adhesion molecule
VMNIS	vitamin and Mineral Nutrition Information Service
WBC	white blood cell
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research;
WHO	World Health Organisation
WMD	weighted mean difference
Zn	zinc

ABSTRACT

The EURopean micronutrient RECommendations Aligned (EURRECA) Network of Excellence explored the process of setting micronutrient recommendations to address the variance in recommendations across Europe. Work centred upon the transparent assessment of nutritional requirements via a series of systematic literature reviews and meta analyses. In addition, the necessity of assessing nutritional requirements and the policy context of setting micronutrient recommendations was investigated.

Findings have been presented in a framework which covers nine activities clustered into four stages: stage one 'Defining the problem' describes activities 1 and 2: *' Identifying the nutrition-related health problem*' and *' Defining the process'*; stage two 'Monitoring and evaluating' describes activities 3 and 7: *'Establishing appropriate methods'*, and '*Nutrient intake & status of population groups*'; stage three 'Deriving dietary reference values' describes activities 4, 5 and 6: *'Collating sources of evidence'*, *' Appraisal of the evidence'*, and *' Integrating the evidence'*;

stage four 'Using dietary reference values in policy making' describes activities 8 and '*Identifying policy options'*, and ' *Evaluating policy implementation'*. These activities provide guidance on how to resolve various issues when deriving micronutrient requirements and address the methodological and policy decisions which may explain the current variation in recommendations across Europe.

INTRODUCTION

In Europe, micronutrient recommendations established by national and international committees of experts are used by public health-policy decision makers to monitor and assess the adequacy of the diets of population groups (Dhonukshe-Rutten et al., 2010a). There is no standardised approach for deriving recommended intake levels of micronutrients in Europe (Berti et al., 2010; Blanquer et al., 2009; King et al., 2007; Prentice et al., 2004). In 2007 the EC-funded Network of Excellence, **Eur**opean **Rec**ommendations **A**ligned (EURRECA) was established as a direct result of the socio-political climate in Europe and tasked with identifying the means by which to align micronutrient recommendations. Alignment includes the scientific content (objectivity, transparency, common basis), the processes to collate and summarise evidence, and the application of results by regional, national and international stakeholders who evaluate their policy options and implement the chosen applications (Dhonukshe-Rutten et al., 2010a).

EURRECA has outlined what it considers to be the different stages that are core to the process of deriving and applying micronutrient recommendations:

- Defining the problem
- Monitoring and evaluating
- Deriving dietary reference values

- Using dietary reference values in policy making

Each stage consists of two or three activities (Figure 1) that those involved in deriving and applying nutrient recommendations need to consider.

The first stage 'Defining the problem' (Activities 1 & 2) sets out the process by which dietary reference values will be set and includes defining the underlying problem to be addressed.

The purpose of the second stage 'Monitoring and Evaluating' is to define appropriate methods to be used to estimate population nutritional health and identify groups at risk of malnutrition. It is needed throughout the process of both establishing micronutrient recommendations and their subsequent application in policy and practice. In this stage involving Activity 3 & 7 the intake and status of the micronutrient in question is monitored and evaluated.

The stage 'Deriving dietary reference values' consists of three sequential activities (4, 5 & 6). It describes how a variety of sources of evidence can be collected, interpreted and integrated into average requirements in a harmonised and standardised way. From these, reference values for micronutrient intake for specified proportions of the population (resembling the definition of AR and PRI) can be derived.

The stage 'Using dietary reference values in policy making' includes two activities (8 & 9) where policy makers identify appropriate policy goals and options and evaluate policy implementation. This stage then also, feeds back into the 'Defining the problem' stage.

----Please insert Figure 1 here----

THE EURRECA FRAMEWORK FOR DERIVING AND USING MICRONUTRIENT REQUIREMENTS

Defining the problem: Identifying the nutrition-related health problem (Activity 1)

At the beginning of the 20th century reference values addressed the nutrient needs for the prevention of deficiencies and related health problems. Currently, these health problems are not highly prevalent in the Western societies. There has been a shift in the way that dietary reference values are set which is more focused on the increasing prevalence of chronic disease. Increasingly, nutrient recommendations setting bodies now include optimal health and the prevention of chronic diseases when setting new reference values.

Currently in Europe, however, only 10 countries included 'prevention of chronic diseases' in addition to 'prevention of deficiency diseases' in their definition of adequacy (unpublished work of EURRECA). The derivation of new or updated nutrient reference values should ideally be based on specific health outcomes related to functional capacities or the avoidance of disease. However, as convincing scientific evidence on the dose-response relationships between intake and health is often not available, other criteria of adequacy are used, such as subclinical nutritional health conditions identified by specific biochemical or functional measures, or requirements to maintain physiological balance. These markers are useful to the extent that they can be considered as intermediates in the pathway between nutrient intake and the ultimate health or disease endpoint. As a separate approach, the nutrient balance in apparently healthy subjects can be used as a starting point for setting recommendations; this refers to maintenance of stores, losses, tissue growth. Although this is a widely used approach in nutritional science, it is strictly speaking based on apparently healthy people, and will thus lead to estimates of

Adequate Intake (AI) rather than Average Requirements (AR) and Population Reference Intakes (PRI).

Although similar concepts and definitions are used around the world for the different reference values, the exact terminology differs. Because of its European scope, EURRECA used the EFSA terminology (AR, PRI) for practical purposes of (dietary) reference values (DRVs), and the neutral UNU terminology where this was required from the scientific point of view (Median INL or INL50 corresponding to Average Nutrient requirement (ANR) or AR when the requirement follows a standard normal distribution; Individual Nutrient Level or INL97.5 for PRI) (King et al., 2007). The EURRECA network focused on the process of deriving the average requirement and its distribution. The average intake requirement (AR: Average Requirement) is based on the median of the intake-requirement distribution of individuals and defined as the intake sufficient to meet the requirements of 50% of a specific population group, and recommended intake values are in practice defined as the PRI, which denotes the intake sufficient to meet the requirements of the majority (~97.5%) of a specific population group.

The ultimate choice of the health criteria will depend not only on the available scientific evidence but also on the actual public health situation and health goals of each specific country (Taylor, 2008). Scientists should provide policymakers with tools such as health criteria and their implications in order to make choices and set priorities. As a consequence of prioritising different health outcomes or the criteria for acceptable health outcomes, it is possible to have multiple average nutrient requirements for different functional outcomes. Nutrition and public health policymakers should then determine which level of adequacy is preferred or achievable.

Health outcomes considered in EURRECA

EURRECA considered and reviewed the following health criteria in order to choose the health outcome:

1. The occurrence of diet-related chronic disease or precursors of disease; these health criteria can be considered as “health outcome”.
2. Clinical biomarkers of key biochemical micronutrient functions relevant to nutritional health status; these health criteria are briefly labelled as “status markers”.
3. Nutrient balance; maintenance of body stores by adequate compensating obligatory losses and providing needs for reproduction and growth during the life cycle.

EURRECA identified the most relevant health outcomes by determining the number of hits that emerged in preliminary searches of the literature combined with the opinion of scientific nutritional experts (see also Activity 6, Expert consultation). **Supplementary table 1** shows the health outcomes studied for the micronutrients which were reviewed within the framework of EURRECA for different life-stage groups.

Principally EURRECA covered two different concepts which are effective in order to derive reference values (King et al., 2007). They include the factorial approach and the dose-response approach which is illustrated in Figure 2 and which will be described in more detail in Activities 4, 5 and 6. The final component, i.e. the formulation of recommended micronutrient intake for specific population groups is the outcome of both approaches together with a number of policy issues that are further detailed in Activities 2 and 8.

----Please insert Figure 2 here----

Population groups

Definition of apparently healthy

Reference values are designed for the planning and evaluation of a diet to keep populations healthy. This involves studying the association between intake, status and health outcomes. The question of what constitutes a healthy population has become more complex during the past 50 years as a result of better understanding of health and chronic disease aetiology and because there is no overall definition or consensus (Sheffer and Lewis Taylor, 2008; Taylor, 2008). In the EURRECA network, apparently healthy was defined as the absence of diseases based on clinical signs and symptoms of micronutrient deficiency or excess and normal function as assessed by laboratory methods and physical evaluation (World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO), 2004). However, depending on the specific research question the exact definition of apparently healthy varied slightly, i.e. was tailored, in EURRECA's research activities.

Defining life-stage population groups

As nutrition-related health problems may differ between population groups, it is important to identify and clearly define the population groups of concern. Within Europe, operational categories of age groups vary, especially for children, adolescents and elderly people (Doets et al., 2008). The age of transition from 'adult' into the 'elderly' category varied between the age of 50 and 76 years. Moreover, some countries defined an additional category of 'late' elderly thus acknowledging the specific needs of a growing population group in Europe. Pregnant and lactating women are defined in almost all countries and some countries distinguished various

stages of pregnancy (usually according to trimesters, sometimes weeks) and pre-pregnancy. For some micronutrients, specific population groups are mentioned, i.e. post-menopausal and menstruating women (iron), sunlight exposed people (vitamin D) and smokers (vitamin C) and formula fed infants (calcium and zinc). The EFSA panel on Dietetic Products, Nutrition and Allergies (NDA) (EFSA, 2010) recently proposed to use nutrient-specific age ranges depending on the nutrient and the available scientific data to derive reference values.

To define age groups three options were considered: 1) chronologic age, 2) physiological age; use of functional characteristics (e.g., growth and puberty), or 3) social age. These were all potential purposes for which the reference values might be used (e.g. complementary feeding programs). To avoid confusion EURRECA decided to use the same life-stage groups for all nutrients as proposed by the United Nations University (UNU) (Atkinson and Koletzko, 2007). Special attention must be paid to the needs of infants and the elderly (above 65 years) as they have a relatively high requirement of certain micronutrients per unit body weight and energy intake.

Population groups considered in EURRECA

Before the research activities commenced, EURRECA defined the following life stage groups when reviewing best practices and evidence for setting requirements:

- infants (0-12 months: ~5 % of the EU27 populations),
- children and adolescents (1-18 years: ~15-20% of the EU 27 populations),
- adults (19-64 years: ~60% of the EU 27 populations),
- elderly (65+ years: 15-20% of the EU 27 populations),

- pregnant women
- lactating women

These categories are in line with the population groups defined by the EFSA panel (2010).

In addition to age and life cycle, other population grouping criteria used were related to physiological, biological and cultural factors. This included factors related to body size (such as height and weight, obesity, physical activity); and biological variation in needs further addressed in Activity 6.

Finally, factors such as ethnicity and socio-economic status may be relevant to increased vulnerability to inadequacies resulting from limited access to nutritious foods. Health policymakers may decide to include socio-economic and political aspects in the context of surveillance of the actual micronutrient intake and status, and nutritional health problems in specific population groups. Therefore, in addition to the different age groups studied (from infants to elderly), EURRECA also addressed low income and immigrant status as potential determinants of inadequate micronutrient intake. (Activity 7).

Micronutrients

The prioritization of micronutrients

Reasons for updating reference values vary from statutory obligations, discrepancies with other countries' recommendations, health status or disease incidence through to the emergence of new science or lobbying from those within or outside the scientific advisory boards of the nutrient recommendation setting bodies (Dhonukshe-Rutten et al., 2010a). Reviewing and evidence-based updating of micronutrient recommendations is, however, costly both in time and money.

EURRECA developed a simple systematic prioritisation process to decide which micronutrients to focus on first. This fits within the adoption of evidence-based decision making in public health recommendations and helps move the process away from sole reliance on expert opinion and towards thoughtful consideration of the total body of evidence. In this process, it is important to question whether there is enough evidence to warrant re-assessment of the current requirements. The process (schematically outlined in Figure 3) was guided by three main, content-related criteria for reviewing and revising micronutrient recommendations:

a) Amount of relevant and functional, new scientific evidence available for a particular micronutrient for different life-stage population groups;
b) Public health relevance of the micronutrient through measures of dietary inadequacy and disease burden for the different population groups, including vulnerable groups such as low income and immigrant population;
c) Heterogeneity defined as between-country differences in current micronutrient recommendations in Europe.

Although the three criteria were easily measurable and reproducible in a short time frame, eminence-based expert opinion was required to compensate for the lack of a comprehensive overview of micronutrient inadequacy in different population groups in Europe. Alternatively, a more thorough and time consuming process involving the same basic principles could evaluate more thoroughly the amount of new evidence, to identify new outcomes, and to provide additional information on dose-response relation such as described by Yetley et al (2009).

----Please Insert Figure 3 Here----

Micronutrients considered by EURRECA

The above process was applied to a long list of 28 micronutrients provided to EURRECA by the EFSA Panel. Based on this process the micronutrients vitamin D, iron, folate, vitamin B12, zinc, calcium, vitamin C, selenium, iodine and copper were prioritised (Cavelaars et al., 2010). This priority list of micronutrients was further refined by factors such as (i) avoidance of duplication of work already started by other organisations e.g. vitamin D and calcium, and (ii) micronutrient expertise available in the network, and (iii) available resources within the EURRECA network. Therefore, EURRECA eventually focused on the following micronutrients: iron, zinc, folate, vitamin B12, selenium, and iodine. In summary, the selection process included evidence derived by a scientific protocol, whereas the other three criteria refer to driving factors in the socio-political context, such as the efficient use of available expertise and financial resources. These process-related issues are further detailed in Activity 2.

Defining the problem: Defining the process (Activity 2)

Deriving DRVs and setting recommendations provides a tool for policy makers to set public health nutrition policy; thus, although the use of DRV ranges widely (e.g. in medical care, to aid development of policy options such as food labelling, towards food composition data), they are developed with policy purpose in mind. Public health nutrition policy has been variably conceptualised in terms of values and intentions with a public health nutrition outcome in mind (Lawrence, 2007), as a process of influence and power relevant to public health nutrition (Walt, 1994) and as a decision relevant to food and nutrition (Margetts et al., 2004). Common to all these conceptualisations is recognition that public health nutrition policy includes a consistent

approach to a nutrition problem that can change over time; that it includes a statement of values and intentions; and that it is legitimised by authority of individuals, offices or organisations.

Following the definition of the problem and the recognition of the public health nutrition dimension, any discussion about which policy option to adopt requires the establishment of the breadth and strength of scientific evidence on the relationship between micronutrient intake and health status (e.g. increased sodium intake links with increases in blood pressure); health status and health outcome (e.g. blood pressure links with coronary heart diseases); and micronutrient intake and health outcome (e.g. sodium intake and coronary and heart diseases). A summary of such evidence and the resulting micronutrient DRVs should ideally be conducted by an independent scientific advisory body (SAB) brought together for its (inter)national credibility and expertise relevant to the problem to be addressed.

The EURRECA Network of Excellence examined the processes of establishing micronutrient DRVs and the present activity represents a summary of research to define this process, with a particular emphasis upon normative aspects of the workings of SABs. This has been done by bringing together the key findings from the following data collection activities (see Table 1).

--Insert Table 1--

The focus on three micronutrients across six European countries ensured development of contrasting case studies (N=18) in terms of historical context as well as current micronutrient recommendations-setting processes and nutrition policy decision-making.

Scientific Advisory Bodies (SABs)

Scientific advisory bodies (SABs) are groups through which expert advice enters the political process. They can be established institutions, short-term commissions, ad hoc and standing committees and informal networks of experts. Their key role is to feed technical recommendations into the policy development process (Morestin et al., 2010; Timotijevic et al., 2011a). The type of SAB varies by its statutory and legal role. EURRECA work has identified a diverse institutional architecture of SABs for nutrition operating across Europe including scientific advisory committees (SAC, often called "advisory councils"); public health institutes and research centres; nutrition societies and individual experts (Timotijevic et al., 2011a). Evidence suggests that SABs play a crucial role in advising government on development and implementation of nutrition policies in Europe: WHO have noted the possible link between the existence of SABs and the degree to which nutrition policies are developed and implemented (Trübswasser and Branca, 2009). Extending this work, EURRECA case studies examined the extent to which the type of SAB influences policy options recommended and showed that the likelihood of adopting regulatory micronutrient policies (e.g. mandatory fortification) does not vary by type of SAB. Nevertheless, it upholds the findings (Trübswasser and Branca, 2009) that the existence of a dedicated Scientific Advisory Committee is linked with a greater public health nutrition orientation of policy champions and a more evolved nutrition policy landscape – both institutionally and politically (Timotijevic et al., 2011a; Timotijevic et al., 2011b). Thus,

although costly, establishing such a committee (if it is not present already) is an important step towards transparent micronutrient DRVs.

EURRECA work suggests that, before setting up such a committee, a careful deliberation about the terms of reference is required. This will determine substantial aspects of the workings of the SAB: the composition and purpose of the committee; the scientific and normative aspects of decision-making both within the committee (e.g. the criteria for assessing scientific evidence and making conclusions) and beyond it (e.g. how to deal with stakeholder comments). The terms of reference must be specific enough to enable identification of appropriate expertise. Nevertheless, a degree of autonomy should be granted to the SAB to define the problem in a way that enables it to work within the realm of the existing knowledge. This definition should be explicit about how uncertainties and assumptions will be dealt with (Timotijevic, in prep.-b).

SAB composition

There are many ways to identify suitable expertise for a SAB relevant to micronutrient recommendations. Individual expertise, institutional authority, representation of a sector and representation of different types of knowledge are common and often overlapping criteria for selection. In some cases, the decision about who will be invited is made by the standing SAC (e.g. the UK) (Timotijevic et al., 2011a), whilst in others, the policy maker engages in recruitment of suitable expertise (Timotijevic et al., 2011a). Identifying the right skills/expertise mix and the appropriate experts is a complex process often criticised for lack of transparency and bias (Bijker et al., 2009). The selection of SAB experts should ideally follow a protocol, both in terms of disciplines represented but also in terms of what counts as “expertise” (Timotijevic et

al., 2011b). In addition, key to recruiting experts into SABs is to ensure that conflicts of interests are dealt with appropriately. Requirement for the expression of conflict of interest is not only a route to transparency but also to ensuring legitimacy of a SAB's decision by removing the questions of decision bias. In reality, however, expertise relevant to specific micronutrients may be scarce and access to it may be further limited due to the increased pressures (through research funding policies) upon scientists to engage in "impactful" research by collaborating, for example, with industry (Rockey and Collins, 2010).

The type of expertise (in terms of the disciplines represented at the SAB) involved in setting micronutrient DRVs for a single micronutrient and the type of body involved (based on its statutory role) varies widely across Europe (Timotijevic et al., 2011a). Based on the Europe-wide survey of the process of setting of micronutrient recommendations conducted by EURRECA partners, we can conclude that most countries mention at least three of the following fields of expertise: nutrition, (public) health, medicine, biochemistry, food technology, epidemiology, food hygiene and toxicology (Table 2). In several countries (e.g. UK) as well as at the European level, lay or consumer representatives are included in the SAC or the working groups. The way in which expertise is defined and SAB are structured, determines how a problem is framed, which in turn influences the decisions around the inclusion or exclusion of particular perspectives and the way in which facts are selected and interpreted and conclusions are drawn. The nature and source of expertise may also be significant factors in whether scientific advice is taken up in the policy-making process. Such diversity appears to reflect a) the diverse "terms of reference" presented to the SAB; b) the extent of the public health nutrition orientation within the country including the way it is institutionally embedded (e.g. see table 2 OR 3) – that is,

how central and explicit the public health nutrition agenda is to the national health policy (Jeruszka-Bielak, in prep.); c) the scientific resources, i.e. the development of science, the range of technical expertise available (Timotijevic, in prep.-a); d) the broader societal engagement (e.g. institutions other than government and the public at large) with the generic problem of public health nutrition; e) the financial resources (Timotijevic et al., 2011a).

----Please Insert Table 2 Here----

Stakeholder involvement and normative decision-making

Whilst there are many frameworks for collating and interpreting scientific evidence, the protocols for how to deal with the normative aspects of decision-making that include issues of disagreement between scientists (on matters of nature of evidence, interpretation of evidence and implications of the evidence for public health and/or policy), consultations with stakeholders on matters under discussion within SAB, and how to respond and take on board stakeholder submissions to consultations, are scarce yet critical, as EURRECA work has shown (Timotijevic et al., 2010b; Timotijevic, in prep.-b) Wider involvement in decision making of SAB is called upon by a range of EU policy documents (e.g. Science in Society Action Plan (European Commission, 2001a, c); Communication on Collection and Use of Expertise (European Commission, 2002), as it is thought to increase transparency and accountability, improve quality of decisions and contribute to the democratic capital of the decision-making body and science governance. For instance, EFSA specifies the following steps for consultations: the draft report is put up for public consultation for at least 60 days during which opinions are collected (mostly in written format) and considered. EFSA typically produces response to consultation where it

justifies the way the comments have been incorporated into the report, usually within 3 weeks from receiving the comments.

However, we know little about how this evolves in practice even when consultations are conducted publicly and posted online. The role of stakeholder consultations within the workings of SAB is of particular relevance in the context of recent questions about the utility and ethics of such an endeavour. For instance, in the UK, there have been increased calls for scientific independence from vested interests (which stakeholder consultation can act to obscure) (Government Office for Science, 2009). Similarly, recent academic literature has shown that stakeholder consultations are particularly problematic in the domain of science where vested interests seek to influence decisions (Bijker et al., 2009), such as the case of sodium.

EURRECA have conducted research in this domain and tried to describe the processes of stakeholder consultations where they are actively endorsed. Where stakeholder consultation is explicitly permitted, (it is with an aim of: a) identifying relevant evidence to take into consideration and/or b) as a way of getting feedback on draft reports in preparation for a final report. These consultations are usually written communiqués that invite comments from relevant stakeholder groups. It is at the SABs discretion as to whether to engage with these comments, thus upholding the principle of scientific autonomy. Nevertheless, the Eurreca examination of the 2 cases of stakeholder involvement (UK SACN and EFSA) shows that it is not always made explicit how different stakeholders' contributions are weighed for their relevance and what mechanisms are in place to ensure that stakeholder comments are reflected in the decisions. There is limited information about the procedures in place to simultaneously manage the

potentially contradictory rationale for scientific independence and stakeholder involvement (Timotijevic et al., 2011b; Timotijevic et al., 2010b), which places an added pressure upon the SABs to engage in a complex manoeuvring of the often irreconcilable objectives of independence and engagement.

----Please Insert Table 3 Here----

Risk assessment and risk management

The EURRECA case studies (please see (Timotijevic et al., 2013) for information about the methodology employed in the case studies) have demonstrated that the purpose of a SAB for Nutrition will be partly premised upon definition of the problem, but also partly upon the regulatory context and the existing nutrition policy objectives (Timotijevic, in prep.-a). Thus for instance, there is often an explicit call for the clear much of the activity of dietary modelling and nutrient recommendations setting within the framework of risk analysis (or RAF, (MacKerras,2012)). The key feature of RAF is an explicit separation between risk assessment and risk management (as is the case with EFSA and the UK SACN, whereby the SAB activity is often delimited as a risk assessment exercise) deemed necessary in order to as a way of achieving a clear demarcation of demarcate accountabilities and modes of operation between scientific and political actors. But this may not always be possible due to, for instance, institutional characteristics of the public health nutrition policy (the institutional contexts within which policy is developed differ across countries, see Table 2 OR 3 and Figure 20 for examples of the types of organisations involved in the process), nor ideal as a way of achieving optimal public health nutrition policy. At the institutional level, researchers have shown that risk assessment is

inextricably bound with social and political context, power relations and practices (Bieirle, 1990; Wynne, 2003) which makes demarcation of risk assessment and management difficult to uphold. There are calls for greater transparency about the processes of risk assessment (and about the instances when risk assessment is partly premised upon political realities), however this may also have a possibly unintended consequence of selective transparency, whereby SAB members make explicit only those aspects of risk assessment that are characterised by scientific consensus (Walls et al., 2010).

Communicating findings to policy decision-makers

SABs review evidence of associations between micronutrient intake, health status and health outcome to derive micronutrient DRVs, and in some cases also provide recommendations about selection and suitability of a policy option (e.g. mandating for food fortification with a micronutrient, (Dhonukshe-Rutten et al., 2010b; Timotijevic et al., 2010b). For a policy option based on micronutrient DRVs, evidence needs to be established of the risks as well as benefits, e.g., risk of overconsumption. Clear protocols for selecting, weighing and interpreting evidence are a norm across the EU and are in line with the principles of conducting scientific research (Brown, in prep.). Such protocols (for instance the 'SACN Framework for the Evaluation of Evidence' (Scientific Advisory Committee on Nutrition, 2011) or 'A Guide for Conducting Systematic Literature Reviews for the 5th edition of the Nordic Nutrition Recommendations' Nordic Council of Ministers, 2011 (NNR5 working group, 2011)) structure the decision-making, act as guidance and ensure transparency about the final recommendations. However, even with the existence of such protocols, the evidence base is complicated by several factors, including great variation in the terminology used for micronutrient requirements and heterogeneity of

recommended micronutrient values; variations in definition of population groups and the various approaches to establishing micronutrient requirements (for more information please see Activities 1,3,4). This is certainly a challenge to both the SAB and the policy makers and it is critical that these assumptions are made explicit in communicating conclusions to policy makers. Nevertheless, there is also an intrinsic problem in communicating uncertainties and assumptions to policy makers particularly in the context of policy areas that often lack explicit political support and prioritisation, such as public health nutrition.

The way in which the SAB conclusions are communicated to policy makers is sometimes a significant hindrance to the way science informs and ultimately influences policy. Scientific activity is characterised not by pursuit of the ultimate truth (or the final proof) but to the contrary, by the efforts to disprove the hypotheses as falsifiability (the potential to disprove the hypothesis) is an essential criterion of scientific method. As such, scientific endeavour is based upon the implicit acceptance of uncertainty. Policy however is often communicated through statements of certainty and hence policy makers seek assurances of certainty from scientists that would give credibility and ensure effectiveness of the policies they mandate. There is a general agreement that scientific and technical knowledge can improve policy as it is understood to be committed to addressing and communicating best available evidence to decision-makers (Timotijevic et al., 2011b). How this evidence is to be relayed to the policy maker, however, is a moot point. The key is to identify a way of communicating the nature and the degree of uncertainty that paints an appropriate picture of the state of knowledge in the scientific community and the extent to which such knowledge can be relied upon to derive optimal solutions. It is widely accepted that communicating uncertainties is beneficial not only from the

normative point of view (since openness about the nature of knowledge is a key value in our society and increases trust), but also has an instrumental value (as it can help derive the best policy). However, communicating uncertainty can also be a deterrent to a policy maker who seeks assurances from science in contexts characterised by controversies and vested interests. SABs must therefore be aware of this conflict and reflectively deal with those in the process of communicating DRVs and the associated assumptions/uncertainties.

Monitoring and evaluating: Establishing appropriate methods (Activity 3)

Understanding the function, physiology and biochemistry of a micronutrient is essential for the accurate derivation of dietary requirements. In the case of micronutrients with no sensitive or specific biomarker of status, understanding the physiology and biochemistry may provide insight with the use of –omics technologies to identify potentially novel indicators of status. The EURRECA network has summarised the function, physiology and biochemistry of a set of 20 micronutrients in the Best Practice Guidelines: Biomarkers of status/exposure (Harvey et al., 2011). Whilst the principal functions of the majority of micronutrients are well-characterised, it should be acknowledged that it is vital to explore the most recent data for newly identified physiological roles as compared with previous estimations these may seriously impact on the derivation of dietary requirements in some or all population groups.

In practice the above translates into the identification of robust data for both dietary intake and status. These data, and their inter-relationships, in conjunction with those for relevant health outcomes, facilitate the determination of dietary requirements for specific population groups (Matthys et al., 2011). Selecting the most robust methodology available to assess dietary intake and status maximises data reliability; however the choice of technique may be influenced by the

analytical environment e.g. studies in the field may impose practical limitations compared with laboratory-based research. As a result EURRECA has endeavoured to identify current best practice for assessing micronutrient intake and status (Fairweather-Tait and Harvey, 2008; Fairweather-Tait et al., 2009; Serra-Majem, 2009a; Serra-Majem et al., 2009b) and has collated relevant information useful for deriving individual micronutrient requirements. Ideal methods for assessing both dietary intake and status are not always available; therefore, best practices have been developed for identifying robust dietary assessment instruments relevant to harmonising the science of estimating micronutrient intake and nutritional adequacy in Europe (Serra-Majem et al., 2009b). In addition, computer-assisted training tools for the validation and calibration of such dietary assessment instruments have also been developed by the network (Busstra et al., 2010; Noroozi et al., 2012) and demonstration material is available on the EURRECA website (www.eurreca.org/everyone/8321/7/0/32 and www.eurreca.org/Courses/demo/index.html). Regarding biomarkers, the EURRECA network provided a platform on which the use of -omics techniques to identify novel data related to inter-individual variability could facilitate the future identification and development of new biomarkers of micronutrient status (van Ommen et al., 2008).

Assessment of dietary micronutrient intake

Establishing accurate dietary micronutrient intakes to allow valid comparison between population groups and evaluate changes in nutrient intake over time requires the use of rigorous methodology which may be micronutrient specific. A summary of the main problems and issues associated with dietary assessment is reported in Matthys et al. (2011). EURRECA has established best practice for dietary assessment of the European population through undertaking

a series of systematic reviews (Serra-Majem, 2009b; Serra-Majem et al., 2009b). The reviews covered a range of topics related to micronutrient intake focusing on specific population groups outlined in Activity 1, where intake assessment is acknowledged to be particularly challenging, and highlighted the potential use of new methodologies to increase accuracy. Reviews were undertaken to establish the best and most commonly used methods for assessing nutrient adequacy, including the consideration of dietary patterns in the context of European populations. Evaluation of the strength of various methodologies was undertaken by appraising the magnitude and origin of measurement errors. Specific aspects of research undertaken by the EURRECA network are considered in more detail in the following sections.

Diversity in dietary assessment methods

The choice of dietary assessment methodology will depend on various factors including study design and the associated practicalities of conducting the research, along with the explicit aims of the study being undertaken. No method is free from random or systematic errors, or prevents subjects changing their food habits. Specific factors that need to be considered when choosing a method are the characteristics of the subjects within the study population e.g. life stage, or immigrants and low income groups etc., the respondent burden of the method, and the available resources. Some methods may be unsuitable for elderly subjects with poor memory, busy adults with young children or those individuals with poor reading skills. Other methods require specialised equipment and computer facilities or highly trained personnel. The most accurate methods are generally the most costly with greatest respondent burden and ultimately lower response rates (Gibson, 2005). For nutrition surveillance studies, for example, the standard is to use replicates of 24 hour recalls whereas for proof of principle studies on the relation between

dietary intake and health outcomes FFQ-like methods are the standard. The latter have, though, very different measurement characteristics that prohibit direct comparability and necessitate validation and calibration approaches when appropriate.

In a study undertaken by the EURRECA network, the risk of dietary inadequacy was found to be dependent on a combination of the dietary assessment methodology employed and the micronutrient being assessed (Ribas-Barba et al., 2009). More specifically, it was evaluated how applying different dietary methods affects risk assessment of inadequate intakes at the population level and it was revealed that the prevalence of inadequate intake decreased in conjunction with the method utilised in the following order: single 24hour, mean of two 24hour recalls, FFQ and usual intake based on 24hour recall duplicates adjusted for within subject variation. For example, the effect of utilising two non-consecutive 24hour recalls when compared with a single 24hour recall showed a slight decrease in the prevalence of inadequate intakes for the majority of nutrients. In the majority of cases, but not all, methods that measured usual intakes i.e. retrospective food pattern methods such as food frequency questionnaires (FFQ) or diet histories, identified lower values of inadequacy than those obtained by quantitative daily consumption methods including 24hour recalls. The study also assessed the impact of underreporting on the levels of dietary inadequacy (Ribas-Barba et al., 2009). As expected, the exclusion of under-reporters led to a decrease in the prevalence of dietary inadequacy; however this has again been shown to be micronutrient and methodology dependent.

Assessment of food intake is challenging and prone to reporting error, especially among infants, children, and adolescents. A review conducted by the EURRECA network attempted to assess whether FFQs are suitable for the evaluation of micronutrient intake adequacy in infants,

children and adolescents (Roman-Vinas et al., 2010). For several micronutrients the results of the review highlighted a lack of sufficient data to assess the usefulness of FFQs to provide robust estimates of intake. In addition, it was noteworthy that very few potentially relevant validation studies in children incorporated the use of status biomarkers, which for some micronutrients may provide a surrogate measure of intake. Consequently, the review identified the requirement to undertake further research to address specific concerns related to FFQ validation in infants, pre-schoolers, children, and adolescents, particularly with regard to irregular patterns of intake (small portions, snacking) that is prevalent in these population groups.

Whilst dietary assessment of populations frequently attempts to obtain reliable information on supplement use, establishing accurate intakes is generally difficult. A true picture of intake can only be ascertained if regard is paid to supplement consumption patterns, the numbers of non-consumers, those with sporadic consumption in times of illness and those who take supplements on a regular basis (Ribas-Barba et al., 2009).

Quality scoring of dietary intake data

Evaluating the quality of dietary micronutrient intake assessment is vital to ensure the validity of data that may be used in the process of establishing dietary reference values. Following EURRECA's in depth review of all available dietary assessment validation studies, which analysed the utility of a range of dietary micronutrient intake questionnaires (Henriquez-Sanchez et al., 2009; Ortiz-Andrellucchi et al., 2009a; Ortiz-Andrellucchi et al., 2009b; Ortiz-Andrellucchi et al., 2009c; Øverby et al., 2009; Serra-Majem et al., 2009c), it was concluded that a scoring system was required to facilitate straightforward evaluation of the reliability of FFQ data (Serra-Majem et al., 2009a).

A scoring system was developed as a three step process; step 1 considered variables such as sample population and size, statistics (group level, correlations, agreement), type of data collection, seasonality and supplements. Scores ranged from 0 to 7, and validation studies were classified as very good (≥5), good (5–3·5), acceptable/reasonable (3·5–2·5) and poor (<2·5). The second and third steps included an adjustment/weighting of the correlation coefficient according to the quality score in addition to a rating of the adjusted/weighted correlation. The 124 validation studies assessed, which reported data from at least one vitamin were also categorised into three groups dependent on the reference method or gold standard applied in each case. The overall results highlighted that only 5.6% of the studies were rated as very good quality whereas 16.9% had a poor rating. Despite the fact that the model weighs for several methodological variables, the reference methods can also contain some bias and therefore the authors cannot rule out remnant bias in the final model. However, this evaluation tool could be used as guidance for studies validating dietary intake questionnaires or to assist researchers select and weigh the results of existing epidemiological studies; in both cases, its use can ultimately contribute to increasing the quality of evidence in nutrition research (Serra-Majem et al., 2009a).

Use of a whole-diet approach (using dietary patterns)

It is increasingly recognised that as foods and nutrients are not consumed in isolation, the combination of possible antagonistic and synergistic effects between dietary components is likely to have a significant impact on health. The likelihood that overall dietary patterns potentially have a greater effect on health than any single food or nutrient (Jacques and Tucker, 2001) probably explains the pathogenesis of many chronic, nutrition-related diseases and in addition the health benefits derived from diet. Consequently, there has been a gradual shift away

from assessment of single nutrients and foods towards the evaluation of whole diets and dietary patterns, particularly in relation to nutrition and health (Hu, 2002; Kant, 2004). Assessment of dietary patterns can provide valuable data on disease prediction and may facilitate investigations on interactions between intake and other health behaviours, or diet and other confounders of exposure-disease relationships. Dietary pattern analysis is also useful in the monitoring and surveillance of populations with regard to dietary trends and compliance with food-based dietary recommendations, and consequently is highly relevant to policy aspects of DRV setting discussed further in Activity 8.

The various methods used to characterise dietary patterns within a population generally fall into two categories. The first category involves *a priori* evaluation (hypothesis-oriented) using score based approaches, whilst the second relies on *a posteriori* analysis using data-driven dimension reduction techniques, such as principal components analysis (empirically-driven) (Dixon et al., 2001; Hu, 2002; Kant, 2004; Michels and Schulze, 2005; Newby and Tucker, 2004; Roman-Vinas et al., 2009; Sánchez-Villegas and Serra-Majem, 2005). Whilst rare, some studies have combined both types of approach (Wright et al., 2004). However, there is generally little consensus on which approach to employ in various circumstances. Consequently, the EURRECA network addressed this issue in relation to pregnancy and maternal and infant health outcomes. A systematic review was undertaken in this population group to review the literature exploring associations between dietary patterns obtained from FFQs and relevant health outcomes (Sánchez-Villegas et al., 2010). Of the seven relevant studies identified, only four employed questionnaires specifically validated for use in pregnant women and the use of differing analytical techniques made data comparison difficult. However, the review concluded that whilst

using appropriately validated FFQs was essential, specific consideration should also be given to mineral and vitamin supplements and the timing of data collection in this population group. In addition, results should be adjusted for lifestyle and educational characteristics, and any *a priori* evaluation requires appropriate selection of scoring components.

Data selection

As a result of the culmination of a series of reviews and activities undertaken by the EURRECA network (described above) with respect to the assessment of dietary micronutrient intake in the European population, consensus was reached and best practice guidelines (Claessens et al., 2013) were developed to enable identification of the most robust intake data that would be relevant for the derivation of DRVs (Garcia-Alvarez et al., 2009). Specifically, a decision tree was developed which facilitated the screening and selection of appropriate studies for inclusion in the meta-analysis of intake-status-health relationships for a series of priority micronutrients. The aforementioned EURRECA systematic reviews were comprehensive in nature and only included studies of the utmost quality. Whilst development of the tool was originally for a specific requirement, it may also be used generically in the evaluation of intake data from a range of studies and for a variety of purposes. The original tool that was developed consisted of a twenty question scoring system, and whilst rigorous and robust, it proved unwieldy to utilise in the evaluation of significant numbers of studies. As a consequence, a honed version of the scoring tool was developed in the form of an abbreviated decision tree (version 1), which was subsequently further refined into a less restrictive tool (version 2) (Figure 4). In the final version, each study is taken through a series of seven questions which allow the user to evaluate the

robustness of dietary intake data enabling the identification of data of the required standard (data to 'include') which may ultimately be used in the derivation of DRVs.

In addition, one of the key achievements of EURRECA in relation to dietary intake assessment was the development of a best practice guide for the identification of quality surveys for nutrient intake adequacy assessment in populations on a country by country basis. A step-by-step set of guidelines which summarised the process developed to select the 'best' or the 'highest quality' dietary survey/study in each country is shown in Figure 5 (Garcia-Alvarez et al., 2009). These guidelines were developed to increase comparability of the dietary data obtained. The methodology is a two-step process, with the first phase consisting of the identification of the most appropriate survey in each country. It was determined that ideally, selected surveys should focus on nutrition, however in their absence the second choice should be health surveys including nutritional data, or lastly household budget surveys with nutritional data. Briefly, the best practice criteria for identifying surveys in this initial phase were as follows:

- Data should be collected through use of a standardised instrument
- Only one survey/study per country can be considered
- Surveys/studies of cross-sectional nature
- The most representative survey/study of the country's population (to maximise external validity) – ideally at the national level (otherwise regional or, lastly, local levels)
- The most recent surveys/studies (only include those conducted after 1990)
- Surveys/studies with the best methodology in accordance with their objectives (to maximise internal validity)

----Please Insert Figure 4 Here----

Following identification of appropriate surveys it was established that a quality scoring system should be applied in the second stage of the evaluation process. The six variables considered in the quality analysis stage, in priority order, are dietary assessment methods, validation, food composition databases, under-reporting, other factors including anthropometric measurements, physical activity etc., and finally the year the survey was conducted.

In order to test the validity of the Best Practice Guidelines on Nutrient Intake Assessment, following requests from the EURRECA network, 29 out of 32 countries (28 European and four European Free Trade Association countries) responded to questionnaires requesting information on national surveys, which ultimately resulted in suitable data being identified from a total of 24 studies/surveys of the adult population (Blanquer et al., 2009). The resulting analysis of the data established that the best practice guidelines form an appropriate strategy, which can be adopted for the identification of the best cross-sectional dietary intake data available (Garcia-Alvarez et al., 2009).

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Assessment of micronutrient status

Examples of types of status biomarkers include plasma concentration, size of body pools, enzyme levels and activities, urinary excretion and a range of other biochemical and/or functional indicators which have varying degrees of specificity and sensitivity. However, a more integrated approach to the assessment of micronutrient status would ultimately involve measurement of multiple biomarkers that are key components central to the maintenance of health, metabolic, oxidative, inflammation and psychological processes. These intermediary markers of metabolism could therefore be considered as surrogate markers of nutritional status.

Novel analytical methods, including nutrigenomics, metabolomics, and proteomics, have been applied by the EURRECA network to assess these markers (Bouwman et al., 2012; van Ommen et al., 2009). An example of a metabolomics approach to assess micronutrient related health status is described in the micronutrient specific sections on selenium (Hurst et al., 2013). There is a well-established need to develop improved biomarkers of status for many micronutrients, and the EURRECA network embraced network biology and nutrigenomic technologies in an attempt to progress the development of novel approaches that will ultimately facilitate the derivation of more accurate and specific dietary requirements and recommendations.

The EURRECA network undertook a rigorous process with the aim of identifying and evaluating biomarkers of micronutrient status, which culminated in the production of a set of Best Practice Guidelines (BPG) of micronutrient status (Harvey et al., 2011). The BPGs were initially conceived by the Biomarkers of Status Working Party, which comprised a group of international micronutrient experts and EURRECA partners who met in Norwich, UK in early 2008. Publication of the workshop proceedings (Fairweather-Tait and Harvey, 2008), included articles on several micronutrients where the authors critically reviewed traditional biomarkers employed in surveys, and the development of a network biology model of micronutrient related health, which may be utilised in future dietary guidelines. In addition the working party also produced a table of Biomarkers of Status and Exposure: Minerals and Vitamins, which consisted of a non-exhaustive list of micronutrients for which dietary reference values have been produced. The table included a brief description of biomarkers of status and/or exposure for each micronutrient, accompanied by a rating of the methodological limitations and its application in research (suitable for research only and/or for fieldwork). A star rating (3* = excellent) was used to

classify the biomarkers, and a summary of available 3* indicators for selected micronutrients is available (Matthys et al., 2011). As the original remit was to assess biomarkers relevant for use in epidemiological studies, the EURRECA network has generally focused on the use of biochemical markers that can be obtained from blood or urine, rather than functional (e.g. immune function, cognitive function) and non-specific tests (e.g. grip strength).The table was subsequently updated to include data obtained from a series of systematic reviews undertaken by the EURRECA network, which focused on a selection of micronutrients with either public health significance, or a strong scientific requirement to establish the validity of status biomarkers (Biomarkers of Status Working Party, 2011) (see Evidence-based assessment of potential biomarkers).

Finally, at the end of the review process the BPGs were produced for a non-exhaustive list of micronutrients for which dietary reference values had been produced, and included data from the EURRECA systematic reviews along with the expert opinions of the working party (Harvey et al., 2011). The BPGs provide a basic introduction to various aspects of intake, function, metabolism etc, along with details of relevant biomarkers of status or/and exposure for each micronutrient.

Evidence-based assessment of potential biomarkers of micronutrient status

Understanding the relationship between micronutrient status and health can only be achieved by using robust biomarkers of status. In order to establish the validity of status biomarkers and identify the circumstances in which they may be relied on in terms of population groups, deficient or replete states etc., the EURRECA Network undertook a series of systematic reviews, focusing on a selection of micronutrients with either public health significance, or a strong

scientific requirement. Systematic reviews of biomarkers of status were conducted for vitamin B12, zinc, iodine, copper, riboflavin, magnesium, vitamin D, polyphenols, n-3 long chain polyunsaturated fatty acids and selenium (Fairweather-Tait et al., 2009; Pérez-Jiménez et al., 2010; Witkowski et al., 2011). A common review methodology was developed on the basis of identifying studies that altered micronutrient status, with a subsequent pooling of the data for each specific biomarker (Hooper et al., 2009). Inclusion criteria were tailored for each micronutrient depending on the quantity and quality of available data. If sufficient data were available included studies were restricted to randomised controlled trials (RCT), but where there was a paucity of data both before-after and nonrandomised controlled trials were also included. Inclusion criteria also took into account the form of supplement used in the study and the minimum duration of intervention (supplementation or depletion) required to elicit a response in the biomarker following a change in status. The highest dose and longest duration intervention data were selected to statistically analyse biomarker validity. Studies were sub-grouped by population, dose, duration, sex, supplement type and analytic method as appropriate in order to assess the consistency of response for each biomarker.

Use of this methodology highlighted specific micronutrients where a plethora of data allowed evaluation using data almost solely obtained from RCTs e.g. vitamin D (Seamans and Cashman, 2009), and others where there was a lack of suitable RCT studies, and consequently evaluation had to be undertaken using lower quality data e.g. copper (Harvey et al., 2009). In addition to demonstrating the usefulness of systematic review methodology to validate the use of biomarkers of status for a range of micronutrients, it has also highlighted the need for further research to identify and evaluate novel biomarkers of micronutrient status.

Biomarkers for micronutrient related physiological processes

To date, significant emphasis has been placed on researching the biological activity of single micronutrients, or interactions between limited combinations of micronutrients. However, with the development of a systems biology approach, the potential to study the multiple processes that collectively underpin molecular, cellular and whole body physiology may enable an integrated perspective to be taken with regard to the impact of metabolic effects on health (van Ommen et al., 2008). The EURRECA network undertook research to establish novel approaches that may be applied to the assessment of micronutrient status in relation to health. Apart from established biomarkers micronutrient status may also be assessed by measuring health status biomarkers reflecting processes that require sufficient micronutrient availability. Therefore, information on the effects of micronutrient intake and/or status on selected biomarkers related to the overarching metabolic, inflammation and oxidative processes, was extracted from studies that were included based on the criteria described above (see Evidence-based assessment of potential biomarkers). This information was captured by the EURRECA network in collaboration with the European Nutrigenomics Organisation (ENO) on the respective micronutrient pages of the '**NuGOwiki**' (European Nutrigenomics Organisation, 2012, www.nugowiki.org), an open source ENO database where anyone can edit / add information in a typical wiki manner (mediawiki) (Claessens et al., 2013). To fully appraise the impact of micronutrients on health, a more holistic view of the biological effects of multiple micronutrients is needed, including building micronutrient-centered biological networks (van Ommen et al., 2009) and developing suitable statistical methods for assessing individual micronutrient-health effects (Activity 6: 'health space' model) (Bouwman et al., 2012).

Evidence of the direct or indirect effects of individual micronutrients on selected biomarkers for key physiological processes (immune, oxidative and metabolic process) is captured on the micronutrient pages of the NuGOwiki (www.nugowiki.org/). Micronutrient-centered biological networks prepared from extensive literature mining for selenium, vitamin B12 and folate, are also publicly available (www.wikipathways.org). For the purpose of deriving micronutrient requirements, where there are known interactions, it may be useful to investigate and define the complex micronutrient biology network based on micronutrient markers, markers of target function and biological response, micronutrient related health status metabolites and micronutrient related disease parameters.

As an example of this EURRECA approach, information collated from human studies that met the above-mentioned selection criteria (NuGOwiki micronutrient portal, http://www.nugowiki.org/) was used to construct micronutrient biology network models. As an example, the mathematical model for the multiple micronutrient dependency of the inflammatory process can be found in Supplemental Figure 1.

Deriving dietary reference values: Collating sources of evidence (Activity 4)

There is significant disparity in the evidence base for micronutrient recommendations between population groups (Dhonukshe-Rutten et al., 2010a). Figure 6 conceptualises average requirements (AR) for micronutrients as a function of age (population group and age across the life cycle), and highlights the widely different types of evidence and research approaches that underlie these data. RCTs and epidemiological studies provide evidence for the adult population group on optimal nutrition in relation to specific health outcomes and end points; whilst factorial approaches, combined with estimates of bioavailability, are generally used during periods of

growth and development. In order to derive reliable recommendations the most robust data need to be identified and integrated, whilst accounting for exercise and body composition and size (scaling). As illustrated by this Figure, identifying and collating relevant data for the derivation of dietary recommendations should ideally be undertaken using a clearly defined systematic approach which accounts for the micronutrient, the population group, and the health outcome/end point under assessment (Matthys et al., 2011).

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As outlined above (and in Activity 2), nutrient recommendation setting bodies are compelled to use a variety of sources of evidence to derive dietary micronutrient requirements. The availability of data from different types of study with various methodological principles and designs will influence whether the 'factorial' or 'dose response' approach is adopted in the derivation process (Table 4). The factorial approach principally depends on physiological data related to micronutrient losses in balance with absorption. This approach relies on measurements of a variety of factors including requirements for growth, pregnancy and lactation and faecal and urinary losses that determine requirements to maintain plasma levels or body stores resulting in normal tissue and body function and prevention of adverse health effects. Reference values derived by this approach also rely on the application of a bioavailability factor (Fairweather-Tait and Collings, 2010) to convert the physiological requirement into a dietary intake value. The dose response approach is based on the prediction of a physiologically relevant outcome which could be the measurement of an accepted micronutrient status biomarker in response to dietary intake, or the assessment of clinical disease endpoints in relation to intake or status. Therefore, there is a range of study designs that may generate pertinent data including intervention trials on

micronutrient exposure up to cohort (nested case control) studies on micronutrient intake or status as related to intermediate or late health endpoints. The selection of relevant combinations of micronutrients, population groups and health endpoints was discussed previously (see Activity 3).

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Systematic Data Selection

As illustrated by Figure 6, Identifying and collating relevant data for the derivation of dietary recommendations should ideally be undertaken using a clearly defined systematic approach which accounts for the micronutrient, population group, and health outcome/end point under assessment (Matthys et al., 2011). Following adoption of best practice for intake, status and health outcome measures (see Activity 3). EURRECA undertook a series of systematic reviews with the primary aim of identifying robust data for all age and life stage population groups, useful for the derivation of dietary recommendations for the prioritised micronutrients (vitamin B12, iron, zinc, folate, iodine) (Cavelaars et al., 2010). Standardised systematic review protocols and search strategies were developed within EURRECA to facilitate collation of data in three key areas, namely intake-status-health (association) relationships, micronutrient absorption (bioavailability) and factorial estimates. Whilst the rigorous systematic review process ensured comprehensive data retrieval, each protocol and search strategy was specifically tailored to explicit research questions and issues associated with individual micronutrients. Meta-analyses of collated data were conducted to summarise the relevant estimates (Activity 6).

The standardised systematic review process designed and adopted by the EURRECA network is summarised in Figure 7 with further details reported elsewhere (Matthys et al., 2011). Briefly,

the process initially involved conducting multi-database searches (Medline, Embase (both on OvidSP) and the Cochrane Library CENTRAL database), each including micronutrient specific terms and limited to 'humans'. Potentially relevant studies were identified by searching from database inception, and resulting reference lists were screened and sorted on the basis of titles and abstracts. References evidently not meeting the purposes of the review, e.g. animal studies, were excluded at this stage. In order to ensure consistency between reviewers, and to ensure adherence to the inclusion / exclusion criteria, duplicate screening of a minimum of 10% of titles and abstracts was conducted independently by two researchers and differences of opinion resolved through discussion. Full-texts of potentially relevant articles were collected and assessed according to the pre-defined inclusion/exclusion criteria. Abstracts for which the full article was unavailable were not included, and articles were considered in a range of languages spoken by network partners including English, Dutch, French, German, Hungarian, Italian, Norwegian, Polish, Spanish, Greek and Serbian. Again, a minimum of 10% of full-texts were independently assessed by two reviewers. Reference lists of retrieved articles and specifically reviews on the same topic were also checked for relevant studies not identified in the initial search. If appropriate, experts were also contacted to obtain suggestions for additional articles that may have provided pertinent data for the review. Data were extracted into a standardised database, including bibliographic and methodological information, population characteristics, study group details and outcome data. Internal validity indicators specific to the study methodology were identified, and relevant information collected during data extraction in order to facilitate subsequent assessment of the quality of included studies and the risk of bias. Specific details of the search methodologies and data selection used for various EURRECA

systematic reviews (dose-response and factorial approach) are described in the following sections.

----Please Insert Figure 7 Here----

Building blocks for deriving DRVs

Factorial approach and bioavailability

In order to identify data that may be pertinent for deriving recommendations using the factorial approach, the EURRECA network undertook a series of systematic searches with associated data extraction based on common methodology described above (refer to *Systematic data collection).* The overall aim of this activity was to identify and collate relevant studies and associated data relating to micronutrient homeostasis i.e. the balance between losses and maintenance of body pools. Collation included identifying and summarising the evidence for the micronutrient concentration of breast milk, isotope turnover studies used to assess changes in body pools, and measurements of menstrual blood loss. A tailored search strategy was developed for each micronutrient which, to enable identification of relevant studies across all age ranges, was not limited to specific population groups. However, specific search terms relevant to age and physiological stages in relation to micronutrient requirements were included to allow for consideration to be given to issues such as growth and development, including the formation of new tissues in pregnancy and foetal development. Full details of the methodology can be found elsewhere (Hermoso and Vollhardt, 2010). Data were identified for five prioritised micronutrients, namely iron, zinc, folate, vitamin B12 and iodine, and databases containing all extracted data can be accessed on the EURRECA website (Hermoso, 2010a) along with Endnote

libraries of the results of the searches (Claessens et al., 2013; Collings, 2010; Hermoso, 2010b). Micronutrient-specific results of the systematic reviews can be found elsewhere in 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). The quantitative methodology underlying these reviews is explained and illustrated in Activities 5, 6 and 7.

In many cases the factorial approach cannot be used to accurately derive micronutrient reference values without the application of a bioavailability factor to convert the physiological requirement into a dietary intake value (Fairweather-Tait and Collings, 2010). Figure 8 shows the basic equation that can be employed for the calculation of dietary requirements based on the sum of losses and requirements for growth and development adjusted by the appropriate bioavailability factor. Bioavailability is a function of both food (luminal events relating to the composition of foods consumed at any one time) and the individual (host) (systemic factors relating to physiological need and homeostatic factors) and therefore there is no single bioavailability figure that can be assigned to a single food source of a micronutrient. Consequently, host-diet interactions play a significant role in determining the amount of dietary micronutrient available to enter body pools. In order to assess the state-of-the-art with respect to micronutrient bioavailability issues, EURRECA held an expert workshop jointly hosted with the ILSI Europe Additions of Nutrients to Food Task Force to discuss the priorities and challenges of setting dietary reference values (Fairweather-Tait et al., 2010). In addition to a program of presentations focusing on micronutrient-specific aspects of bioavailability, a series of break-out sessions challenged the attendees to consider a range of topical bioavailability issues and how they may

be addressed. An overarching workshop conclusion highlighted the current lack of micronutrient bioavailability data and the associated need for further research.

----Please Insert Figure 8 Here----

Subsequently, in order to attempt to identify robust data that may be used in the calculation of bioavailability factors, EURRECA undertook a series of systematic reviews to quantify and assess the efficiency of micronutrient absorption from whole diets/meals. The specific aim was to analyse and quantify the impact of various dietary enhancers, inhibitors and host-related factors (e.g. genotype) on micronutrient absorption. The ultimate goal was to provide an evidence base from which bioavailability figures can be derived for setting dietary reference values/intakes. Using a similar systematic review methodology to that described above, specifically designed search strategies were tailored for each micronutrient followed by screening and data extraction. Details on the results of the systematic reviews and meta-analysis can be found elsewhere in 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). Further details on the methodological approach to summarising and interpreting the data, and integrating the evidence can be found in Activities 5 and 6 respectively.

Dose response approach

Deriving dietary recommendations using the dose response approach involves assessing the dose-response relationships between at least two of the following three components: dietary micronutrient intake (I), micronutrient body status (S) and health (H) outcomes. The three relationships of specific relevance are represented in the schematic diagram in Figure 9 and include:

- the effect of intake on functional or clinical outcomes (I – H)
- the effect of intake on indicators of exposure or body stores (biomarkers) (I – S)
- the effect of exposure or body stores (biomarkers) on indicators of functional or clinical outcomes (S – H)

----Please Insert Figure 9 Here---

Potential confounders and effect modifiers for the relationships between intake-status, status-health, and intake-health may include age, sex, country of study, ethnicity, social class/living conditions/income, smoking, physical activity, body mass index, total energy intake, intake of other macro and micronutrients, acute illness and inflammation, life stage (pregnancy, lactation, menopausal stage), exposure and outcome at baseline and genotype. Consequently, careful consideration needs to be given to the inclusion / exclusion criteria to ensure that data from each included study are appropriate for analysis.

EURRECA adopted the standardised systematic review approach outlined earlier (Hooper et al., 2009) (Activity 3) to identify and collate data which were potentially useful for the dose response approach. The review for each micronutrient was guided by a protocol that was specifically prepared for each micronutrient. The protocol outlined the eligibility criteria for studies and data that were suitable for inclusion in the review process. Briefly, these criteria included:

- Population groups: infants, children and adolescents, adults, pregnant and lactating women and elderly.
- Only intervention and observational studies (except for intake-status studies where cross-sectional data were also considered).

- Dietary intake data (if assessed using the standards approved in the Best Practice Guidelines for intake (Activity 3)).
- Status data (if the biomarkers of status used for the assessment were identified in the Best Practice Guidelines for status (Activity 3).

The study selection was a stepwise process. Following the search, the initial step was the screening and sorting on basis of title and abstract (minimum 10% duplicate screening by independent reviewer), followed by sorting by relationship (intake-status, status-health, intake-health and intake-status-health) and population groups (adults & elderly and infants, children, adolescent, pregnant & lactating women). Following full text assessment of all potentially relevant papers (minimum 10% duplicate review by independent assessor) key data were extracted and entered into an Access (Microsoft) database (Claessens et al., 2013).Variables of interest included intake, status and health outcomes and measures of the relationship; other relevant extracted data included information on study design, confounders, population size, study duration and methods of intake and status measurement. In addition, a set of indicators of internal validity specific to the type of study e.g. RCT were collected in order to assess the quality of the study and the risk of bias. This included method of sequence generation and allocation, blinding, potential funding bias, number of participants at start, dropouts, dose check, outcome comparability and reproducibility, and similarity of most and least exposed groups at baseline. Based on these indicators, two reviewers decided on the overall risk of bias. Disagreements were resolved by discussion. The criteria for judging these indicators were adapted from the Cochrane Handbook (Higgins and Green, 2008). Databases and search libraries for each of the EURRECA priority micronutrients can be accessed on the EURRECA website

(Berti et al., 2010; Claessens et al., 2013). Details on the results of the systematic reviews and meta-analysis on specific micronutrients can be found elsewhere in 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). Further details on the methodological approach to summarising and interpreting the data, and integrating the evidence can be found in Activities 5 and 6 respectively.

Inter-individual variability

The variation in requirements between individuals within different population groups is generally assumed to be normally distributed, but definitive data are limited to only a few nutrients. Where data are available, the Population Reference Intake (PRI) is set at the average requirement (AR) plus two standard deviations, thus meeting the requirements of 97.5% of the population. In cases where requirements are not normally distributed, appropriate transformation of the data is undertaken to achieve normality. In the majority of cases where data on the inter-individual variation in requirements are unavailable, a coefficient of variation (CV) between 10-20% is used assuming a normal distribution. The selection of CV is made on a case-by-case basis and is set at 1.2, 1.3 or 1.4 times the average requirement for CVs of 10, 15 and 20% respectively.

Variability is due in part to influences of gene polymorphisms on nutrient function within the body. Therefore, the EURRECA network identified data pertinent to understanding or explaining inter-individual variability in micronutrient requirements for different population groups.

Regarding biological variation in requirements, EURRECA explored effects of single nucleotide polymorphisms on micronutrient metabolism, metabolomics data from a multiple micronutrient intervention, and examined biological networks to better understand the interplay between

micronutrients and health at the individual level. To this end, extensive description of the subjects being studied and foods or diets consumed is central to characterise the so-called nutritional phenotype. For this purpose a "Nutritional Phenotype database" (dbNP) was developed in collaboration with Nutrigenomics Organisation (NuGO) and the Netherlands Metabolomics Centre (www.dbnp.org) (van Ommen et al., 2010). The primary aim of this activity was to generate a module for this database containing relevant information on the relation between functional gene polymorphisms on micronutrient metabolism and intake. Specifically, this involved identifying data assessing the impact of functional polymorphisms (e.g. single nucleotide polymorphisms, or SNPs) on micronutrient status biomarkers and associated health outcomes. Five micronutrients were evaluated namely iron, zinc, vitamin B12, selenium and folate.

Inclusion in the polymorphism database required studies to report a statistically significant association between a genotype of relevance to the micronutrient and a EURRECA status biomarker (Activity 3). Searches were conducted using the CENTRAL Cochrane Library, Medline and Embase (both on OvidSP) databases and were based on specific micronutrient, status biomarker and polymorphism terms and limited to humans. Potentially relevant articles were screened and identified in accordance with the process described above. Data from relevant papers were extracted into a tailored database (Claessens et al., 2013) designed to ensure capture of all relevant data. Statistical data on significant relationships pertaining to relevant genotype-status associations were recorded along with specific information on the polymorphisms and demographic details of the population group under evaluation. The resultant database is available as a web resource at http://web-php06.tno.nl/eurreca/index.php and further details on key

polymorphisms associated with micronutrient status are included in each of the micronutrient summary papers for iron (Harvey et al., 2013), zinc (Lowe et al., 2013), selenium (Hurst et al., 2013) and folate (Hoey et al., 2013). To date, due to the lack of relevant data, no information related to SNPs have been used in the derivation of DRVs. The collation of polymorphism data into a single database by the EURRECA network is an initial step towards recognizing future developments and the likelihood of such data being incorporated into the derivation of micronutrient requirements.

Deriving dietary reference values: Appraisal of the evidence (Activity 5)

Once the relevant papers are identified and the data extracted, it is critical to transparently summarize and interpret the available evidence. Systematic literature searches provide the basis for narrative reviews that summarise the studies one by one and qualitatively compare and interpret their results qualitatively. If the health outcomes and exposures are sufficiently comparable, systematic literature searches also provide a basis for quantitative reviews or meta-analyses to go beyond this qualitative review process by systematic extraction and presentation of the quantitative pieces of information, to analyse their variation, and – if possible – pool them to obtain a summary estimate.

Because of unavoidable shortcomings in study design, recruitment, measurement of dietary exposure and health outcomes, etc, the scientific data are subject to random and systematic error and scientific expert opinion is required to decide on in- or excluding studies for further quantitative summary. Therefore, the available studies need to be evaluated according to the quality of their information. To improve transparency of this expert-based qualitative step, the quality indicators of the reviewed papers should be clearly and consistently described.

Study design: observational studies & RCTs

Historically a framework based on 'hierarchy of evidence' has been applied for basing to judge the strength of evidence according to study design. This is because different study designs have different strengths and weaknesses and, thus, different value in informing decisions. Typically, more weight is given to good quality randomised controlled trials (RCTs) and less weight to observational (non-intervention) studies. The rationale is that observational studies are potentially subject to bias and additionally cross-sectional and case control studies may be subject to reverse causality. In spite of this, observational data can also provide useful information if studies meet rigorous quality criteria as set by different authorities (SACN, IOM, EFSA, NORDICS). To examine intake-status-health (I-S-H) associations, systematic reviews were conducted within the framework of EURRECA. RCTs and observational (cohort and cross-sectional) studies, were considered, while case control studies were excluded (nested case control studies were included). Cross-sectional studies were considered only to evaluate associations that describe steady state relations, e.g., between usual nutrient intake and concentration markers, or between socio-economic indicators, micronutrient intake and concentration markers. Depending on the sources of evidence, there are different ways to assess data quality through the application of criteria to assess internal validity (see below). In the framework of the EURRECA systematic reviews, indicators of internal validity were collected during data extraction in order to assess the risk of bias. The indicators are based on Cochrane guidelines and others (Higgins and Green, 2008).

Observational studies

For cohort studies, the following indicators of internal validity were considered: similarity of most & least exposed groups at baseline (in terms of stated confounders), adequate adjustment of potential confounders in the analysis, adequate exposure assessment, completion of dropouts and outcome data, potential funding bias, and other threats to validity.

For cross sectional studies, the following indicators of internal validity were considered: similarity of most & least exposed groups at baseline (in terms of stated confounders), adequate adjustment of potential confounders in the analysis, adequate exposure assessment, and potential funding bias and other threats to validity (see supplementary document 3 for more details).

Randomised Controlled Trials

For studies employing a RCT design, the following indicators of internal validity were considered: method of sequence generation and allocation concealment, blinding, dropouts and dropout reasons, potential funding bias, number of participants at start, dose check (amount of micronutrient provided), dietary intake data reported, outcome comparability and reproducibility, and baseline comparability for determinants of the outcome in the intervention and control groups. Specific criteria are defined in order to assess if the judgement for each item is *yes*, *no*, or *unclear*. For instance, the allocation sequence of an RCT will be adequately generated if the investigators describe a random component in the sequence generation process such as: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, or minimisation (see supplementary document 3 for more details).

For all study designs, based on their respective indicators, two independent reviewers decided on the overall risk of bias (low, moderate, high). For example, in the case of RCTs, low risk of bias was established if internal validity criteria 1-6 were met. Disagreements were resolved by discussion. The criteria for judging these indicators were adapted from the Cochrane Handbook (Higgins and Green, 2008). Further tests can be applied to assess the methodological quality of interventional studies. For instance, the Jadad score is a tool where studies are scored according to the presence of three key methodological features of randomisation, blinding and accountability of all patients, including withdrawals. The methodological quality of the study is then classified into low, medium, or high quality (Houthuizen et al., 2012).

Evaluation of heterogeneity

The overall grading of the evidence is based on the totality of evidence and contains elements of judgement in addition to the assessment of the internal validity as such. The first step is to evaluate whether heterogeneity of results can be attributed to differences in internal validity. Therefore, in the meta-analysis for each of the study types (RCT, prospective and cross sectional) sensitivity analyses were conducted by stratification for ‘low risk’ and ‘> low risk’: the overall evidence was graded as low risk if there were ‘low risk’ studies present and if the results were stable upon exclusion of the studies with ‘> low risk of bias’. In addition, study results were compared between the design types using the RCT (if available) as the reference design; the highest graded study types and study quality was used for arriving at conclusions.

Secondly, once the usable evidence has been identified, in-depth knowledge about specific characteristics of the study populations (e.g. physiology, clinical aspects) is necessary for adequate judgement of the generalizability of results. This judgement will permit deriving

appropriate conclusions which will have important implications for practice and further research. Therefore, based on the number of studies and number of participants, the numerical result and its 95% CI, the heterogeneity of the results is evaluated (which includes statistical tests of heterogeneity). In this process, also characteristics of the micronutrient exposure (dietary or pharmacological doses, chemical species, food matrix) and population characteristics are accounted for (serious nutritional deficiency, or generally adequately fed; in children, adults and the elderly, men and women, etc). Thus, the judgement is therefore based on the consistency, strength and quality of the studies, and takes into account all the available evidence obtained with the various methods, including the knowledge on the mechanism linking nutrient intake and the occurrence of chronic disease (EFSA, 2010; Sheffer and Lewis Taylor, 2008).

In EURRECA the heterogeneity in status or health outcomes was mainly related to dose, and to some extent to life cycle and sex, but not clearly to other covariates. As long as individual patient data are not available to better account for covariates, this implies that the heterogeneity is a real phenomenon that describes the extent to which different populations behave differently. Because the results of DRVs are being applied to different populations in different contexts this variation has to be part of the pooled estimate and has been incorporated in the derivation of DRVs.

Overall quality of the evidence

The assessment of the quality of the data, the inclusion of elements of judgment and the remaining heterogeneity will result in quantitative estimates that do need a number of qualifiers to inform both scientists and decision-makers about the appropriate use of these data for deriving DRVs.

An example of the judgemental issues can be seen in the EURRECA analysis for Vitamin B12. Estimates on micronutrient losses and of bioavailability were derived from different populations but were integrated to arrive at an estimate of the AR. Regarding the dose response approach, there was a sufficient number of adequate RCTs and observational studies to evaluate the intake-status (I-S) association in order to derive ARs in adults and elderly, but extrapolation to younger age groups would be required. On the other hand, there was insufficient sound epidemiological evidence for deriving ARs based on the I-H or S-H relationship when considering cognitive function as the health endpoint.

Scientific decisions concerning the micronutrient needs of populations should be informed by the best available research evidence. Decision-makers are encouraged to make use of the latest research and information, and to ensure that decisions are demonstrably rooted in this knowledge. However, this can be difficult given the large amounts of information generated by individual studies. Carrying out and clearly documenting the meticulous task of summarising data and their well-informed interpretation will lead to a more transparent and reliable decision making process.

Deriving dietary reference values: Integrating the evidence (Activity 6)

Deriving dietary reference values originated in dates from the era of deficiencies. Their ability to meet the present health challenges must be evaluated and new approaches need to be developed to are required that can incorporate epidemiological evidence on chronic diseases, are be in line with concepts in risk assessment, build on aetiological models of disease causation, and are be consistent with current approaches to evaluate and recommend on population nutrient intake (Sheffer and Lewis Taylor, 2008). As explained in Activity 1, there is a gradual shift from

setting dietary reference values (DRVs) based on preventing deficiencies and on amounts needed to maintain body stores (Activity 4) to optimise health, prevent chronic disease, and avoid consuming too much of a nutrient. The interest in using risk reduction of chronic disease as the basis for establishing micronutrient recommendations requires insight in the causal relationship between micronutrients and the disease or health outcome (Activity 4). This places greater emphasis on which nutritional intermediates or health outcomes are being considered and where the resulting distribution of requirements is positioned for the apparently healthy population rather than using a distribution which suffices to repair a single micronutrient deficiency until normal function is achieved (see Figure 6). Additionally, the relationship between the intake of a nutrient (I) and the risk of disease (D) based on scientific evidence needs to be quantified. Consequently, a dose-response relationship between intake (I) and status/functional markers (S) must be determined. The integration of the evidence has to accommodate systematic variations between studies originating from (1) differences in study quality (assessed by internal validity), (2) study population (age, gender, body composition and energy needs), (3) micronutrient dose (level, range, duration, mode of administration), and (4) other population characteristics (growth, pregnancy, lactation, etc.).

Quantification of the evidence

The principles of meta-analysis to quantitatively summarize research data, have been sufficiently described (refs). In this Activity specific issues relevant to the meta-analyses conducted in EURRECA are briefly outlined. As described in Activity 4, standardised systematic review protocols and search strategies were developed within EURRECA. Following appraisal of the evidence, study results were visualised by forest plots, (see Supplementary document 4). Of

course, this approach requires assumptions on the shape of the dose-response relationship. To quantify the strength of the dose response relationship, the rigorous but flexible transformation to a double loge-scale was chosen. This transformation is suitable to describe dose response as a non-linear but monotonic concave function of dose, i.e. the same additional dose is less effective at higher levels of intake, which is considered a common phenomenon shape in biology (see Figure 10). This transformation can be applied to both RCT data and observational data and also allows one to compare and integrate RCT and observational studies on intake and biomarkers of status (Bar et al., 1991). Clearly, the use of this double loge scale is specific for continuous responses and not applicable for dichotomous outcomes (although risk is usually also modelled on the loge scale). In principle, when the health criterion for the specified health outcome or status has been defined, an appropriate average requirement (AR) can be derived. In addition to measures of dose-response, it is also possible to meta-analyse data on the correlation between the intake and response. This can be used to arrive at a stochastic model to derive ARs and PRI. The regression slopes of this model are based on results from intervention studies using high doses of micronutrients, whereas the intercept for the regression lines is determined by the means of the usual dietary intake and the mean value of the concentration marker. As the range in intake in intervention studies is large as compared to usual dietary intake, it is at present assumed that the well-known errors in the latter assessing the mean baseline population intake are not likely to cause large systematic errors in our approach. For the transformation of extracted estimates, the derivation of study-specific regression slopes and the pooling of these slopes, we refer to Supplementary document 4.

----Please Insert Figure 10 Here----

Expert consultation

Expert knowledge and critical evaluation will always be needed for the appraisal of the collected data, interpretation of the results and potential refinement of the analysis. Transparency and alignment of (the process of setting) micronutrient recommendations is necessary to improve the objectivity and transparency of values that are derived by national, regional and international groups; provide a common basis or background for groups of experts to consider throughout processes that lead to micronutrient recommendations; supply a common basis for objectives and national policies such as fortification programmes and for addressing regulatory and trade issues (King and Garza, 2007). Following this procedure the expert consultation is pivotal at several moments in order to keep track of content-related issues, nevertheless the expert's opinion should aim for transparency (EFSA, 2009; European Commission, 2000, 2001b). As introduced in Activity 1, experts should be consulted to check the prioritisation process. Scientists who already are familiar with the topics (either micronutrients or health outcomes) should ideally perform the systematic reviews. For the integration of the available data, the experts should be re-consulted in order to address remaining issues to be solved, check for completion and for correct representation of the data.

Factorial & bioavailability approach

Activities 4 and 5 described the data collection of factorial and bioavailability studies. The resulting pooled estimates of needs (numerator) and bioavailability (denominator) are used to derive the AR which represents the intake at which an individual has a 50% chance of meeting his or her requirements. In case the requirements apply to specific population groups, such as infants, children, pregnant women or lactating mothers, the requirements depend on basic

physiological needs plus an additional amount to account for growth or additional needs (lactation), which requires a combination of factorial and other methods to derive ARs.

To allow for between-subject variation in requirements, a distribution of individual nutrient levels is postulated, with its SD usually set at a CV of 10-20% of the AR. Moreover, deriving an AR is associated with many uncertainties. For instance, most factorial estimates and bioavailability studies included relatively small selected population groups, did not address all factors in the factorial model, did not always address whole meals or food patterns (essential to calculate a universal bioavailability factor), etcetera. Therefore the estimated AR also contains scientific uncertainty. If there is much uncertainty in the estimation of the AR and little is known on the distribution of individual requirements, then usually the higher CV is selected. In principle, high quality studies or variables that can explain biological variability in nutrient needs could lead to the choice of a smaller CV for subgroup-specific ARs.

When using the factorial approach to derive reference values, information on dose response studies and other health outcomes must be considered as well. In principle, the factorial estimates and dose response estimates on intake-status-health relationships are based on methodologically independent data and for setting the reference values, the combined quantitative information of the factorial estimates and dose response data should be both considered (see Figure 2 and Activity 1).

Dose-response model

The dose-response approach ideally combines I – S, I – H, and S – H data. Within the scope of the EURRECA network, a bivariate stochastic model was initially used to describe the relation between micronutrient intake and status (I – S) by incorporating the variability between

individuals for both intake and status measures (Bar et al., 1991). Although most nutritionists are not familiar with this type of bivariate models, this approach is commonly used in food safety. Although Carriquiry (Carriquiry, 1999) has used a stochastic model to underpin the AR-cutpoint method for evaluation of population intakes, our stochastic model is different as it uses biomarkers and intake data to derive the AR. Apart from a meta-analysis of associations (Activity 5), the model additionally requires information on the correlation between the two variables (the stochastic component) as well as average intake and average status (e.g. from monitoring data) to allow for the predictive component of the model. Dullemeijer et al (1991) based the associations of their stochastic model on the RCTs and the intercepts on observational studies identified for vitamin B12 intake and status: The joint distribution of $\log_e$ intake and $\log_e$ plasma or serum vitamin B12 concentrations is assumed to be bivariate normal with means (μX, μY), standard deviations (σX, σY) and correlation ρ, implying a linear dose-response relation on these scales.

Using the assumption that the AR represents an intake which is sufficient for 50% of the population (Activity 1), the PRI may be derived under the assumption of parallel individual lines as the intake at which the probability of reaching vitamin B12 status is equal or less than the cut-off of 2.5%. Finally, for the derivation of reference values the bivariate marginal distribution I-S is of interest once thresholds on the health or status variable are set; the trivariate model could simultaneously account for the I-H and S-H associations as well. Scenarios regarding desirable changes in nutrient intake are considered as shifts of the bi/trivariate distribution along the regression line for predicting the status or health outcome. The model can be used to derive intake levels which would be required to attain desirable values of I or S for specified

proportions of the population (resembling though not analogous to the definition of AR and PRI) (Figure 11). It should be noted that the bivariate I-S model is based on physiological health criteria, similar to most applications of the factorial approach.

----Please Insert Figure 11 Here----

A major advantage of the stochastic method is that it largely extends the evidence base for deriving DRVs because it allows the use of widely available dose response data on I-S and I-H associations from different types of studies (RCT's and observational). However, the practicability of this stochastic method for deriving the AR and recommended intake depends on the justification of the assumptions made. Further work needs to be done to evaluate the sensitivity to these assumptions and to allow for these limitations.

So far, EURRECA explored a bivariate stochastic model, but it can be extended to a trivariate model, which also includes health outcomes in addition to intake and status. The trivariate intake-status-health (I-S-H) model could incorporate all published information from randomised controlled trials (RCT) and observational studies on the I-S, I-H and S-H dose-response association, as the basis for deriving micronutrient reference values. In short, the trivariate model combines the evidence of the three I-S, S-H and I-H dose-response associations in separate meta-analyses, the results of which are combined using the assumption of conditional independence, i.e. the effect of I on H is fully mediated by S. This integrated evidence is then combined with the results of the meta-analyses of the data on the marginal distribution of I, S and H to obtain the final trivariate stochastic model. Future extension of the model could incorporate covariates and/or individual patient data (rather than meta-analysed data).

Scaling of ARs to other population groups

When no original research data are available for certain population groups – most often this concerns infants and children – other methods need to be applied to define and align reference values or Ars. The derivation of DRVs for infants and children in current dietary reference standards is often based on methods of extrapolation or interpolation (or in other words *scaling*) from adult data or breast milk, owing to the paucity of relevant research data available, but these are not consistent across reports (Atkinson and Koletzko, 2007).

Currently, the different methods used for the derivation of DRVs for infants and children in Europe and worldwide have led to considerable differences and inconsistencies in DRVs and age groups between countries for the same age group of infants or children. (Atkinson and Koletzko, 2007) (Prentice et al., 2004). This diversity of values may be attributed to one or more of the following points: a) no universally accepted growth or (considerable differences in) reference data, b) source documents often do not provide detailed information on the derivation of the reference values, c) lack of nutrient-specific growth factors that take into account specific metabolic properties and the turnover of each micronutrient, d) varying content of nutrients in breast-milk among different studies, e) use of different extrapolation methods to obtain DRVs and recommendations in each country, f) inconsistent application of scaling methods within one age group.

There are several methods for extrapolation which are based on different assumptions. Within EURRECA we selected two methods which are used most often and which are considered adequate to estimate requirements (see Figure 12).

----Please Insert Figure 12 Here----

Biological modelling for multiple micronutrients

For personalised multi-micronutrient recommendations information at biological process level should be integrated and visualised. To this end, the 'health space' model was developed (Figure 13). This model is a statistical visualisation method, which addresses the effects of treatment in individual subjects. The visualization is based on predefined biological processes as determined by systems-biological datasets (metabolomics, proteomics and transcriptomics). This allows one to evaluate biological effects depending on shifts of either groups or subjects in the space predefined by the axes, which illustrate specific biological processes. We built a conceptual multivariate model for each axis to represent several biological processes. In this space each subject has his or her own score on each axis/process, indicating to which extent the treatment affects the related process (Bouwman et al., 2012). For instance the oxidation status can be represented by an axis which is quantified by a combination of markers (Bouwman et al., 2012; van Ommen et al., 2008). Assessment of the individual's health status by measuring these markers combined with the collated evidence for micronutrient (e.g. vitamin C and E) effects on these markers (Activity 3) allows for individualised micronutrient recommendations based on the nutritional health space. Applying the health space method on data of a human intervention with an anti-inflammatory dietary mix, has shown that the model allows visualization of an individual's health status based on the assembly of omics data in biologically relevant processes multiple results and facilitates the interpretation (application of the health space is extensively described in (Bouwman et al., 2012)). The health space in the published example was built on treated (with a dietary anti-inflammatory mix) and untreated subjects. The model in his example presents treatment group effects, subgroups and individual responses, since all subjects are

represented individually in the health space visualisation. In this example, it was assumed that treated subjects were more healthy than untreated. Unfortunately As health does not have an absolute definition, which makes it is hard to define the precise location of the origin , which reflects by definition the most healthy status in the health space visualisationof the space. However, the model may help to define a healthy area and may show that the health area may be different for certain subgroups. With the underlying models linking micronutrients to specific processes, different dietary recommendations may be derived for these different subgroups. This concept is currently applied and further extended at IABC (www.iabc.ch). Regarding micronutrient function, within EURRECA, the relationship between micronutrient intake and/or status and a range of biomarkers (e.g. metabolomics), representing inflammatory, oxidative stress and metabolic stress processes, was reviewed (www.micronutrientgenomics.org or http://wiki.nugo.org/index.php/Category:Micronutrients). The selected biomarkers are metabolites that are known to respond to dietary interventions and are associated with (or are predictive of) certain chronic metabolic diseases. For selenium, folate and vitamin B12 biological networks have been developed on the basis of metabolic connections between micronutrient markers of exposure to food components, markers of target function and biological response, micronutrient-related status metabolites and micronutrient-related disease parameters (see http://www.wikipathways.org/index.php). This concept is an interesting option to be further explored for mechanistic underpinning and incorporation of the individual's genetic information (van Ommen et al., 2010). The health space model could eventually provide a mechanistic underpinning for other models such as the Intake-Status bivariate model and the I-S-H trivariate model.

----Please Insert Figure 13 Here----

Monitoring and evaluating: Nutrient intake & status of population groups (Activity 7)

Dietary Reference Values are the main instrument in diet planning and nutritional assessment. In addition to evaluation and monitoring of nutritional situation, they also supply the information necessary for the development of food labels, nutrition programs and for regulations related to fortification.

In Europe, data collected by surveillance are used to evaluate population nutritional health and give early warning information on malnutrition and nutrition health related problems. That implies that surveillances are considered as a first "screening test" to identify potential nutritional problems.

Within EURRECA, nutrient intake values were used for evaluating the dietary adequacy of population groups and for identification of those that are at risk of low intake. Upper levels of micronutrient intake that could induce a risk of excessive intake both from the diet and supplements were not addressed by EURRECA.

Assessing dietary intake and nutritional status

Assessment of dietary intake and nutritional status is used to estimate the proportion of the population that is at risk of inadequacy, that is, whose nutrient intake and status levels are below the reference cut off values (Jensen et al., 1991). Within the EURRECA Network, the dietary assessment instruments and population surveillance data and the methods to evaluate inadequacy of micronutrient intake in Europe were reviewed (Activity 3).Two methods are preferable to

evaluate adequacy of intake at the population level: the probability approach and the cut-point method (Carriquiry, 1999), with the latter used most widely (Tabacchi et al., 2009).

For application of either method, a reliable estimate of population usual intake is needed. Usual intake reflects only the variation in usual intake among members of the population and should exclude day to day variability in daily intakes (Jensen et al., 1991). It implies shrinking the distribution of observed intake to accommodate for random measurement errors, i.e. assuming no systematic error. In addition, estimated usual intakes of individuals should be independent of each individual's requirement. To use the probability approach the joint distribution of usual daily intakes and of requirements should be known. Figure 14 presents an example of how risk of inadequate intake can be estimated if the distribution of requirement or a given micronutrient is known.

-----Please Insert Figure 14 Here----

However, although data on usual nutrient intakes are available, information on requirement distribution are seldom explicitly known and thus for many micronutrients a rough estimate of the AR and its SD is often used for the life stage groups considered.

The cut point method does not require such extensive data on the distribution of requirements, but some other assumptions must be fulfilled: i) when intakes and requirements must be independent or have low correlation, ii) the requirement distribution must be symmetric (e.g. the iron requirements distribution in menstruating women is known to be highly skewed due to iron losses) and iii) variability in intakes among individuals in the group must be large compared to the variability in requirements of the individuals (Institute of Medicine, 2000). The cut point method estimates the prevalence of inadequacy as the proportion of individuals whose usual

intake is below the AR (AR: amount of nutrient that covers 50% of the population's requirements). Figure 15 shows an example of the application of the AR- cut point method for joint intake and requirement data.

----Please Insert Figure 15 Here----

To identify vulnerable groups with inadequate micronutrient intake and/or status, a search was conducted in open access and grey literature sources. The aim was to collect the best quality data that report on micronutrient intake and/or status, and that fulfil a priori quality criteria for study characteristics (Activity 3). Studies that were included in the analysis had focused on the EURRECA prioritized micronutrients and had used the EURRECA recommended best practice dietary intake assessment methods and biomarkers of nutritional status (Activities 1 & 3). Data were collected for all life- stage groups including low income and immigrants. Despite limitations on the intake data gathered this way, primarily lack of data for some age groups and non-harmonised study methodologies, the cut point method was applied to evaluate the proportion of the population at risk of nutritional deficiency. There were used Average Requirements derived for the Nordic countries (Nordic Council of Ministers, 2004) as these are the most recent references values set for a series of European countries. If ARs for micronutrients in Nordic countries were not reported (calcium and vitamin D in adults, all micronutrients in children), ARs published for the USA/Canada by the Institute of Medicine of the National Academies, Food and Nutrition Board, were used (Institute of Medicine, 1998).

Data on intake of vitamin C, vitamin D, vitamin B 12, folic acid, calcium, zinc and iron (males only) from seven European countries were used for assessment of inadequacy by applying the cut point method. Figure 16 shows the proportion of micronutrients, for which there are

inadequate intakes above 20%. Among males, the highest ratios of inadequate intakes were found in Finland and Sweden: out of seven micronutrients analysed, there was observed inadequate intake of three and four micronutrients, respectively. Among females, for which inadequacy was estimated for six micronutrients, the highest ratios of inadequate intakes were found in Ireland and the UK: six and five micronutrients, respectively.

----Please Insert Figure 16 Here----

For the populations where the study data did not meet the best practice criteria for intake methods (Activity 3) the AR cut-point method could not be applied: for example, methodologies to assess micronutrient intake differed widely between nutritional surveys from Central and Eastern Europe. More specifically, for estimating micronutrient intake, the remaining random error was large for FFQs, whereas for the 24hR-based surveys, it was dependent on the number of replicates and the use of shrinkage methods. Therefore, the width of the distribution of intakes lacked comparability between the surveys, which prohibited estimation of the prevalence of micronutrient inadequacy. However, their ability to (roughly) estimate mean population intake was considered sufficient, so reported mean intake levels were compared with the ARs proposed by Nordic Nutrient Recommendations (Nordic Council of Ministers, 2004). Figure 17 shows mean calcium intake in milligrams per day (standard deviation) by country, for males (M) and females (F) (Novakovic et al., 2013). For those countries where the mean intake was below the AR, there is clearly a risk of inadequacy: in CEE, four out of eight countries had a mean intake of calcium below the AR among males, and in three countries among females.

----Insert Figure 17 here-----

With respect to evaluation of biomarkers for adequate micronutrient status, the EURRECA Best Practice Guidelines were followed (Activity 3). Cut-off values to indicate a risk of inadequacy in micronutrient status were defined on the basis of a literature review and were mainly based on values proposed by the World Health Organisation and other authorities. Figure 18 shows an example of evaluation of iodine status for children and adolescents in Europe: data from Central and Eastern Europe indicate to mild iodine deficiency in some countries (Novakovic et al., 2013).

----Insert Figure 18 here----

The former approaches to evaluate micronutrient inadequacy have intrinsic limitations. To enable comparison of the data that stem from the studies with different dietary methodologies. The best practice guidelines required that a single 24hr recall or food records, or replicates for at least 3 days, if less than 3 days then adjusted for intra-individual variability, or a validated FFQ (Activity 3).For micronutrients found in a limited number of foods, using a short term reference period will probably miss information on frequency of intake, whereas an FFQ will overestimate the intake of certain food groups such as vegetables (Roman Vinas et al., 2011). These reporting errors will affect the validity of the prevalence of nutrient intake inadequacy when applying the cut point method.

For the cross country comparison, even though when countries had applied the same methodology for estimation of prevalence of inadequacy such as the cut point method, diversity in country specific dietary reference values (e.g. AR) can induce a substantial variation in estimating the prevalence of inadequacy.

Assessing health status reflecting the nutritional status

Biomarkers for measuring nutrient status identified by EURRECA are to be used for epidemiological analysis and can be obtained from blood or urine. The list of biomarkers used in EURRECA for evaluation of inadequacy in status was a result of the literature review of the key publications issued by the World Health Organisation (WHO), the Institute of Medicine and other authorities, as well as consulting micronutrient experts. More details on other biomarkers and the methodology of Best Practice Guidelines (BPG) (Activity 3).

Reported levels of priority micronutrients (folate, vitamin B12, zinc, iron and iodine) were compared to reference values proposed in Activity 3, the latter being based on key references mostly published by the World Health Organization in cooperation with other institutions (Activity 3). The levels below the cut off or below the optimal range point to a risk for inadequacy, i.e. depending on the marker used, there were indicated that the dietary intake was insufficient over the medium or long term.

These biomarkers can be used either in analysis of epidemiological data or to be applied in field work. Some of them are used those to indicate a health risk. For example, the most common cause of anaemia is iron deficiency and the blood levels of haemoglobin concentrations can be used to detect long term inadequate intake of iron. From the public health perspective if the prevalence of anaemia at 4.9% or less, it is categorised as acceptable proportion of inadequacy (Gorstein et al., 2007). Another example is iodine: median level of urinary iodine concentration reflects iodine nutrition and it is used to detect mild to severe iodine deficiency.

Identifying vulnerable groups

In Activity 1, population (sub) groups which are vulnerable because of higher requirements, accounted for in deriving DRVs have been addressed. Here, we focus on vulnerability because of high risk of low intake rather than increased physiological needs. Low income and immigrant groups tend to have less optimal nutritional status because of a lower intake (Church et al., 2006; Darmon and Drewnowski, 2008; James et al., 1997). Identification of such groups may be relevant to the formulation of micronutrient policies. Therefore, EURRECA collected European-wide data on micronutrient intake and status in order to identify such vulnerable population groups for a selected set of micronutrients. To do so, an initial step was to have clear definitions, i.e. search terms to be used for identification and analysis of the studies from scientific electronic databases.

To define low income groups, key documents were screened on poverty, socio-economic status/position and diet: systematic reviews available in open access database (PubMed), The WHO and collaborating bodies' publications (DETERMINE Project Working document No1, www.health-inequalities.eu; http://www.who.int/en), EC/Eurostat statistical information (www.ec.europa.eu) and data from grey literature (Brandolini, 2009). Based on these data, search terms for low income groups were defined: low income, indigenous population, social class, poverty and socioeconomic factors.

Search terms for immigrants involved commonly used descriptors as proposed in PubMed database: emigration and immigration, migration, foreigner, resettlement. With respect to definition of host country, European Union was limited to those comprising the former EU-15 till 1st May 2004. To collect the data on intake in low income and/or immigrants, a

comprehensive review was conducted that included a structured Medline search, related references screening and key expert consultations. Study inclusion criterion followed general EURRECA guideline on dietary intake and study characteristics (Activities 1 & 3).

Immigrant and low income/low SES groups

Evidence suggests that immigrant populations constitute a vulnerable group for inadequate nutrient intake, of which the most marginalised and isolated groups, such as the Roma/Gypsy populations, present higher risk (Ngo et al.). They often try to maintain their traditional food pattern and the food chains in their new societies do often do not provide the opportunity to do so. On top of that, the language and financial means may inhibit socialisation putting them on the lower socioeconomic strata of the recipient country. Poor socioeconomic status and life style factors, including diet might contribute to their nutritional vulnerability.

People from low-income households typically have less nutritionally adequate diets, especially those who live for long periods of time on limited incomes. In addition, among other factors, lower literacy, numerical and language skills, physical disabilities and mental health problems are more common in low-income groups, as well as low motivation, and as such, constitute obstacles when identifying and assessing this population's food and nutrient intakes (Hoey et al., 2013). The above-mentioned evidence indicates the need to identify different dietary assessment methods that are appropriate for low-income groups.

Table 5 shows the definitions and the proportion of low income and immigrants reported by Eurostat, the statistical office of the European Union, on foreign citizens in the EU27 Member States, EFTA and Candidate countries.

----Please Insert Table 5 Here----

Determinants of micronutrient inadequacy

Dietary inadequacy can be observed in populations because of limitations of the measurements instruments, that affecting either the systematic or random errors (see above); in principle, such uncertainties should be bypassed by well-applied inclusion criteria (when existing data are used) or sufficiently standardised surveillance methodology (for future pan-European nutrition surveillance). For immigrants and low income/low SES groups additional considerations apply. Evaluating dietary intake of immigrant populations requires special attention to:

- sampling and recruiting, instruments used, method of administration, food composition database, acculturation;
- consumption in those eating from a shared serving dish/pot, understanding of food terms and concepts, scarce information on ethnic dishes and recipes, culture-specific foods and portion sizes;
- language issues: the use of forward and back-translation is a widely used method in cross-cultural research, and when combined with additional bilingual and monolingual post-translation testing, it is considered as the most complete instrument translation process (Ngo et al.).

Similarly, when assessing the dietary intake of low income / low SES groups, the following points require specific attention:

- poor motivation of the low income populations
- variations in the level of language and numeric skills across the whole sample could induce difficulty in completing dietary records unless assistance is provided by either interviewers or other household members.

Four multiple-pass 24 h recalls were shown to be the most appropriate method for a study of diet and nutrition in low-income households (Vucic et al., 2009).

Current evidence suggests that apart from income, there are other socioeconomic and cultural factors that influence micronutrient intake and/or status: education, occupation, employment, urbanisation, marital status, race/ethnicity.

Therefore, EURRECA included education and occupation as two proxy key determinants of micronutrient intake and evaluated their association with differences in micronutrient intake and/or status. Methodology comprised a search in Medline and Embase to collect original studies that followed general EURRECA guideline on dietary intake and study characteristics (Activities 1 & 3).

For the evaluation of micronutrient adequacy in low SES groups there are several aspects to consider when analysing available data: i) existing evidence on micronutrient intake and/or status across different SES levels in Europe is scarce, especially for children and for all life stages in Central and Eastern Europe; ii) available publications differ in their categorisation of groups for indicator of interest (e.g: for education studies have stratified subjects within 2- 4 groups, for occupation 2-3, for income 2-4 groups); iii) studies applied different dietary intake instruments, etc. Figure 19 shows example result from this publication: mean intake of vitamin C in lowest and highest socioeconomic (SES) group in adults/elderly and children by different socioeconomic indicator, and in comparison to AR (Novakovic et al.).

----Please Insert Figure 19 Here----

To overcome these methodological constraints and produce the results that are based on harmonised and comparable data, EURRECA has included additional work on evaluation of data

from two European projects, i.e. HELENA (www.helenastudy.com) and EPIC (www.epic.iarc.fr). Work on assessment of micronutrient intake in adolescents (HELENA) and adults and elderly (EPIC) in association with SES indicators is on-going and the results from these publications will be made available for supporting nutritional policy in Europe.

Using dietary reference values in policy making: Identifying policy options (Activity 8)

This activity describes the complex processes through which public health nutrition policy development is linked to micronutrient recommendations.

The drive towards evidence based policy has been typified by: 1) a tendency to treat cost effectiveness and feasibility as key criteria for policy selection, as exemplified by a rise of health economics and impact assessments as evidence for policy; 2) a proliferation of frameworks and decision-making tools, usually linear in character, developed in order to increase evidence pull and utilisation through anticipatory problem-solving, planning and rational choice and often focused on developing institutional forms that would act as bridges between research and policy communities (e.g. Scientific Advisory Bodies) (Lavis et al., 2009; Oxman et al., 2009).

The need to expand the range of evidence that influences the preferred policy option has become apparent following a EURRECA case study based on folate recommendations (Timotijevic et al., 2011a). It was shown that the link between DRVs, as the scientific evidence underpinning decisions about nutrition policies, and final policy action is not always made explicit and that the scientific advisory committee's recommendation of mandatory food fortification with folic acid in order to achieve recommended intake is variably applied in policy across Europe (Timotijevic et al., 2011a).

Based on these observations, EURRECA has developed steps for decision making that link DRVs with the final policy action, depicted in figure 20. These steps correspond to some extent to the depiction of the linear model of RAF (MacKerras, 2012), though is more detailed about the range of considerations that are typically considered. It is developed with an aim of depicting the thinking requirements for linking DRVs and policy action. The choice of an appropriate public health nutrition policy option (or a combination thereof) is premised upon policy makers' considerations of a range of evidence. At the heart of the policy process is defining the policy goal and identifying appropriate policy action.

----Please Insert Figure 20 Here----

Identify policy goals (e.g. health outcome)

A public health nutrition policy goal can be framed as achieving a desirable or decreasing the risks of undesirable nutrition-related health outcomes. Key to identifying the policy goal is clarifying the strength, relevance and degree of uncertainty around the evidence linking nutrient intake to nutrient status as well as nutrient intake/status to a health outcome (Dhonukshe-Rutten et al., 2010b). This work is typically conducted by SABs resulting in a set of DRVs. These DRVs can provide reference points for adequate and optimal intakes for a population or sub-population which can be combined with other sets of information (e.g. monitoring data from national nutritional surveys, advice from key stakeholders, over exposure data) and used (by the SAB, government or another body) to set nutrient/dietary recommendations and goals.

Although nutrient intake is ultimately a nutritional measure, it is achieved through several food-related behaviours that may include food choice, food storage, preparation and food occasions

(when and how it is eaten). Social & behavioural science provides useful insights into the hugely complex dynamic of food choice (Jensen et al., 2012). First, clarity about the contexts that define nutrient intake, which include the sources of the targeted nutrient, the targeted population and the availability of foods, is a necessary starting point in considering nutrient-relevant behaviours (and the range of policy options for behaviour change). It is also important to be clear about the kind of behavioural changes required to achieve a nutrient-relevant change - whether the nutrient intake needs to be increased or decreased - and to understand that the link between food and nutrient intake is complex since food choices are interrelated. The challenge is even greater when considering the intake of several nutrients. EURRECA have argued that moving beyond simple models of behaviour change to consider a range of behavioural mechanisms underpinning behaviour changes is an important step in unpicking multiple influences on dietary behaviour (Jensen et al., 2012).

Public health nutrition policy options relevant to micronutrient recommendations can broadly be divided into those that require voluntary behaviour change, those that incentivise or punish through economic means (awards/taxes), those that enforce a particular behaviour or choice (e.g. regulation through mandating fortification) and those which rely on collaborations (e.g. private-public partnerships) and self-regulation (e.g. voluntary codes of conduct) (Timotijevic et al., 2010a). Considerations of the key objectives of the existing policy, their timeline (both historically and in the context of further policy development and application), cost and who is involved in both the development and delivery of the policy are some of the key parameters of policy options selection (Kingdon, 2003). In addition, the key values for consideration of policy options - equity, efficiency, security and liberty - will be guiding principles of policy making.

Evidence derived from stakeholder participations is also sought to establish the dominant values for policy making. Table 6 below summarises some of the common policy options and 'catalysts of change' (the specific policy actions and interventions) in public health nutrition policy. In relation to public health nutrition policy social voluntary options (usually targeting general diet), and to a lesser extent regulatory policy options (usually targeting specific nutrients) are preferred policy options (see Table 7).

There is a wider context to considerations that shape decision making. Ethical considerations are often invoked in deliberations of stakeholders about public health nutrition policy. Public participatory approaches or ethical reviews/consultations often engage in balancing the right to the autonomy of the individual in relation to food choice and consumption, with other principles (e.g. equity, social justice). The framing of the problem by the significant opinion leaders such as the media, think tanks or major NGOs is taken into account. Broader beliefs, values and practices are also a part of the wider context. Other important aspects of the evidence from the wider context include international (non-binding) guidelines and recommendations, global trends that are not directly related to public health nutrition (e.g. financial crisis) as well as technical capacities and infrastructure for the delivery of policy options.

----Please Insert Table 6 Here----

Policy action is a product of iterative considerations of evidence within and across each of these steps. Final action will be selected from a number of options (see Table 6).

Explicit and transparent process

EURRECA evaluated the step model of public health nutrition policy making (Figure 20) for its usefulness in capturing the actual processes of micronutrient–relevant policy decisions through:

1. A workshop with key stakeholders with a view of refining the Steps of public health nutrition decision-making and scoping out the supporting materials and guidelines for the framework.
2. Case studies (N=18) based on triangulated evidence from interviews, desk research and the workshop to map the existing nutrition policy decision-making onto the Steps of public health nutrition decision-making

The ideal of a rational-linear model of public health nutrition policy making (Figure 20), with its emphasis upon orderly consideration of different types of evidence is difficult to capturedoes not exist in practice. These findings are not new, it has been long acknowledged that the processes through which public policy is formed are exceedingly complex (Kingdon, 2003). In recognition of this, EURRECA has subsequently developed an alternative depiction of the process (Figure 21). This Public Health Nutrition Policy Framework describes what considerations can influence the way in which nutrition policy goal – a desired health outcome - is linked to policy action. Its main premise is that a) contexts that form a backdrop of public health nutrition policy development vary and therefore the orderly stepwise approach is untenable and can hide the real influences upon policy decisions; b) the same type of evidence can be used to answer different policy-relevant questions and therefore it should not be tied to a specific step; c) questions relevant to each step can be addressed using a combination of evidence. The three sources of evidence are broadly defined as: Science, which includes both natural (e.g. nutrition/bio-medical, epidemiological) and social sciences (e.g. psychology, sociology); Institutions and Policy (which

includes e.g. evidence about regulatory frameworks, data on existing policy, governance networks); and Wider Context (which for instance includes international guidelines, wider ideology, ethics). Unlike the linear model of RAF (MacKerras, 2012), the new representation simply classifies evidence into logical types and leaves it to the decision-maker to decide at what point and for what critical question they will source different evidence. The Public Health Nutrition Policy Framework (Figure 21) aims to support greater transparency through making explicit the sources of evidence in the complex process of decision-making from policy goal to policy action, without constraining the process to a linear format.

---Please Insert Figure 21 Here---

Using dietary reference values in policy making: Evaluating policy implementation (Activity 9)

Policy implementation and evaluation has been included here to acknowledge the role of micronutrient requirements in the wider public health nutrition context (research, policy and practice). The work of EURRECA centred upon the activities previously presented. However, a small number of EURRECA research findings were deemed relevant to policy implementation and evaluation. These have been detailed below to illustrate how data from this activity could be used to inform the selection of effective policy options, as well as feedback information on the need to review a policy or the micronutrient requirements themselves.

Included below are descriptions of currently implemented policies and evaluation measures, as well as perceived barriers to policy implementation. For comprehensive data and guidelines on nutrition policy implementation and evaluation in Europe please see other European Commission

funded research projects, United Nations organisations or European Commission departments that have been recently active in this area e.g. The EATWELL project, the Directorate-General for Health and Consumers European - DG SANCO, UNICEF and WHO (Branca et al., 2009; Capacci et al., 2012; European Commission, 2010; Oxman et al., 2006; Trübswasser and Branca, 2009; Traill et al., 2010).

Current policies in Europe

In 2007, EURRECA conducted a questionnaire survey with key informants representing 35 European countries/regions (see Table 7 (de Wit et al., 2008). Each informant was asked to indicate the policies implemented in their country relevant to 20 pre-defined micronutrients using both open free format and closed multiple choice option questions. Results suggested that across a range of micronutrients the most frequently implemented policies were directed at the general diet rather than specific micronutrients. These took the form of social and voluntary policies, such as food-based dietary guidelines and general health education. Nevertheless, almost a third of those surveyed also implemented policies targeted at one or more of the following nutrients, namely calcium, folate, iodine, iron, sodium, vitamin A and vitamin D. These policy options included regulation and legislation, self-regulation and intervention short of legislation, for example, voluntary/mandatory fortification, supplementation and labelling programmes (de Wit et al., 2008; Dhonukshe-Rutten et al., 2010a). The policies implemented may differ between nutrients and countries/regions for many of the reasons previously discussed in Activities 1-8. For example a policy relevant to iodine was implemented in the majority of countries where 21 out of 35 countries conducted voluntary/mandatory fortification (e.g. salt iodisation). It is likely this was due to the long standing coordinated scientific opinion and international action from

WHO, UNICEF and the non-governmental organisation of the ICCIDD to implement universal salt iodisation policies and eradicate iodine deficiency disorders (Hetzel, 2005).

----Please Insert Table 7 Here----

Policy evaluation measures

The questionnaire results in Table 7 identified nutrition monitoring and evaluation of nutrient inadequacy in a number of countries, particularly regarding iodine. These data from regular national or international monitoring surveys can act as policy evaluation measures and provide change data on disease incidence, health status, nutrient status or dietary intake data pre and post policy implementation to evaluate the impact of a policy. However, the EURRECA questionnaire data suggested that these measures were not always put in place: there were no nutrition monitoring or evaluation programmes implemented for any micronutrient in over half of the countries surveyed (see Table 7).

An absence of policy evaluation measures or available evaluation data was also seen in further work by EURRECA. A systematic narrative literature review on food-based dietary guidelines (FBDG), found that although they were actively promoted as a viable public health nutrition policy there was little evaluation of FBDG effectiveness in terms of whether the general public used the guidelines (Brown et al., 2011). Twenty-eight studies were reviewed which employed a variety of designs and methods to judge the awareness, understanding or use of FBDG by consumers (qualitative interviews, focus groups, field tests; quantitative questionnaire surveys and mixed methods experiments and questionnaire surveys). Some of these were far removed from a targeted health outcome or behaviour, such as the distribution of dietary education leaflets, posters or flyers (indicative of policy implementation rather than policy impact). This

work concluded that there was a degree of consumer awareness and understanding regarding FBDG, but there was little evidence to suggest consumer use of FBDG. However, more importantly the quality and quantity of the studies available for review was questioned and a paucity of available evaluation data highlighted.

Barriers to policy implementation

A series of qualitative studies using questionnaires, in-depth desk research, interviews or case studies (combination of either/or questionnaire, in-depth desk research and interview data), were conducted by EURRECA between 2007 and 2011 (for further study details please see the referenced publications). This work identified a number of possible barriers to policy implementation and evaluation.

One study conducted 57 qualitative interviews with key informants, predominantly representing scientific advisory bodies and national governments, in ten European countries: the Czech Republic, Denmark, England, Germany, Greece, Italy, the Netherlands, Norway, Poland and Spain. Results suggested that budget or economic constraints were a major barrier to policy implementation. Furthermore, co-operation with and between organisations or institutions at a national level (e.g. government departments and all stakeholders - food industry producers, manufacturers, retailers and caterers, research centres, health professionals, consumer groups, media etc.), was viewed as crucial to the successful implementation of any policy. This was in terms of accessing a broad range of knowledge throughout the micronutrient requirement setting process to ensure the policy implementation was sufficiently planned as well as in terms of sharing resources, limiting conflict with existing policies and ensuring shared advocacy and support for a policy (Jeruszka-Bielak, in prep.). However, an additional EURRECA study

(Timotijevic et al., 2010a) suggested that the degree of stakeholders' involvement prior to policy implementation and evaluation differed between countries (the Czech Republic, Denmark, Germany, Hungary, Norway, Spain and the United Kingdom). This appeared to be influenced by the historical, social, political context of the country (e.g. previous food crises such as variant Creutzfeldt-Jakob disease (vCJD/nvCJD) the human prion disease caused by bovine spongiform encephalopathy (BSE) in the UK led to formalised stakeholder involvement throughout nutrition decision-making processes).

Conclusions

A process for deriving and using micronutrient requirements comprising nine activities grouped in four stages (i) defining the problem, (ii), monitoring and evaluating iii) deriving dietary reference values and (iv) using dietary reference values in policy making has been presented. The framework is meant to be comprehensive and includes an exhaustive list of activities that should if at all possible be used for deriving dietary reference values and for providing the evidence-base for policy making (Table 8). The framework should not to be regarded as a prescriptive description of a linear process. 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. The central position of the "monitoring and evaluation" stage communicates that dietary assessment methodology and nutrition surveillance data are crucial to both the definition of the problem (i), as well as to deriving reference values (iii), and to proposing and evaluating policies (iv).

The first activity defines the nutrition-related health problem in terms of i) relevant health outcomes, ii) specific population groups, and iii) the micronutrient of concern. This results in a

prioritisation of the micronutrients which is resulting from the availability of new scientific evidence, public health relevance and heterogeneity of current reference values. In Activity 2 the process by which dietary reference values are derived and applied is established and usually involves bringing together a Scientific Advisory Body (SAB) to provide national and international credibility and expertise relevant to the problem to be addressed. The SAB has to acknowledge that, due to the pressure for scientific consensus, the difficulty of dealing with scientific uncertainty in policymaking contexts, unanimity in communicating findings and the inherently political nature of SAB (as a bridge between science and policy), are particular challenges in efforts to increase transparency of scientific advice to policymakers relevant to micronutrient DRVs.

----Please Insert Table 8 Here----

As mentioned in Activity 3, monitoring the intake and status of certain micronutrients and related health endpoints requires the use of best practice methodologies, definitions and terminologies. In fact, the 'Monitoring and evaluating' stage is relevant to all stages in the diagram. The information derived from monitoring the intake, status and health situation in European countries or populations provides input to the priority setting (Stage 'Defining the problem') and refers to inadequacies and public health problems. Moreover, evaluation measures provide the basis for the policy options and implementation as well. This includes inadequacies based on monitoring data. Activity 7 'Nutrient intake & status of population groups' in particular focusses on evaluation relevant to 'Using dietary reference values in policy making' and then closes the loop to 'Defining the problem'.

The stage ‘Deriving dietary reference values’ consist of three sequential activities i.e. activities 4, and 6. A variety of sources of evidence is used to derive dietary micronutrient requirements. The availability of data from different types of study influences whether the ‘factorial’ or ‘dose response’ approach is adopted in the derivation process. Activity 4 ‘Sources of evidence’ describes a harmonised and standardised approach for the identification and collation of robust data which is indispensable for the elimination of current disparity in the evidence base for micronutrient recommendations. The strength of this approach is that data identification, collation and ultimately analysis can be achieved in a transparent manner. The process can be tailored with relevance to specific population groups and micronutrients and for data to be used in both the factorial and dose response approach. Activity 5 ‘Appraisal of the evidence’ involves interpreting the data by means of quantitative or qualitative analysis, assessing the quality of the data, and including certain elements of judgement which will result in a qualitative scientific conclusion. This conclusion will inform decision-makers about which data could be used for the definition of micronutrient requirements. Activity 6 ‘Integrating the evidence’ involves the quantification and integration of both factorial and dose response approaches into average requirements (ARs) including the derivation of the variation in requirements. Eventually, reference values for micronutrient intake for specified proportions of the population (resembling the definition of AR and PRI) can be derived from bivariate or trivariate models once thresholds on the health or status variable are set.

Finally, as described in Activities 8 and 9 (Stage ‘Using dietary reference values in policy making’), policy decisions regarding the implementation of nutrient recommendations need to be made and include the need for an understanding of food related behaviour and other relevant

evidence needed for developing public health nutrition policy. The framework for considering evidence in public health nutrition policy development that was developed within EURRECA can be used for as a checklist for the types of evidence that routinely enter decision making.

It is important to note that the different activities can be conducted by different bodies. The extent to which each stage will be dealt with comprehensively will depend on the time, resources (including expertise available) and information available in the country or region. It may be the case that some of the activities need not be carried out in full in a particular country or region if it is felt that these have already been adequately dealt with on a previous occasion, e.g. decisions to go with previously established information or the adoption of decisions from other bodies. Where organisations choose to draw on activities carried out elsewhere the framework can act as a check list to ensure all important matters have been addressed. The framework can serve as a structured guide for safeguarding that all issues essential for deriving requirements have at least been considered. Limits on resources, available time and available information will shape the scope of work a given body can take on decisions will need to be taken as what can be regarded as the most relevant and urgent activities.

Acknowledgements

The work reported herein has been carried out within the EURRECA Network of Excellence (www.eurreca.org) which is financially supported by the Commission of the European Communities, specific Research, Technology and Development (RTD) Programme Quality of Life and Management of Living Resources, within the Sixth Framework Programme, contract

no. 036196. This report does not necessarily reflect the Commission's views or its future policy in this area.

The original conception of the systematic reviews was undertaken by the EURRECA Network and coordinated by partners based at Wageningen University (WU), the Netherlands and the University of East Anglia (UEA), United Kingdom. Susan Fairweather-Tait (UEA), Lisette de Groot (WU), Pieter van 't Veer (WU), Kate Ashton (UEA), Amélie Casgrain (UEA), Adriënne Cavelaars (WU), Rachel Collings (UEA), Rosalie Dhonukshe-Rutten (WU), Esmée Doets (WU), Carla Dullemeijer (WU), Linda Harvey (UEA) and Lee Hooper (UEA) designed and developed the review protocol, search strategy and the strategy for data analysis and interpretation.

The involvement of researchers for each activity was as follows: Activity 1: Adriënne Cavelaars, Rosalie Dhonukshe-Rutten, Olga Souverein; Activity 2: Kerry Brown, Lada Timotijevic; Activity 3: Rachel Collings, Linda Harvey, Rachel Hurst; Activity 4: Jildau Bouwman, Rachel Collings, Linda Harvey, Rachel Hurst, Bas Kremer; Activity 5: Maria Hermoso, Mariela Nissensohn, Joy Ngo, Lluis Serra-Majem, Pieter van 't Veer; Activity 6: Jildau Bouwman , Adriënne Cavelaars, Rosalie Dhonukshe-Rutten, Olga Souverein, Bas Kremer; Activity 7: Mirjana Gurinovic, Romana Novakovic; Activity 8: Kerry Brown, Lada Timotijevic; Activity 9: Kerry Brown, Lada Timotijevic. The preparation of this manuscript was coordinated by Mandy Claessens (ILSI Europe). The authors would also like to thank Sergi Migallon (ILSI Europe) for his administrative support during the preparation of this manuscript.

Acknowledgement to all of the EURRECA partners that contributed to the work within each of the activities and the discussions which led to the conception and development of the framework.

Supplementary document 1

Health outcomes studied for the micronutrients which were reviewed within the framework of EURRECA for different life-stage groups.

Micronutrient	Population	EURRECA databases	Outcomes studied
Iron	Infants	1-2	Growth
			Neurodevelopment
	Children & Adolescents	3-6	Immune function
			Cognitive functions & psychomotor development
	Pregnant & lactating women	7-8	Fetal growth (Fetus)
			Preterm delivery (Fetus)
			Preeclampsia (Mother)
			Postpartum depression (Mother)
	Adults & elderly	9-18	Tiredness
			Physical performance
			Immune function
	All population groups	19-20	Polymorphisms
			Bioavailability
Zinc	Infants	21-22	Growth
			Immune response to vaccination
			Neurodevelopment
	Children & Adolescents	25	Growth
			Immune function
			Cognitive functions & psychomotor development
			Dermatitis
	Pregnant & lactating women	23-24	Fetal growth (Fetus)
			Fetal malformation (Fetus)
			Preeclampsia (Mother)
			Preterm delivery (Mother)
	Adults & elderly	26	Immune function
			Cognitive function
			Dermatitis
	All population groups	27-31	Polymorphisms
			Bioavailability
Folate	Infants	32-33 & 45	Growth
			Folate-deficiency anaemia

	Children & Adolescents	34-35 & 46-47	Cancer (DNA synthesis)
			Folate-deficiency anaemia
			Immune function
			Cognitive functions & psychomotor development
	Pregnant & lactating women	43-44 & 48	Fetal malformations (Fetus)
			Fetal growth (Fetus)
			Maternal macrocytic anemia (Mother)
			Preeclampsia (Mother)
			Preterm delivery (Mother)
			Placental abruption (Mother)
	Adults & elderly	36-42	Stroke
			Cancer
			Osteoporosis
			Cognitive function* (Cognitive function test score like MMSE, AD, depression,...)
	All population groups	49	Factorial
Vit B12	Infants	50-51	Neurodevelopment
			Megaloblastic anemia
	Children & Adolescents	52-53	Megaloblastic anemia
			Growth
			Cognitive functions & psychomotor development
	Pregnant & lactating women	54-55 & 61	Fetal malformations (Fetus)
			Fetal growth (Fetus)
			Megaloblastic anemia (Mother)
			Preeclampsia (Mother)
	Adults & elderly	56-57 & 60	Anemia**
			Nervous system disease***
			Cognitive funtion****
			Osteoporosis
	All population groups - polymorphism	58	
	All population groups - absorption	59	
Selenium	Adults & elderly	62-63	Male fertility

			Cognition in elderly populations
			Immune function and infection within populations ≥ 50 years old
			disease progression and status within HIV+ patients/populations
	All population groups - polymorphism	64	
	All population groups - absorption	65	
Iodine	All population groups (including low income & immigrants)	66-67	
Riboflavin	Adults & elderly	68	

* As cognitive function will be covered only once, the 3 primary health outcomes are done

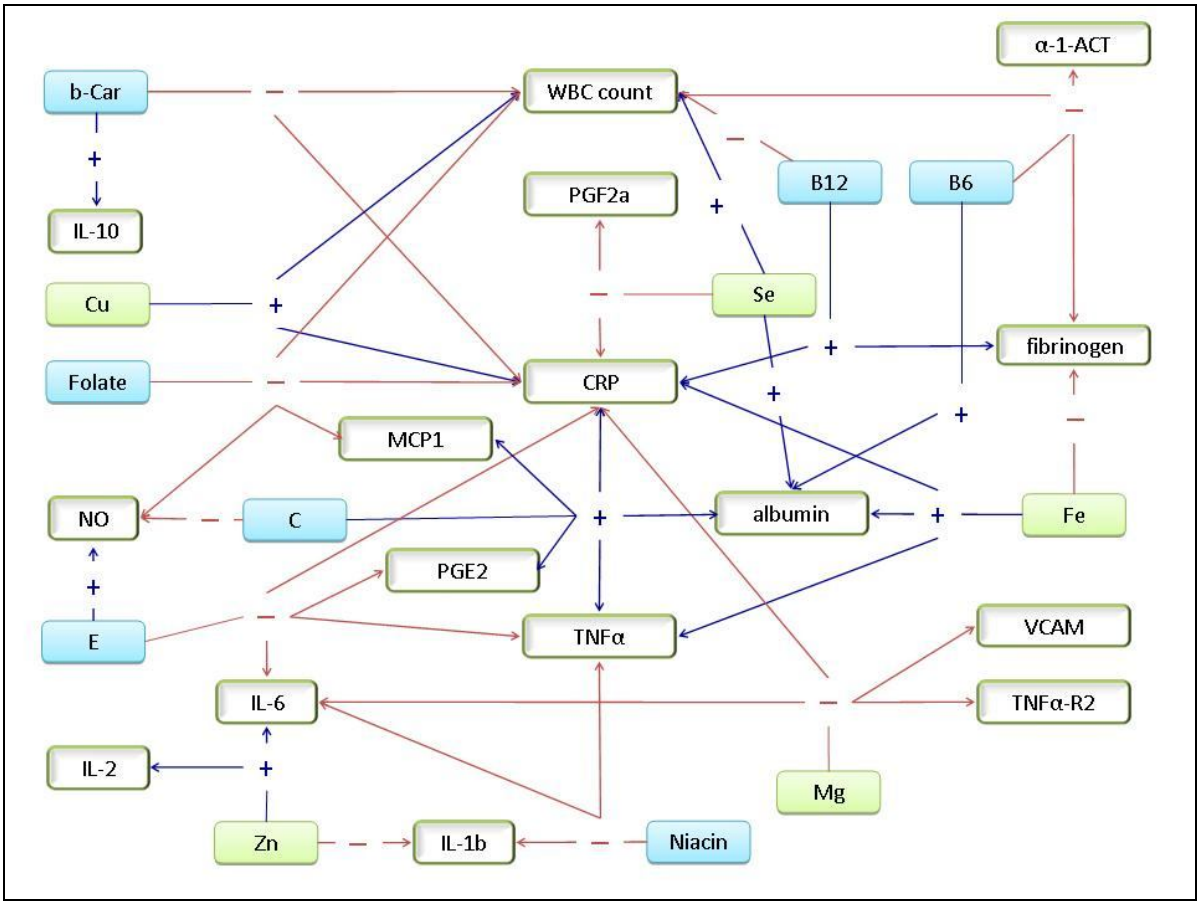
** There are 4 types of anemia associated with vit B12 deficiency: megaloblastic anemia, pancytopenia, thrombocytopenia and leucopenia

*** The most important manifestations related to b12 are: peripheral neuropathy, degeneration of the spinal cord and ataxia

**** The most important manifestations include: dementia, depression, Alzheimer's disease, psychosis

Supplementary document 2

Basic mathematical network model of multiple micronutrient involvement in the inflammatory process.



Abbreviations of immune response markers: α-1-ACT: alpha-1-antichymotrypsin; CRP: C-reactive protein; IL: Interleukin; PGE2: prostaglandin E2; PGF2a: prostaglandin F2a; TNFα: tumor necrosis factor alpha; TNFαR2: tumor necrosis factor alpha receptor 2; VCAM: vascular cellular adhesion molecule; WBC: white blood cell. Abbreviations for micronutrients: B6, B12, C, E: respective vitamins; b-Car: beta-carotene; Cu: copper; Fe: iron; Mg: magnesium; Se: selenium; Zn: zinc.

This micronutrient-inflammation model highlights the interactions of a multitude of micronutrients on immune parameters relevant for health status. Significant correlations between micronutrient and inflammation markers are depicted by blue arrows with a + sign reflecting a

direct correlation or red arrows with a – sign reflecting an inverse correlation. As an example, plasma concentrations of C-reactive protein (CRP), a marker of chronic inflammation, which is a risk indicator for development of cardiovascular disease, have been shown to be positively correlated with plasma concentrations of iron (Fe), copper (Cu), vitamins B6, B12, and C, and negatively correlated with beta–carotene (b-Car), folate, magnesium (Mg), selenium (Se), and vitamin E concentrations. Similarly, it can be deduced that, in addition to its effect on CRP, vitamin C positively affects plasma levels of pro-inflammatory mediators prostaglandin E2 (PGE2), and tumor necrosis factor alpha (TNFα), whereas it is negatively correlated with plasma nitric oxide (NO) levels. This model clearly demonstrates that multiple micronutrients interact at different points in the inflammatory health response, and this knowledge could enable the selection of relevant micronutrient related health status parameters that may feed into the recommendation process based on optimized statistical methods such as those supporting the 'health space' concept. This latter approach has been discussed further in Activity 6.

Supplementary document 3

Assessment of internal validity in RCTs, Cohort and Cross sectional studies

Lee, Adrienne, Rosalie, Rachel and Linda, 23rd June 2010

At the end of data extraction, for each study we have a set of indicators of internal validity. The internal validity focuses on the quality of the study and tells us something about the risk of bias. We know:

- Methodology (RCT, cohort, case control)
- Something about various indicators of internal validity (which vary from methodology to methodology)

Randomised controlled trials (RCTs)

For each review question we need to print out the table of internal validity characteristics for all of the RCTs, for all of the cohorts and for all of the cross sectional studies. We should be able to print this table directly from the data extraction database (Adrienne will help you to do this for each study methodology). A sample table for an RCT data set is printed below (your basic output table may need some neatening up to make it look good and read well). For each table the columns with black and purple headings will already be completed, the columns with blue headings will need to be completed independently in duplicate by 2 reviewers and then checked. In your methodology you will need to state how any disagreements were decided.

RCT validity

Study	Method of sequence	Adequate sequence	Allocation concealment adequate?	Blinding description	Blinding adequate? (3)	Number at start, dropouts &	Dropouts adequate	Funder	Funder adequate? (5)	Compliance check &	Dose check & results	Dietary intake data	Outcome (Status or
X 1	(text)	Yes	Yes	(text)	Yes	(numeric & text)	Yes	(text)	Yes	(text)	(text)	(text)	(text)
X 2	(text)	Yes	Yes	(text)	No	(numeric & text)	Yes	(text)	Unclear	(text)	(text)	(text)	(text)
X 3	(text)	Yes	Yes	(text)	Unclear	(numeric & text)	Yes	(text)	Yes	(text)	(text)	(text)	(text)
X 4	(text)	Yes	Unclear	(text)	Yes	(numeric & text)	No	(text)	Unclear	(text)	(text)	(text)	(text)

The criteria for judging the coloured headings (those in purple, and those in blue) are below, and are adapted from the Cochrane Handbook (General reading is 'Chapter 8: Assessing risk of bias in included studies' in the Cochrane Handbook, available freely on line)[1].

SEQUENCE GENERATION (1) complete during data extraction **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number.

[1] Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

	Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.

ALLOCATION CONCEALMENT (2) complete during data extraction **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based, and pharmacy-controlled, randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed, not opaque or not sequentially numbered);

	• Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

Cohort and nested case control studies

Basic reading on assessment of validity in cohort studies is section '13.5 Assessing risk of bias in non-randomized studies' from the Cochrane Handbook, available freely online[2].

When data extracting:

- 'Dissimilarity of most and least exposed...' here note the confounders from the list above that were similar at baseline
- 'Where dissimilar at baseline, were there adjustments for these factors...' here note the confounders from the list above adjusted for or dealt with (for example, by matching of participants eg according to socioeconomic status and age, or exclusion eg of smokers) in the analysis (under 'clarify')
- 'Were measurement errors in exposure and outcome taken in to account...' Method of assessment of intake or status noted

Cohorts and nested case control studies:

[2] [2] Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Blue coloured columns are filled in after data extraction and once the table is created

Study	Similarity of most & least exposed groups at	List of potential confounders adjusted for in the analysis	List confounders in review list Not similar and Not adjusted for. (8)	Study dealt with confounding factors	Exposure assessment (intake or	Assessment of exposure (intake or status)	Number at start, loss to follow up,	Dropouts adequate and outcome data	Funder (as for number 5 above)	Funder adequate? (5)	Lack of other potential threats	Overall risk of bias (10)
X 1	(text - those confounders that were similar at baseline)	(text - those confounders adjusted or matched for in analysis)	Text	Yes / No/ Unclear	(text from form)	Yes/ No/ Unclear	(numeric & text) xx	Yes/ No/ Unclear	(text)	Yes/ No/ Unclear	Yes/ No/ Unclear	Cohort: low/ moderate/ unclear/ high risk of bias
X 2	(Text)	(Text)	(Text)	No	(Text)	Yes	(numeric & Text)	Yes	(Text)	Yes	Yes	Cohort: moderate risk of bias
X 3	(Text)	(Text)		Yes	(Text)	Yes	(numeric & text)	Yes	(Text)	Yes	Yes	Cohort: low risk of bias
X 4	(Text)	(Text)	(Text)	No	(Text)	Unclear	(numeric & text)	Yes	(Text)	No	Yes	Cohort: high risk of bias

(not during data extraction), while columns in black text are taken directly from data extraction forms (see Adrienne for how to do this).

Blue coloured columns are filled in after data extraction and once the table is created (not during data extraction), while columns in black text are taken directly from data extraction forms (see Adrienne for how to do this).

Cross sectional studies

Study	Similarity of most & least	List of potential	List confounders in review list Not similar and Not adjusted for. (8)	Study dealt with confounding factors adequately (8)	Exposure assessment (intake or status): Method of dietary assessment or status, number of days or measures, validated?,	Assessment of exposure (intake or status) adequate? (9)	Funder (as for number 5 above)	Funder adequate? (5)	Outcome assessment (status or health): data from forms, complete identification/	Lack of other potential threats to validity? (6)	Overall risk of bias (11)
X1	(text-those confounders that were similar at baseline in	(text-those confounders adjusted or matched fo	Text	Yes/ No/ Unclear	(text from form)	Yes/ No/ Unclear	(text)	Yes/ No/ Unclear	(text)	Yes/ No/ Unclear	Cross-sectional: low risk

	e)	r in a n al y si s)									

Overall risk of bias for cross sectional studies complete in table (11) **This is an overall summary of the various issues for this study**	
Criteria for a judgement of 'Cross-sectional, low risk of bias'.	• Where there are no important confounders not dealt with appropriately, and assessment of exposure and funding are both adequate, and there are no serious risks of bias in the other areas: the risk of bias is low
Criteria for the judgement of 'Cross-sectional, moderate risk of bias).	There is only one important risk of bias. Any ONE of the following may be "inadequate" or "unclear": • One important confounder was not dealt with appropriately (if more than one confounder then the study is at high risk) • Assessment of exposure • Funding • There is one serious risks of bias in another area
Criteria for the judgement of 'Cross-sectional, high risk of bias).	There is more than one important risk of bias. More than ONE of the following may be "inadequate" or "unclear": • One important confounder was not dealt with appropriately (any confounder not dealt with counts as an additional bias) • Assessment of exposure • Funding • There is one serious risks of bias in another area

Supplementary document 4

Estimation of single summary estimates (beta's) and the overall pooled estimates

The transformations used to derive coherent single-study estimates from the available summary statistics per study have been described by Souverein et al (2012). In short, the estimation of an

intake-status regression coefficient (β) for each individual study, is based on the assumption of a linear relation on the $\log_e$-$\log_e$-scale (natural logarithm of intake versus natural logarithm of status). Algebraically deriving an estimate from each study of the regression coefficient ($\hat{\beta}$) and its standard error (SE($\hat{\beta}$)) enables to compare the results from studies with heterogeneously reported associations and effects.

Then, the overall pooled $\hat{\beta}$ and SE($\hat{\beta}$) are calculated by using random effects meta-analysis, which estimates the between-study variance using the method of DerSimonian and Laird and then use this estimate to modify the weights used to calculate the summary estimate. Residual heterogeneity between studies was evaluated using the I^2 statistic. Pre-specified potential factors that could modify the association should be explored using stratified random effects meta-analyses. The statistical transformations to obtain $\hat{\beta}$'s and SE($\hat{\beta}$)'s can be performed using GenStat version 13-SP2 (VSN International Ltd., http://www.vsni.co.uk/) and the meta-analysis can be performed using STATA version 11.0 (College Station, TX), with statistical significance defined as $P<0.05$ (Dullemeijer et al., 2012).

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Three micronutrients known for a recent or past history of policy debates	Folic acid, Iodine, Vitamin D[1]
Countries representing different institutional contexts and a north-south gradient in Europe	Czech Republic, Italy, Netherlands, Nordic countries (Denmark, Finland, Iceland, Norway, Sweden), Poland, Spain
Quantitative and qualitative methods allowing triangulation	Quantitative and qualitative online questionnaire (de Wit et al 2008) Qualitative interviews (de Wit in preparation, Jeruszka-Bielak in preparation) In-depth desk research

Table 1: Key characteristics of the case studies to examine the processes of establishing micronutrient DRVs

[1] Part of the case study for vitamin D was based on Denmark as a representative of the Nordic countries

Country	N of members	Selection criteria	Fields of Expertise					
			Nutrition	Public health/ Epidemiology	Medicine	Bio/ chemistry	Risk assessment	Food technology
Czech Republic	8 (self-selected)	Individual expertise / Specific sector	●			●	●	
Italy	4 working groups (8-10 members each)	Individual expertise / Institutional authority / Specific sector	●	●	●	●		●
Netherlands	38	Individual expertise (independent experts)	●	●	●	●		
Nordic countries*	30 (selected by governments)	Individual expertise (scientific) / Institutional authority	●	●	●	●		
Poland	5	Individual expertise (experience) / Institutional authority (long-term employment) / Specific sector	●		●	●		
Spain	3	Individual expertise / Institutional authority	●					

Table 2 Composition of Scientific Advisory Bodies in Europe: fields of expertise

***** Denmark, Finland, Iceland, Norway, Sweden

Table 3 Bodies responsible for public health nutrition policy in Europe

Country	Body Responsible	Type of Body
Czech Republic	Ministry of Health, Department of Public Health, supported by the Scientific Committee for Food - iodine	Governmental, working group for iodine
Italy	Italian Society of Human Nutrition (SINU), supported by the National Research Institute on Food and Nutrition	Nutrition society (scientific with links to governmental bodies)
Netherlands	Ministry of Health, supported by The National Health Council (TNHC)	Governmental, TNHC is an independent scientific advisory body
Nordic countries	Nordic Committee of Senior Officials on Food Issues, EK-Livs., supported by the Working Group on Diet and Nutrition (NKE)	Project group nominated by NKE
Poland	Ministry of Health, supported by the National Food and Nutrition Institute, Warsaw	Governmental
Spain	Madrid University and Spanish Society of Community Nutrition (SENC)	Nutrition society, expert group

***** Denmark, Finland, Iceland, Norway, Sweden

Table 4. Approaches and study types used to derive micronutrient requirements (adapted from Matthys et al (2011))

Approach*	Outcome Measures	Study type	Principle of method	Study design	Applicable population group
FACTORIAL	Physical or metabolic outcome	Metabolic balance studies at various intake levels	Long-term intake = Long term losses Requirement: intake level at which balance (stable body pool, rate of absorption & excretion) cannot be maintained.	Cross-sectional & prospective	All age groups
		Growth studies, biochemical studies	Rate of accumulation of nutrients in the body (foetus, placenta, etc.), breast milk composition & volume	Cross-sectional & prospective	Foetus, infants, pregnant and lactating women
DOSE-RESPONSE	Health outcome	Depletion / repletion studies	Symptoms occur in response to dietary insufficiency & alleviate with sufficiency	RCT	Young adults
		Biochemical / biological studies	Identification of subclinical deficiencies or reduction/lack of function in relation to specific micronutrient	RCT & cross-sectional	All age groups

		Epidemiological studies	Identification of (chronic) diseases (functional outcomes)	Observational, interventional	Adults, elderly

*The factorial approach relies on measurements of a variety of factors including requirements for growth, pregnancy and lactation and faecal and urinary losses that determine requirements to maintain plasma levels or body stores resulting in normal tissue and body function and prevention of adverse health effects (Reference values derived by this approach also rely on the application of a bioavailability factor) to convert the physiological requirement into a dietary intake value.

The dose response approach is based on the prediction of a physiologically relevant outcome which could be the measurement of an accepted micronutrient status biomarker in response to dietary intake, or the assessment of clinical disease endpoints in relation to intake or status.

Table 5 Low social class and immigrant: definitions and proportion in EU27 Member states

Population groups vulnerable to micronutrient inadequacy
Low social class : According to Eurostat definition population in or at risk of poverty comprises all persons with disposable income, adjusted for family size, i.e. equivalised income, that is below 60 percent of the median national value in each year. Within the European Union (EU- 27 member countries), there are 16% (80199 thousands persons) that are in or at risk of poverty. It ranges from 9% in Czech Republic to 22% in Romania. Immigrants: The total number of non-nationals (people who are not citizens of their country of residence) living on the territory of an EU Member State on 1 January 2010 was 32.5 million persons, representing 6.5 % of the EU-27 population. However, more than one third (a total of 12.3 million persons) of all non-nationals living in the EU-27 on 1 January 2010 were citizens of another EU Member State. (source : www.ec.europa.eu)

Table 6 Examples of nutrient related policy options (draws on definitions outlined in Ledbury et al (Ledbury et al.,

Policy type	Policy instrument for	Examples
Social voluntary	Publications	Multiple countries: Food-based dietary guideline messages and
	Campaigns	Czech Republic: 6th March iodine day
	Labelling	Multiple countries: Back of pack nutritional information
	Advisory service	Multiple countries: training & advice provided to health
	Representation service	An expert is appointed to act on behalf of a person or business, e.g.
Economic	Taxation	Multiple countries: tax rate differences between healthy and
	Charges	Government charges for services that are consumed*
	Subsides and vouchers	UK: Healthy Start programme – vouchers to swap for
	Tax credits	The government reduces the cost of an activity*
	Benefits & grants	Finland: Free school meals
	Award auctioning of franchises	Systems under which the right to produce a
	Government loans, loan	Government provides loans and/or a subsidy (e.g. through
Regulation & legislation	Price & market structure	Denmark: Fat-tax
	Production and consumption	Denmark: Mandatory table & bread salt iodisation; Poland:
	Standard setting regulation	UK: Nutrient profiles for “traffic-light” nutrition labelling
	Prescriptions & prohibition	France and UK: Banning of school soft drink dispensers
	Rights and representation	Rules which provide agents with rights and/or
Self-regulation	Voluntary agreement	Spain: Voluntary fortification of low fat milk and milk products
	Codes of practice	UK: Health Food Code of Good Practice (Food & Drink Industry)
	Co-regulation	UK: OFCOM (communications regulator) rules
Intervention short of legislation	Goal setting	EU Platform for Action on Diet, Physical Activity and
	Infrastructure provision	Multiple countries: urban development for health, e.g. urban farming

* Not currently directly related to nutrition

Table 7 Reported policies implemented relevant to micronutrients in the thirty-five countries surveyed in 2007 (n countries, if ≥ 9).

Micronutrient	General health education		FBDG		Monitoring & evaluation		Specific health	
education	Fortification		Supplementation		Labelling	Vol. action	Task force	
Vitamin A	14	12	9		10		9	
Vitamin D	13	13	9		10	14		
Vitamin E	12	11						
Vitamin C	13	13	9					
Thiamin	12	10						
Riboflavin	11	10						
Niacin	11	9						
Vitamin B6	11	10						
Folate	14	13		13		13		
Vitamin B12	11			11				
Sodium	16	15	9	11			11	15
Potassium	11	10						
Calcium	14	13	9	10				
Magnesium	10	10						
Iron	15	12	9	10		10		

Zinc	10	9				
Copper	10	9				
Phosphorus	10	9				
Selenium	10	9				
Iodine	18	15	11	9	21	9

FBDG - food based dietary guidelines; Monitoring & evaluation - monitoring and evaluation of nutritional intake/status; Vol. action - inducing voluntary action in industry; Task force - setting up a task force. Thirty-five countries surveyed: Albania; Austria; Belgium; Bosnia and Herzegovina, Federation of Bosnia and Herzegovina[1]; Bosnia and Herzegovina, Republika Srpska[1]; Bulgaria; Croatia; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Iceland; Ireland; Italy; Latvia; Lithuania; Montenegro; Netherlands; Norway; Poland; Portugal; Romania; Russian Federation; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; The former Yugoslav Republic of Macedonia; United Kingdom. [1]Bosnia and Herzegovina are politically decentralised with two governing entities: the Federation of Bosnia and Herzegovina and Republika Srpska

Table adapted from de Wit et al., 2008

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 & 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 & bioavailability • Dose-response approach • Inter-individual variability
	Appraisal of the evidence (5)	• Study design: observational studies & RCTs • Evaluation of heterogeneity • Overall quality of the evidence
	Integrating the evidence (6)	• Quantification • Expert consultation • Factorial & bioavailability approach • Dose-response model • Scaling of ARs to other population groups • Biological modelling 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

Table 8 Overview of the EURRECA stages, activities and topics dealt with in each activity

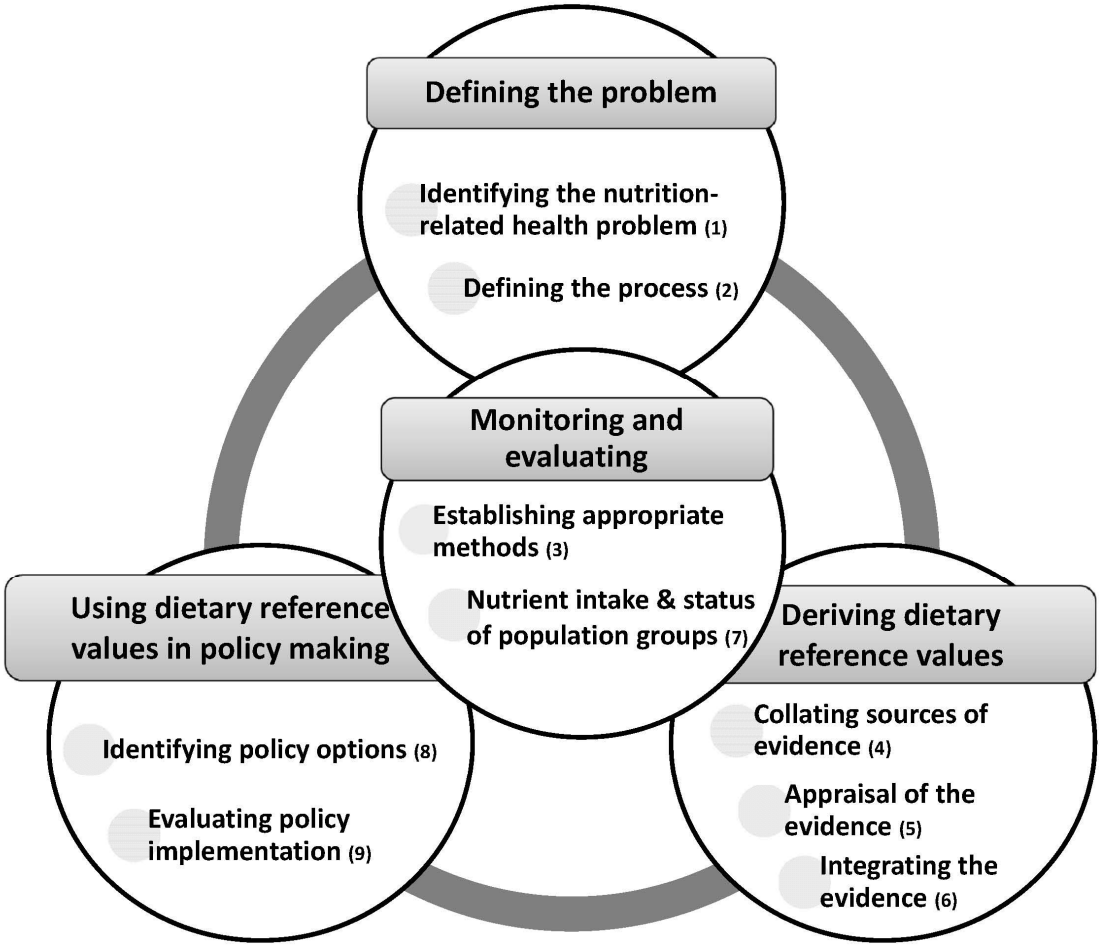


Figure 1 Final EURRECA framework describing the process for setting micronutrient requirements. The framework includes 9 activities that have been clustered in four different stages.

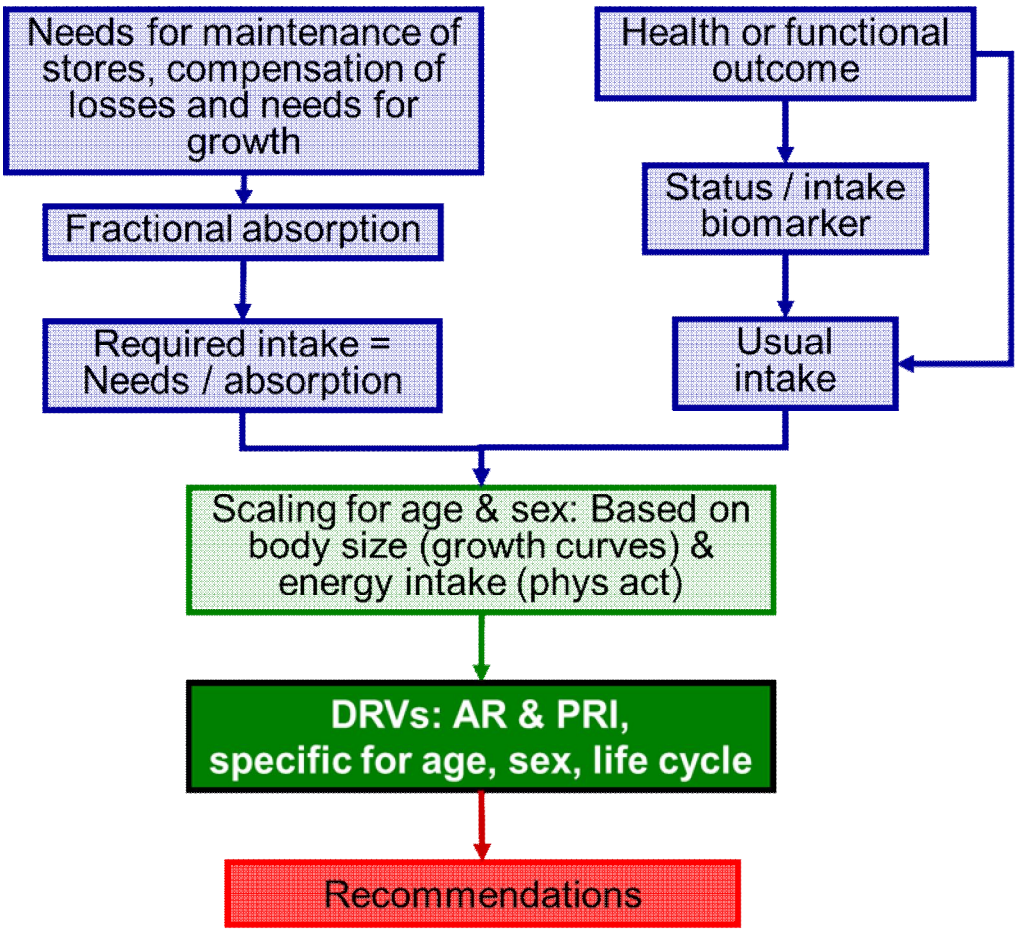


Figure 2 Two concepts which both provide scientific evidence for setting nutritional reference values: Factorial approach (left), Dose response approach (right). The factorial approach estimates losses and needs for maintenance and growth by actually measuring the various (exchanges between) body pools, which usually requires advanced methods in selected study groups. The results lead to Adequate Intake levels, unless a critical pool size has been established. The dose response approach addresses depletion-repletion studies, RCTs and observational studies covering a wide dose range. When a health criterion can be specified and the data allow extrapolation of the dose response curve to the lower end of the intake range, an AR can be estimated as well (see activity 6).usually addresses nutritional

requirements to prevent a critical clinical outcome and leads to an AR but often requires highly selected study groups. For the dose response approach, health outcomes are usually available from observational and intervention data in general population groups; these data can be used to estimate Adequate Intakes. Moreover, when a health criterion can be specified and the data allow extrapolation of the dose response curve to the lower end of the intake range, an AR can be estimated as well (see activity 6). (Figure available in color online)

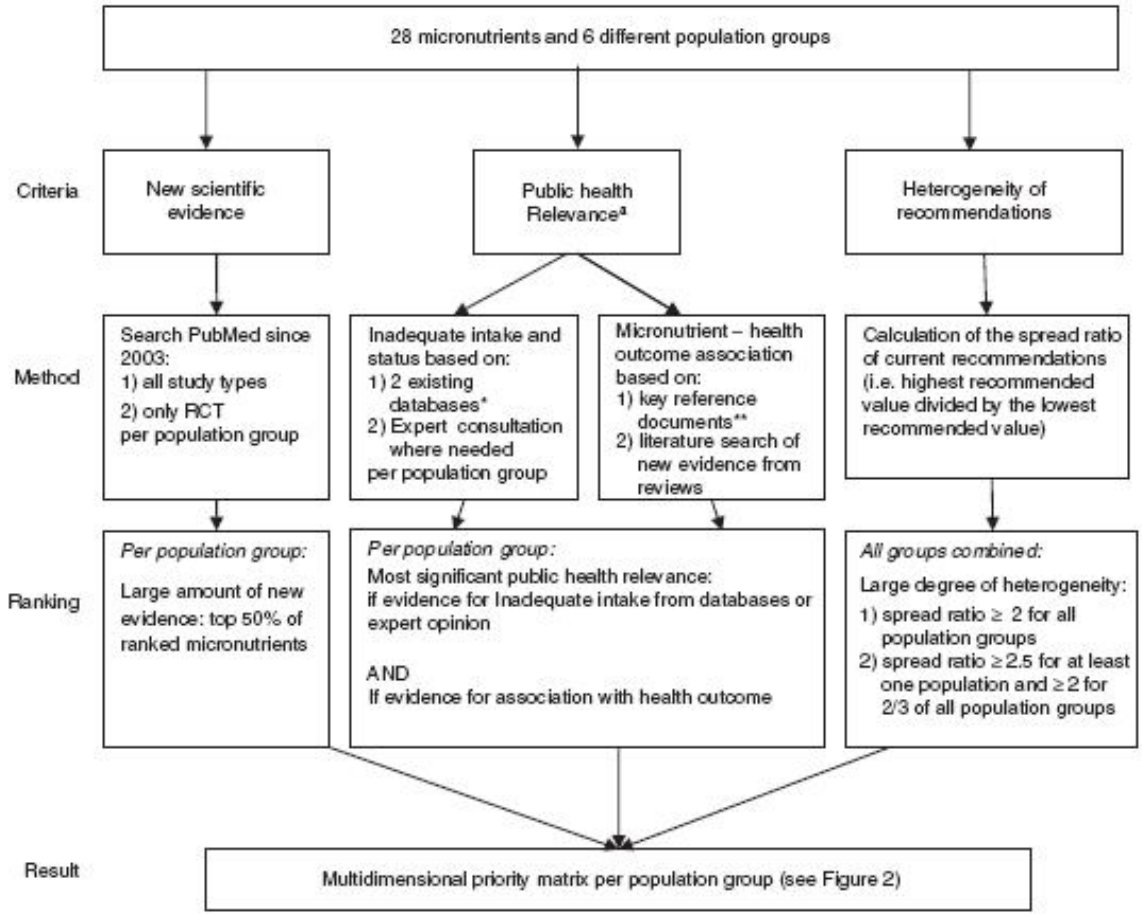


Figure 3 Prioritizing micronutrients for the purpose of reviewing their requirements: a protocol developed by EURRECA (Cavelaars et al., 2010).

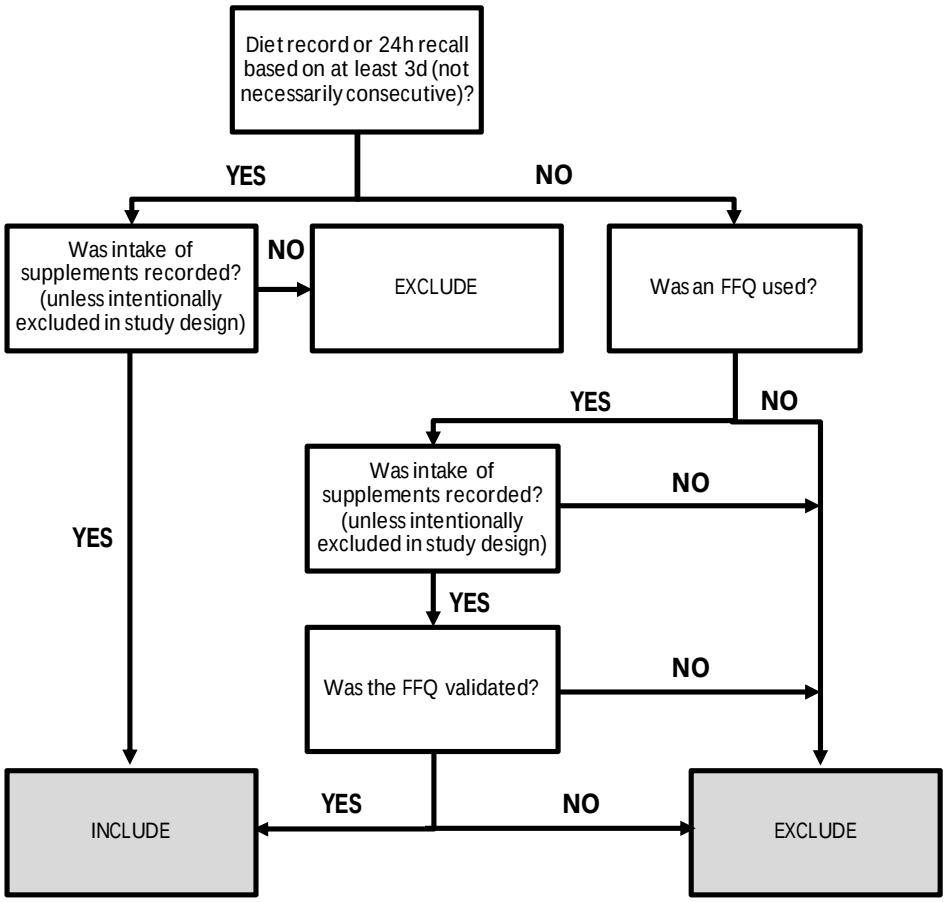
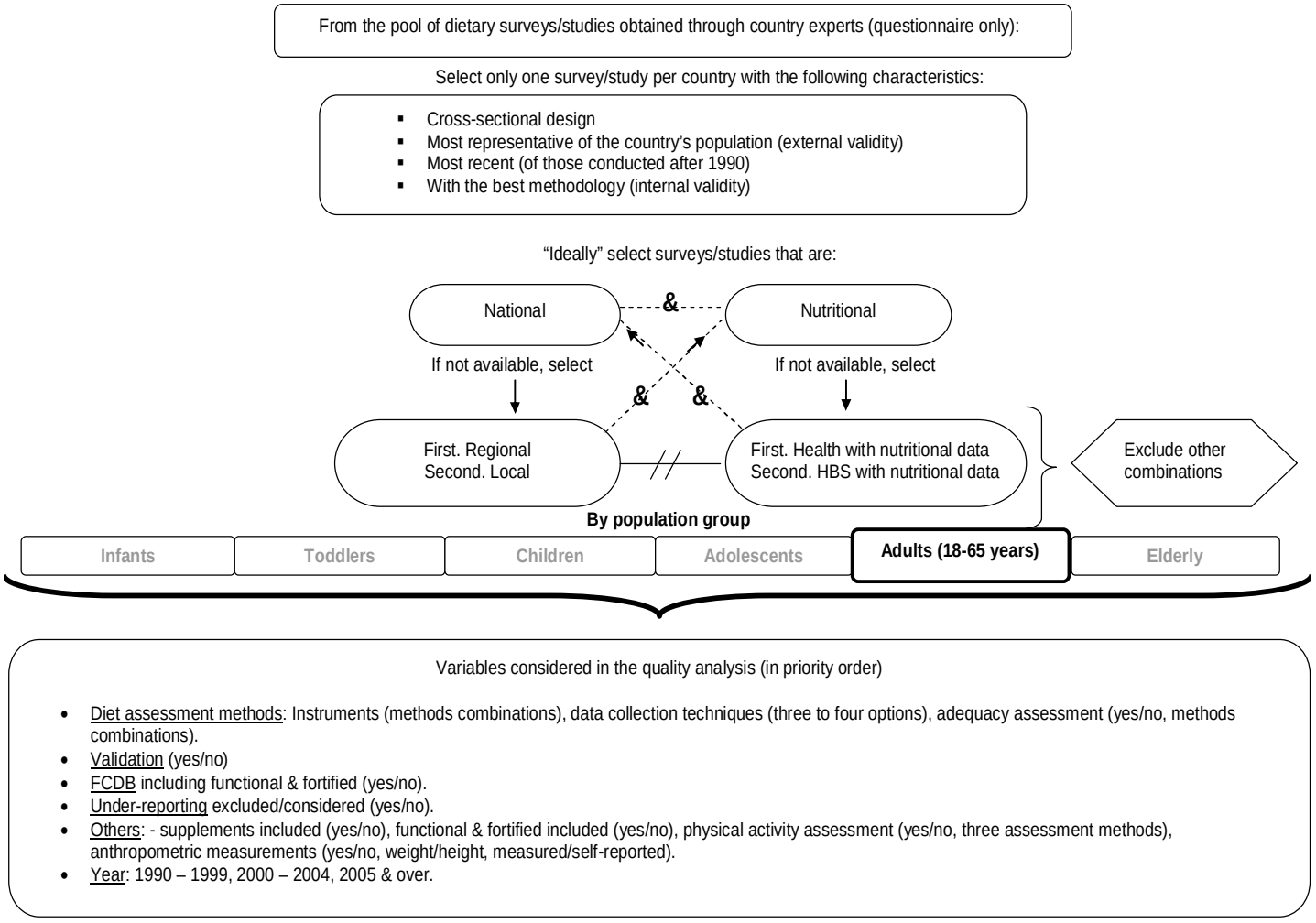


Figure 4 Abbreviated EURRECA decision tree for evaluation of robust dietary intake data suitable for epidemiological studies to assess associations between dietary intake and health outcomes.



Abbreviations: Household budget Survey (HBS), Food composition database (FCDB); *Figure adapted from García-Alvarez et al, 2009*

Figure 5. Summary Best Practice Guidelines on Nutrient Intake Assessment for selecting the best available nutritional intake survey/study per country. More details on the methods and tools can be found under section "Assessment of dietary micronutrient intake" in the current manuscript.

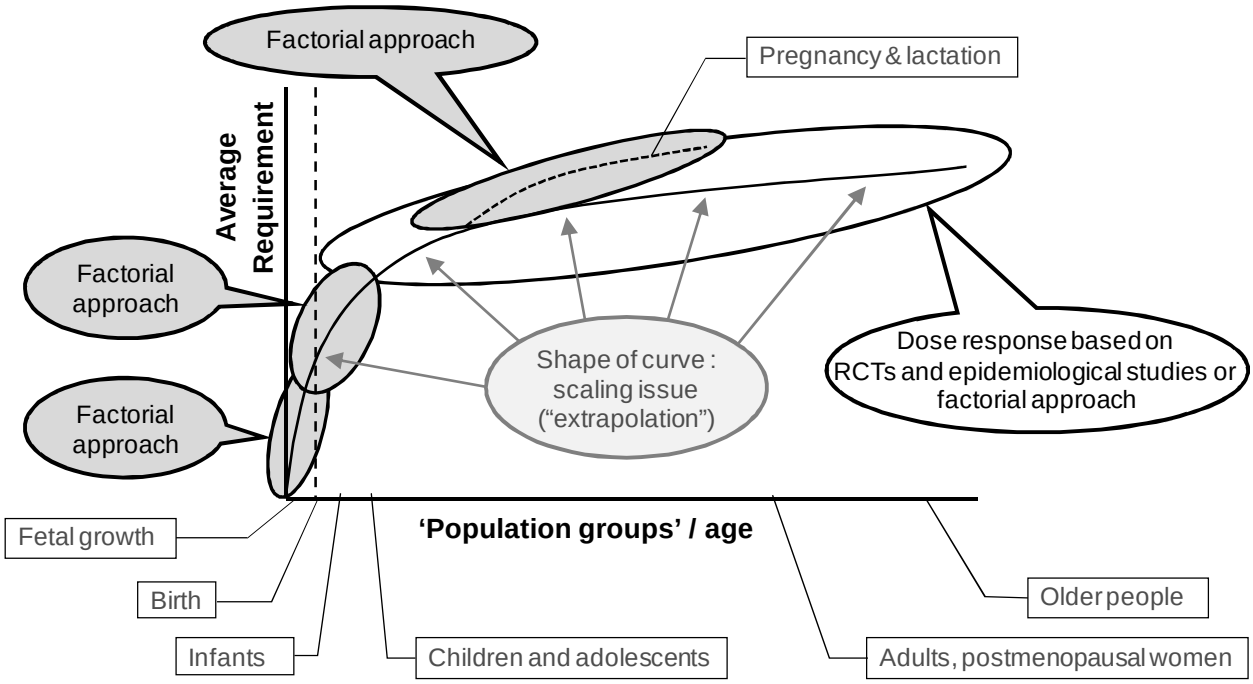
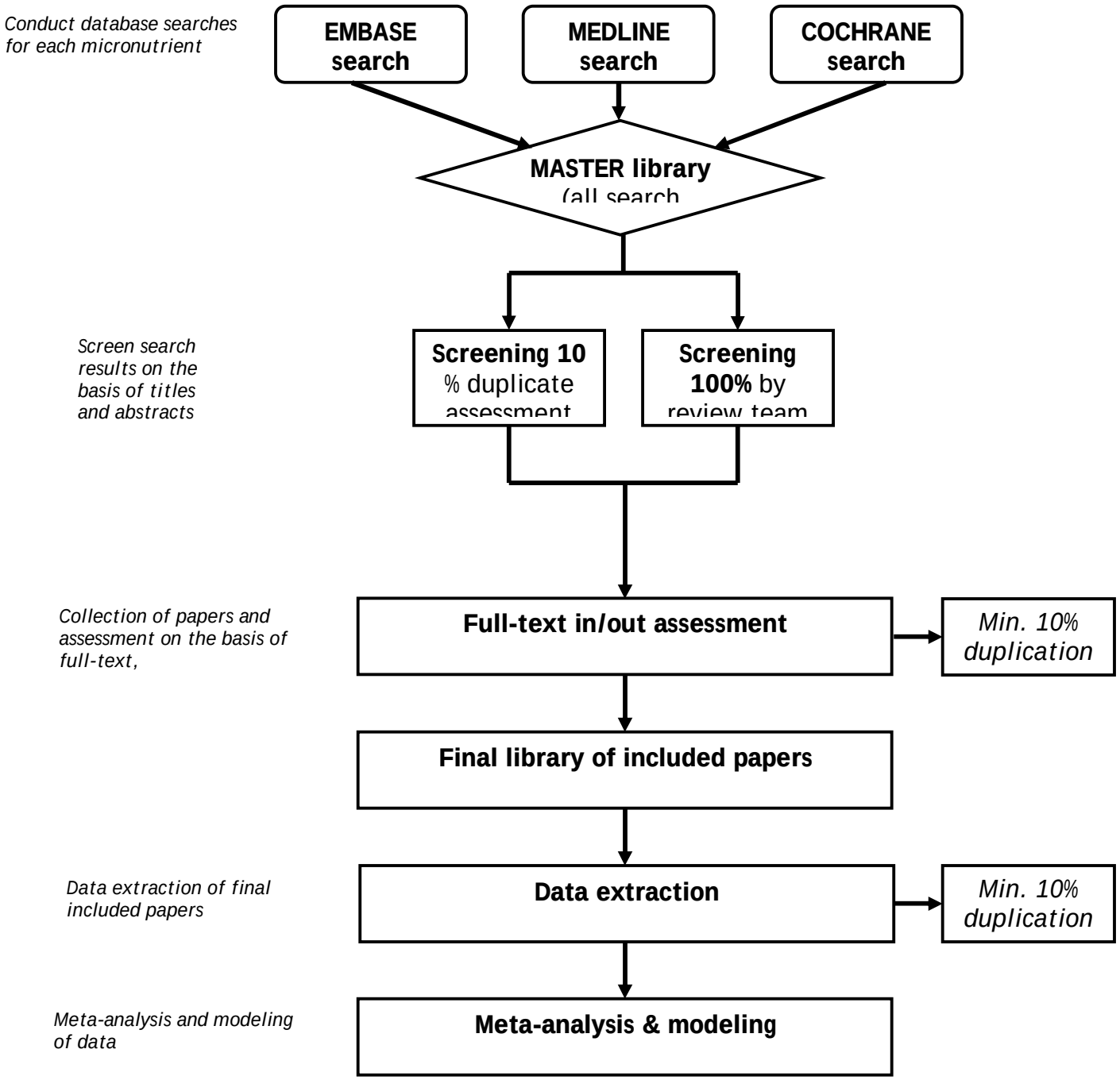


Figure 6 Conceptual representation of average requirements (AR) for micronutrients as a function of age (~~relative to~~ population groups and ~~age~~ across the life cycle~~span~~). The figure highlights~~ing~~ the widely different ~~types of evidence and~~ research approaches and scaling methods that underlie the derivation of ARs. This illustrates the need of standardisation of methods and weighing the different types of evidence. ~~se data~~. ~~Conceptualisation of the evidence base for average requirements according to age and life stage with scientific approaches generally used to derive these recommendations~~

Figure 7 Generalised systematic review process for identification of data relevant to the derivation of dietary recommendations.



$$\text{Dietary Requirements} = \frac{\text{Sum of losses (faeces, urine, skin, menses etc) + Growth \& development requirements (foetus, pregnancy, lactation etc.)}}{\text{Bioavailability factor}}$$

Figure 8 Basic equation for the calculation of dietary requirements based on the sum of losses and requirements for growth and development adjusted by a bioavailability factor.

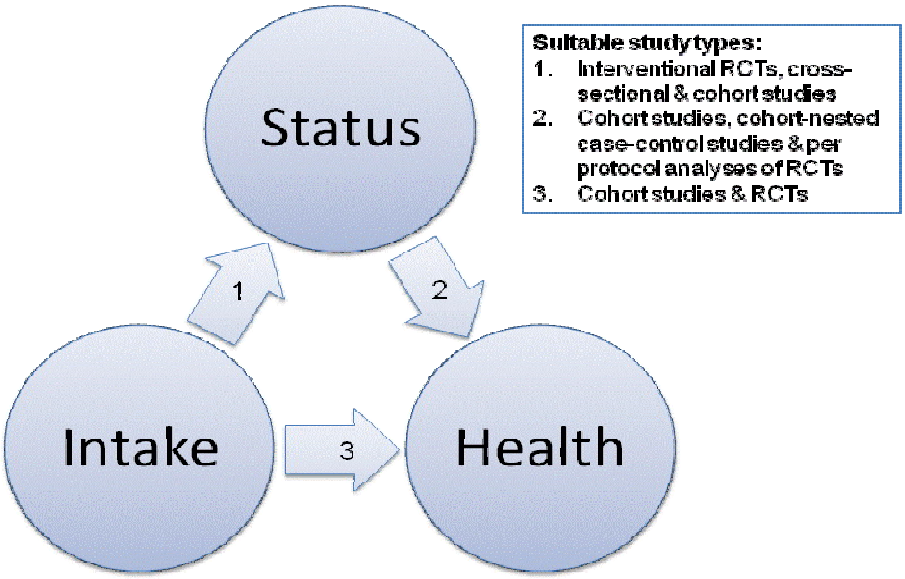
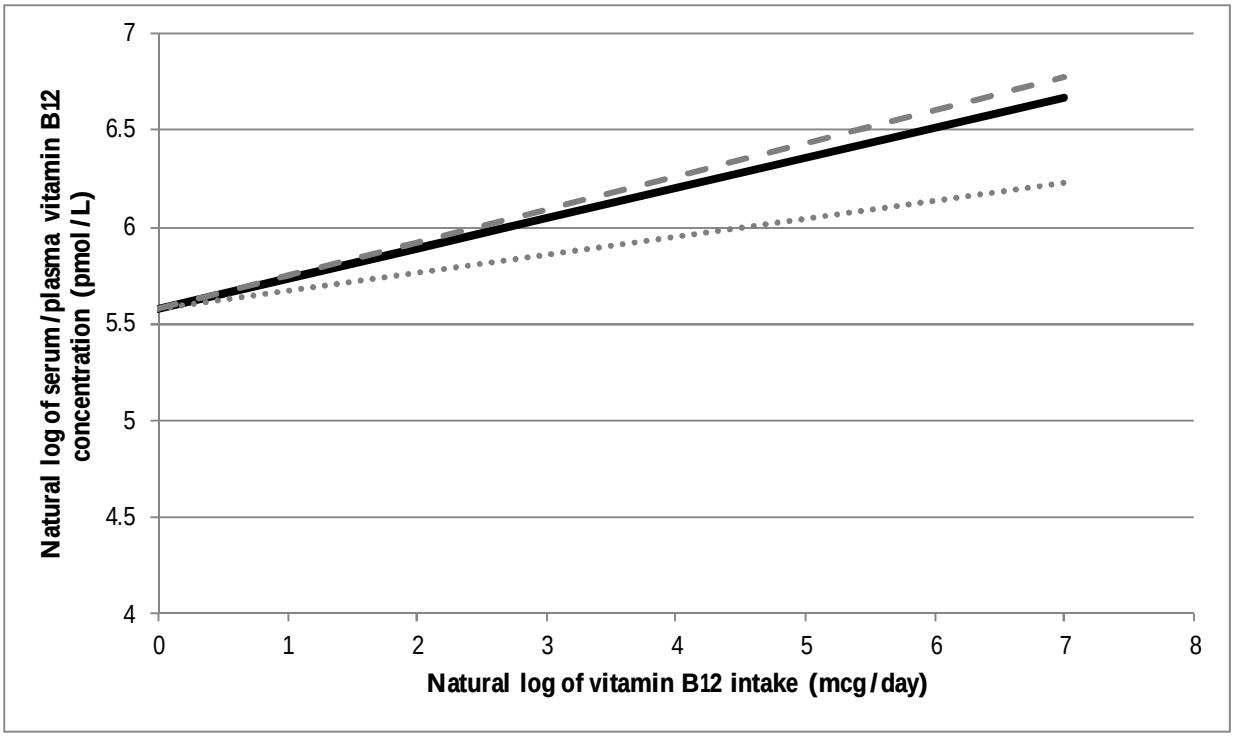


Figure 9 Schematic representation of the relationships of interest for the derivation of dietary reference values using the 'dose response approach'. Study types that may provide data to characterise potential I-S-H associations are suggested for each possible relationship. (Figure available in color online)



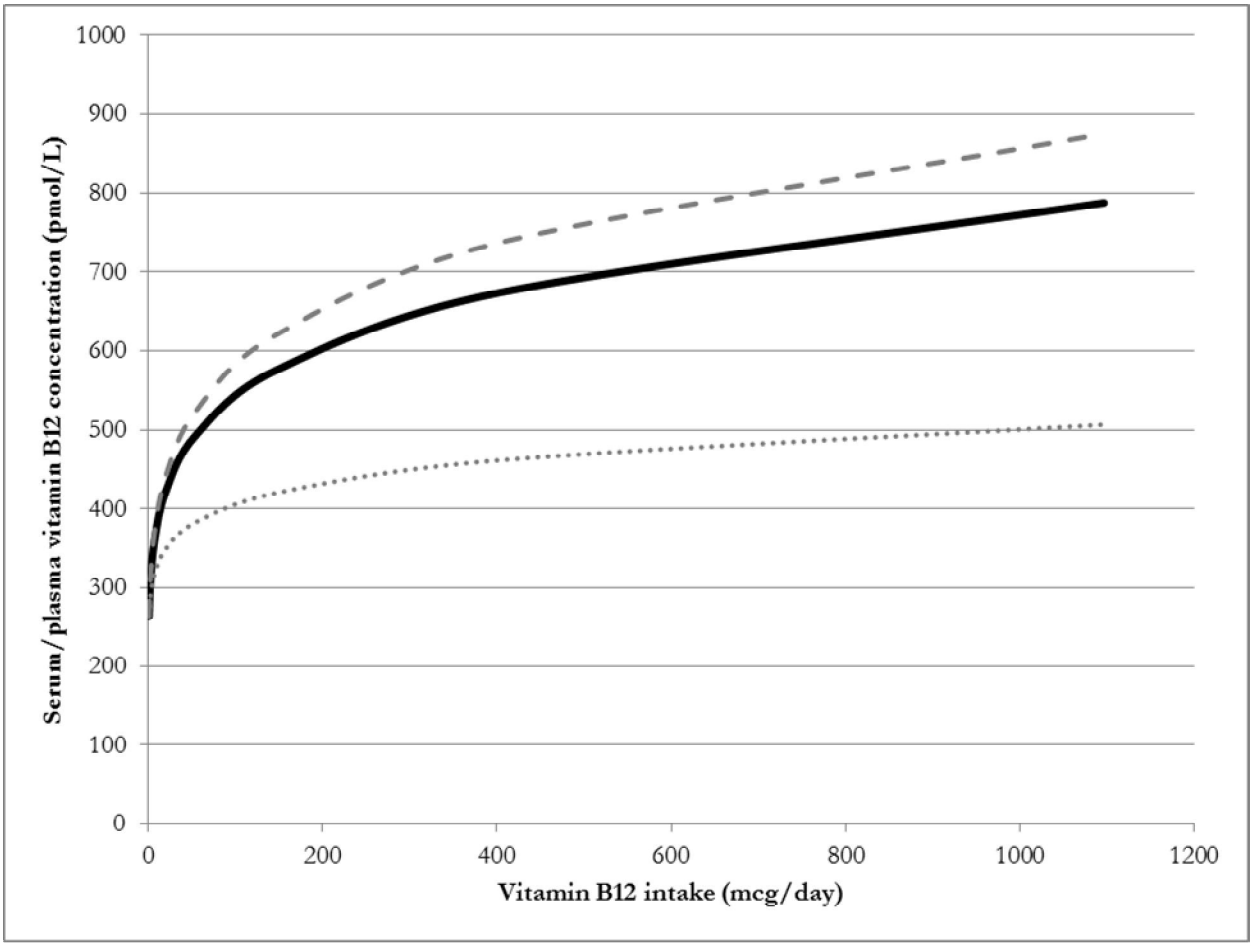


Figure 10 Serum/plasma micronutrient concentration (pmol/L) as a function of dietary micronutrient intake (mcg/day), estimated by random-effects meta-analyses of observational studies (n=19) and RCTs (n=37), on double $\log_e$ transformed scale (upper panel) and backtransformed scale (lower panel). In the upper panel, the line for observational studies is less steep, probably because of measurement errors in intake data and a smaller dose range as in RCTs. The overall pooled regression line (solid) of the $\log_e$transformed vitamin B12 intake and $\log_e$transformed serum/plasma vitamin B12 status, has a slope of 0.15 (95%CI: 0.13-0.17; upper panel ~~I^2=98%~~). This means that for every doubling in vitamin B12 intake, the ~~difference in~~

vitamin B12 serum or plasma concentration increases by a factor ~~is~~ 2^{β} i.e. 11% ($=2^{0.15} = 1.11$). See Dullemeijer et al (2012)

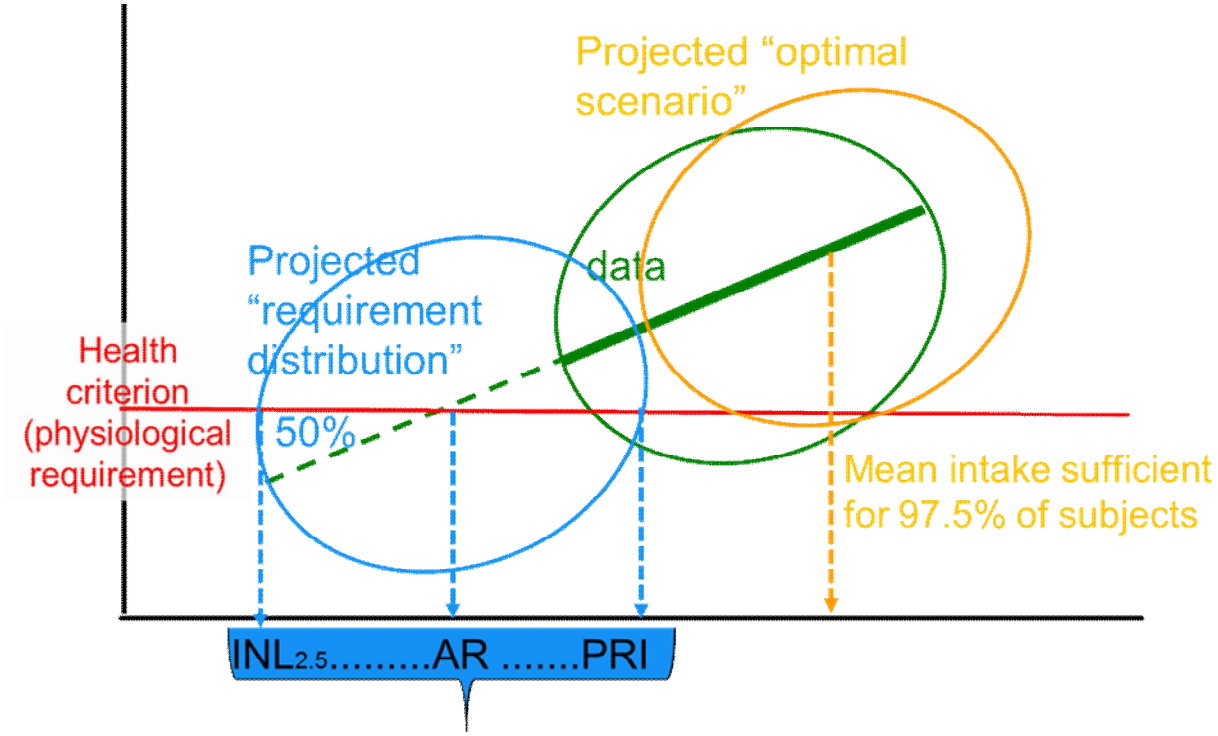


Figure 11 Conceptual model to derive nutrient reference values using a bivariate model for the intake-status relationship. Downward extrapolation results in AR- and PRI-like estimates. Upward extrapolation can predict the average intake of a population to serve the needs of 97.5% of its members. It should be noted that the method applies to populations rather than individuals. (Figure available in color online)

Figure 12 Scaling of reference values based on measures of body size, as selected by EURRECA

Metabolic turnover based on the body surface area (BSA) was calculated as BSA = √(Weight(kg)*Height(cm)/3600), according to Mosteller {Mosteller, 1987 #115}. Therefore, extrapolation can be based on:

$$AR_{child} = AR_{adult} * \frac{BSA_{child}}{BSA_{adult}} = AR_{adult} * \sqrt{\frac{Weight_{child} * Height_{child}}{Weight_{adult} * Height_{adult}}}$$

Metabolic body mass and growth needs. This method for extrapolation is applied by the IOM (Institute of Medicine). Maintenance needs are expressed relative to metabolic body weight, with an extra term for growth , based on protein needs and applied for all nutrients (WHO, 1985). This is, for example, 0.3 (i.e. 30 %) for children aged between 7 months and 3 years and 0.15 (i.e. 15 %) for 14-18 years males and 0.0 for 14-18 year old females (Prentice, Branca et al. 2004).

$$AR_{child} = AR_{adult} * \left(\frac{Weight_{child}}{Weight_{adult}}\right)^{0.75} * (1 + growth\ factor)$$

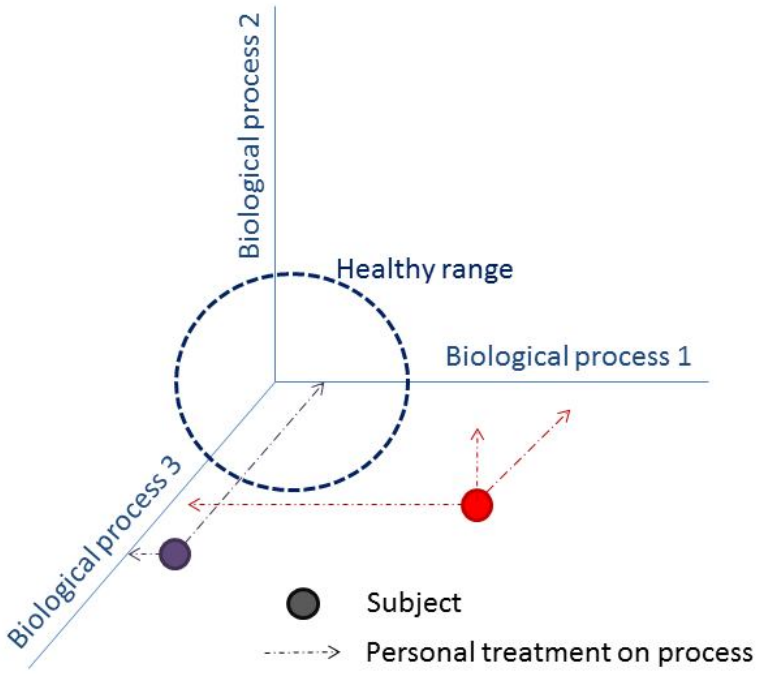


Figure 13 The health space model visualises personal micronutrient recommendations. In the health space each person's individual response to micronutrient interventions is visualised for specific biological processes (e.g. inflammation). For each biological process a multivariate statistical model is built, which is scaled between 0 (the average of all healthy subjects) and 1 (the average of the unhealthy subjects). All subjects are visualised in the resulting space. Intervention-induced changes of the position of subjects in this space, may support involvement of micronutrients in health-related biological processes relevant to long term health and disease outcomes. A 'real life' example on data is published (Bouwman et al., 2012a). (Figure available in color online)

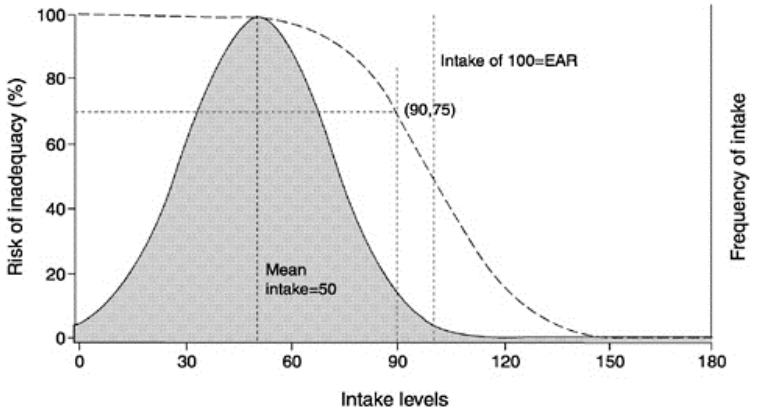


Figure 14 Risk curve combined with a usual intake distribution where the mean intake is less than the Average Requirement (AR). The mean of the usual intake distribution is 50 units and the majority of the intake values are less than 90 units. At 90 units, the risk of inadequacy is about 75 percent. Therefore, in this population, the probability of inadequacy is high.

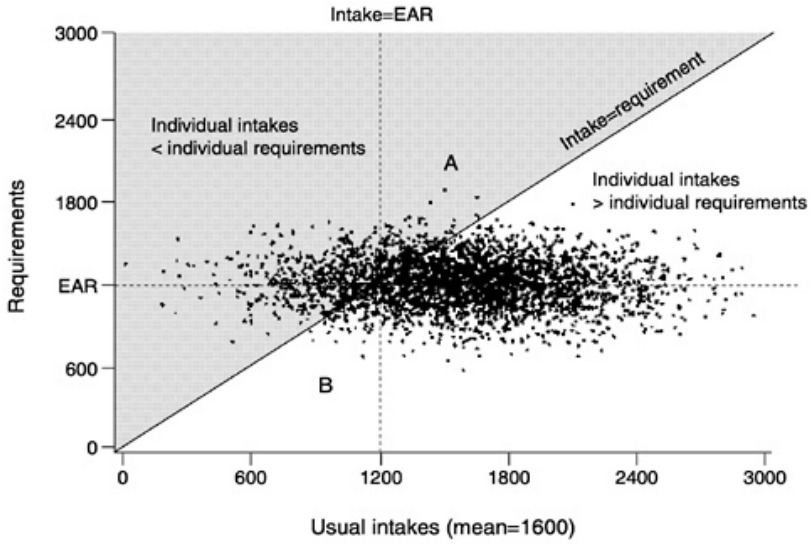


Figure 15 (adapted from Institute of Medicine: Dietary Reference intakes: Applications in Dietary Assessment; (EAR: Estimated Average Requirement) corresponds to AR). Joint distribution of intakes and requirements from a hypothetical population of 3,000 individuals with

the mean intake of 1600 units and the AR of 1200 units. The triangle labeled A is bounded by the intake = AR line and the 45° line where intake = requirement. Points above the 45° line (shaded area), represent those individuals whose intakes are above the AR, but below their own individual requirement. Individuals in triangle B have intakes below the AR, yet above their own requirement. The number of people in triangle A is approximately equal to the number in triangle B.

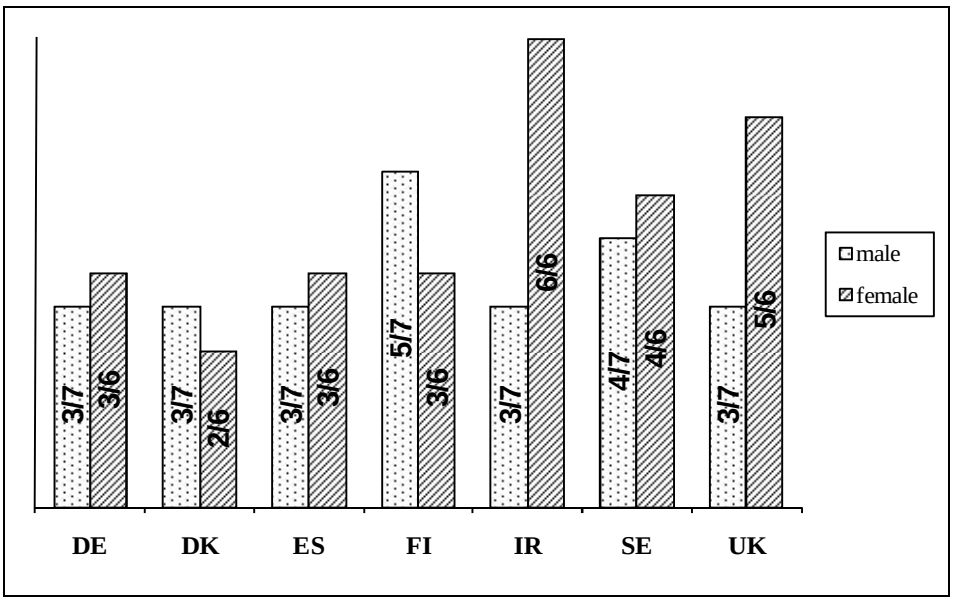
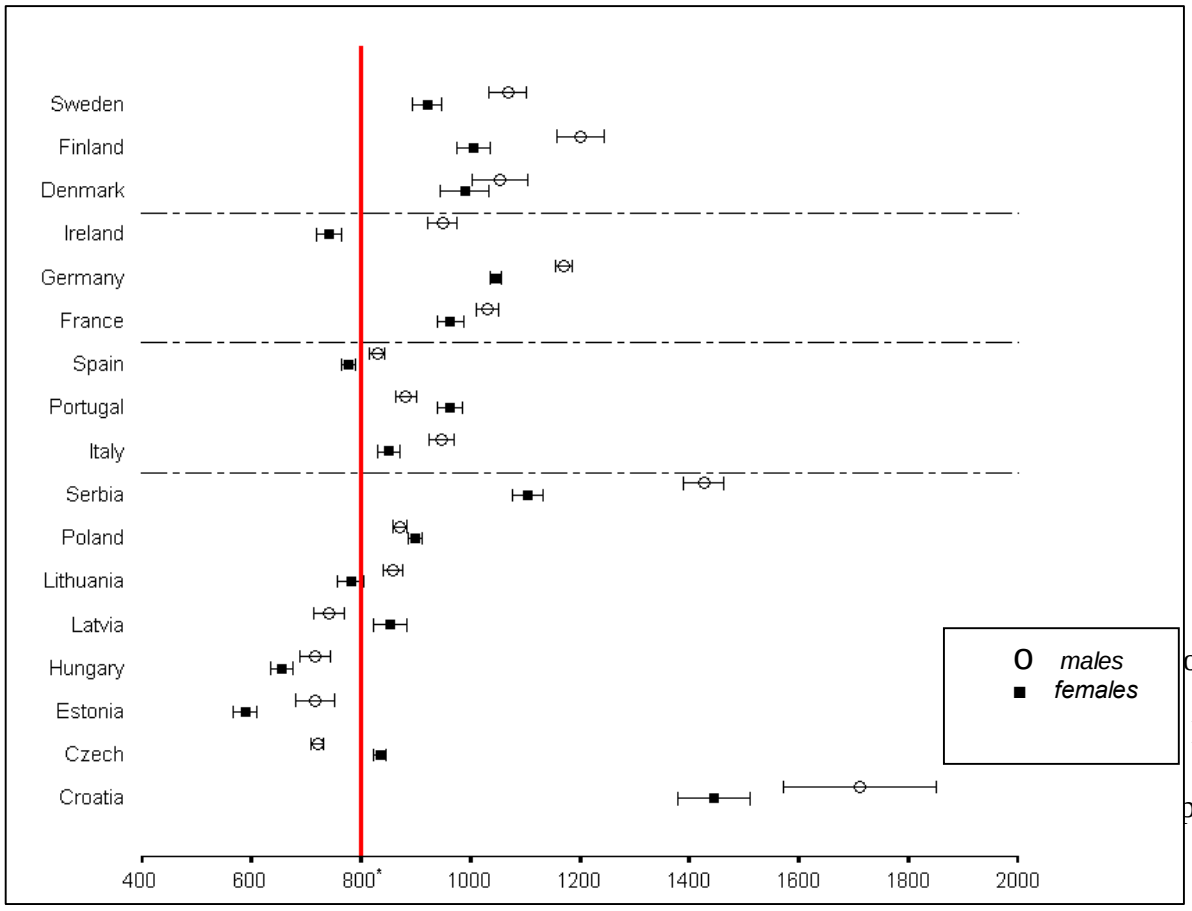


Figure 16 Countries with data for 7 vitamins and minerals (6 for females) classified according to the number of nutrients with inadequate intakes above 20% of the population. (DE= Germany ; DK= Denmark ; ES= Spain ; FI= Finland ; IR= Ireland ; SE= Sweden ; UK= United Kingdom).



or males

Europe,

ponds to

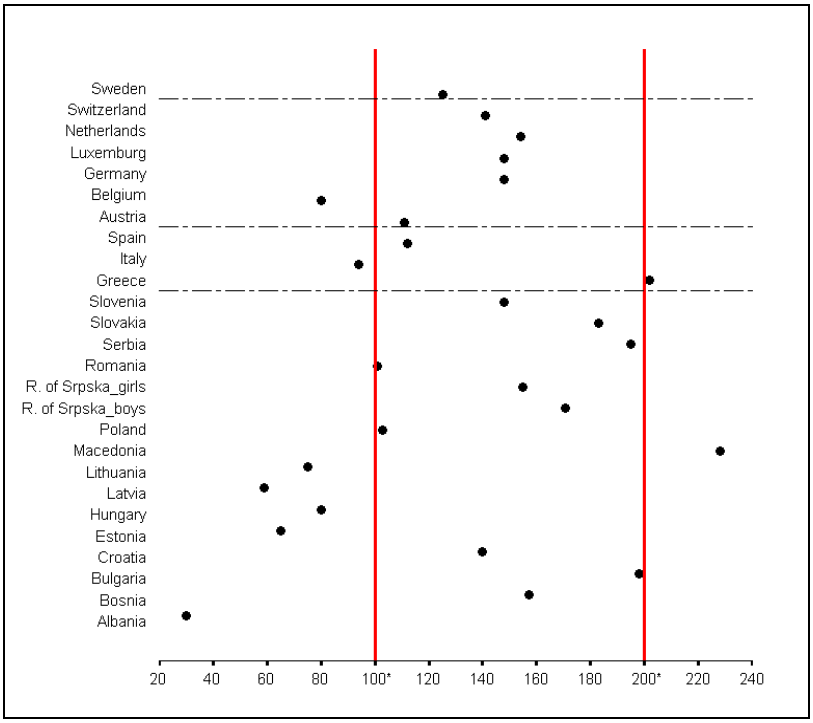


Figure 18 Median urinary iodine concentration in micrograms per litre per day by country, in children and adolescents in Europe (10).

*The optimal range for median urinary iodine concentration: 100-199 μg/L

** Source of data: WHO Vitamin and Mineral Nutrition Information System, except for studies from Republic of Srpska and Serbia

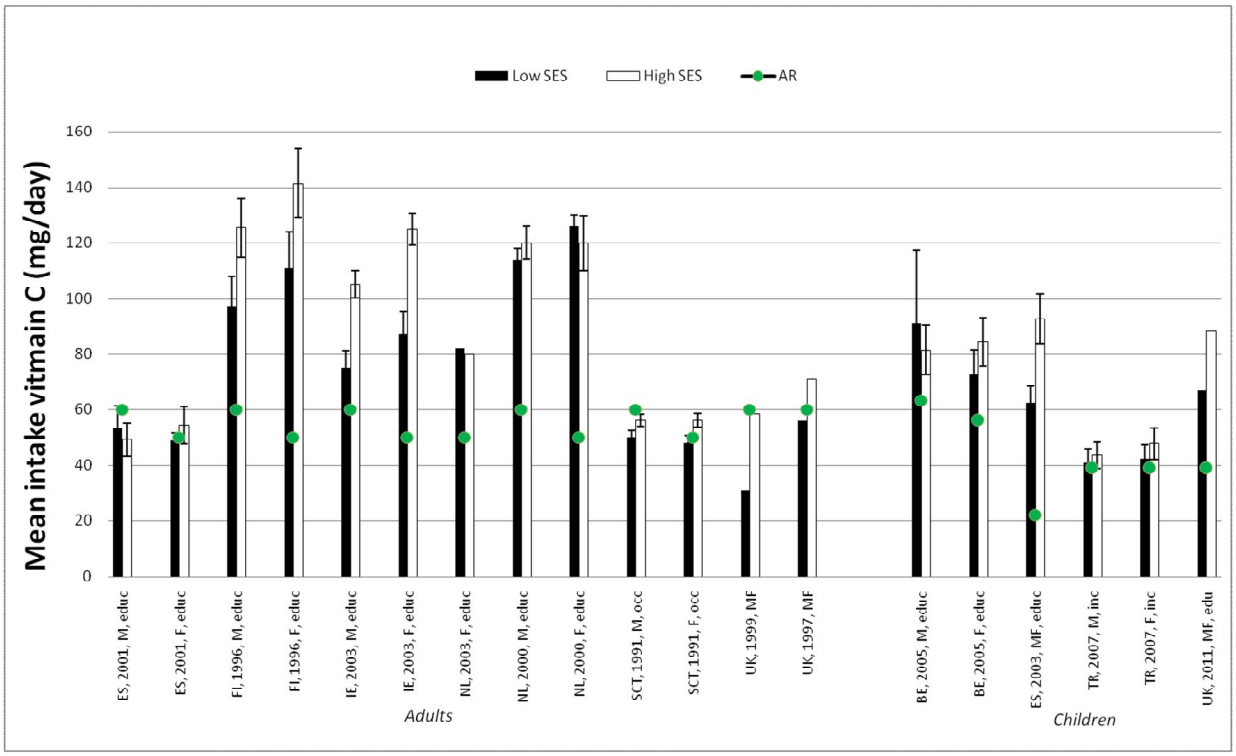


Figure 19 Mean intake of vitamin C (with their 95% confidence intervals where available) in lowest and highest SES group in Europe in males (M), females (F) and in both genders (MF), and in comparison to Average Requirement (AR). Abbreviations for countries: ES- Spain, FI- Finland, IE- Ireland, NL- The Netherlands, SCT- Scotland, UK- The United Kingdom, BE- Belgium, TR-Turkey. Abbreviations for SES indicators: educ- education, occ- occupation, inc- income (Novakovic et al)

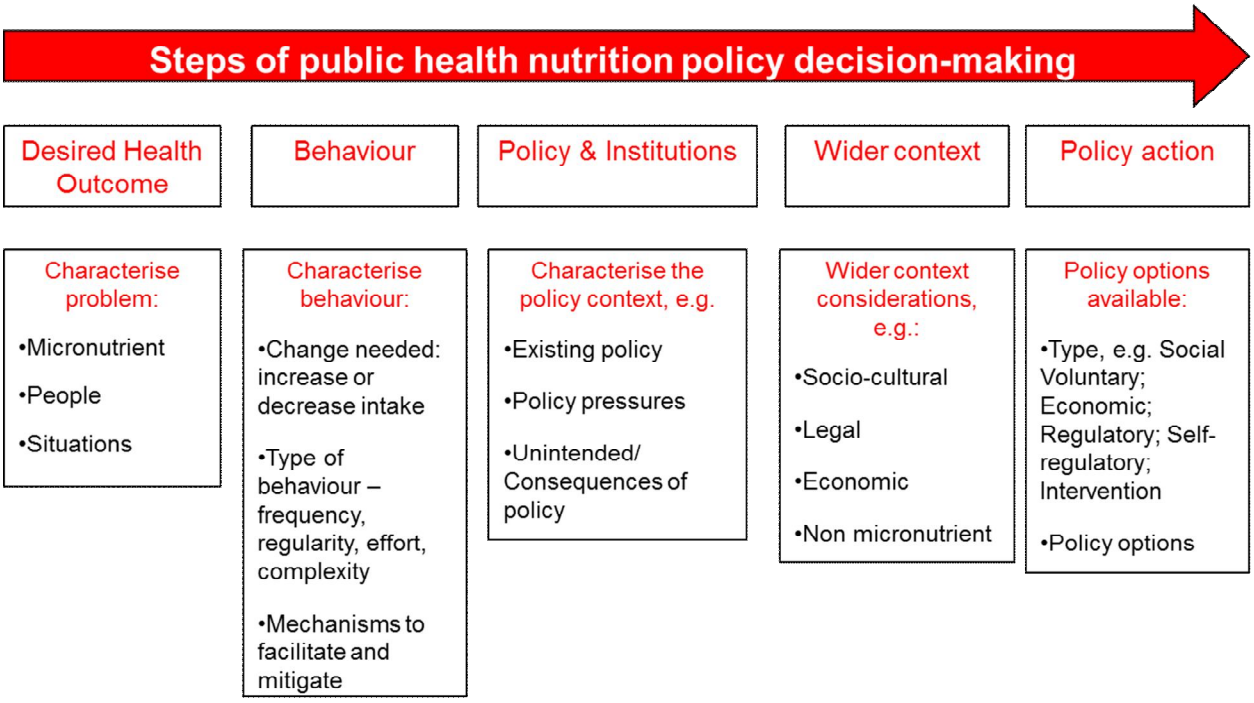


Figure 20 EURRECA's steps for decision making

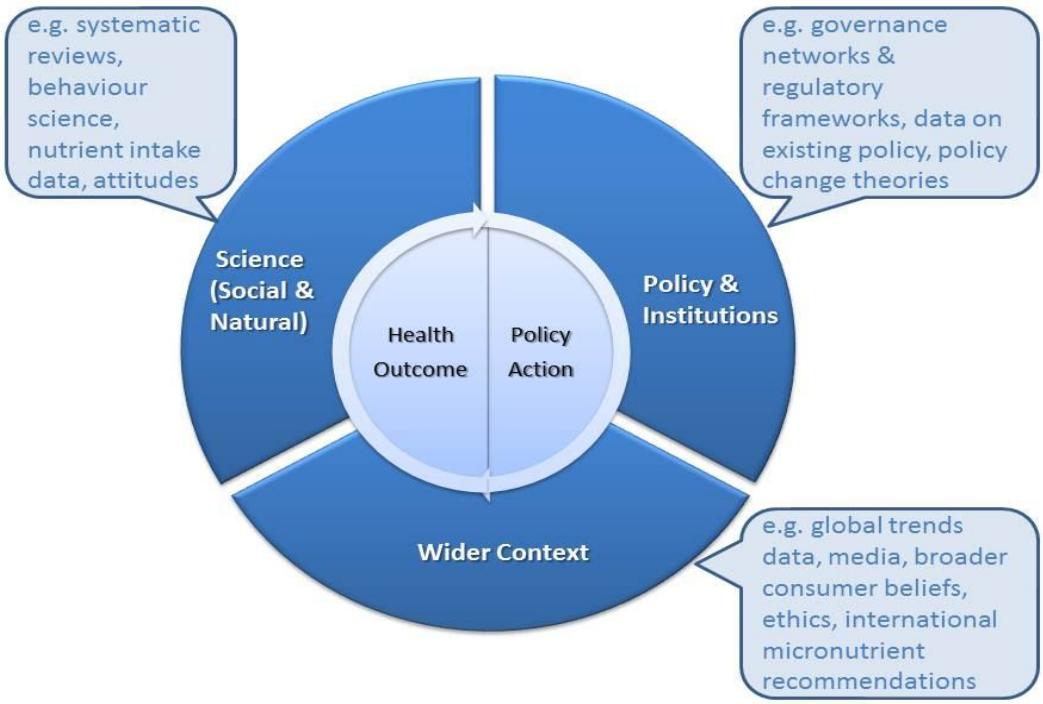


Figure 21 Public Health Nutrition Policy Framework