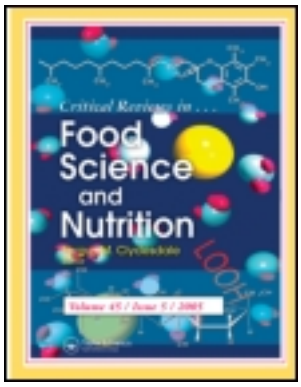

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

EURRECA—Estimating Iron Requirements for Deriving Dietary Reference Values

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Accepted author version posted online: 08 Aug 2013.Published online: 16 Aug 2013.

To cite this article: Linda J. Harvey , Cristiana Berti , Amelie Casgrain , Irene Cetin , Rachel Collings , Mirjana Gurinovic , Maria Hermoso , Lee Hooper , Rachel Hurst , Berthold Koletzko , Joy Ngo , Blanca Roman Viñas , Christiane Vollhardt , Vesna Vucic & Susan J. Fairweather-Tait (2013) EURRECA—Estimating Iron Requirements for Deriving Dietary Reference Values, Critical Reviews in Food Science and Nutrition, 53:10, 1064-1076, DOI: 10.1080/10408398.2012.742860

To link to this article: http://dx.doi.org/10.1080/10408398.2012.742860

Critical Reviews in Food Science and Nutrition, 53:1064–1076 (2013)

ISSN: 1040-8398 / 1549-7852 online
DOI: 10.1080/10408398.2012.742860

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EURRECA—Estimating Iron Requirements for Deriving Dietary Reference Values

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Currently, a factorial approach is used to derive reference values for iron. Calculations include the use of a bioavailability factor to convert the physiological requirement, derived from obligatory losses and requirements for growth and development, into a dietary intake value. A series of systematic reviews undertaken by the EURRECA Network of Excellence aimed to identify data that may increase the accuracy of factorial calculations across all population groups. The selection of robust data was guided by the use of standardized review methodology and the evidence-based selection of status biomarkers and dietary intake assessment techniques. Results corroborated the dearth of relevant factorial data, including whole-diet bioavailability data, and confirmed the need to continue extrapolating physiological requirements across population groups. Data were also unavailable that would allow reference values to be based on selected health outcomes associated with iron intake or status. Ideally, a series of observational and randomized controlled trial (RCT) studies need to be undertaken across all population groups and life stages to generate robust data for setting dietary reference values for iron. It will also be essential to include information on polymorphisms that potentially influence iron absorption and status in the derivation process.

Keywords Iron, dietary recommendations, iron intake, systematic review, iron status, iron bioavailability, iron requirements

FUNCTION, ESSENTIALITY, PHYSIOLOGY, AND METABOLISM

Iron is an essential mineral found in foods such as meat, liver, nuts, beans, green leafy vegetables, and fortified foods. The adult human body contains approximately 3–4 g of iron, most of which is present in hemoglobin (∼70%). Despite the relatively high abundance of iron in foods, iron deficiency (ID) is the most common micronutrient deficiency worldwide and the only nutrient deficiency significantly prevalent in industrialized countries. Over 30% of the world's population (2 billion people) are anemic, and approximately half of these cases result from ID and present significant public health problems (WHO, 2002, 2008; Allen et al., 2006).

Iron is essential to life due to its ability to act as both an electron donor and an electron acceptor. The majority of body iron is located within protein complexes and forms the principal component of a heme molecule, which consists of an iron

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atom contained in a porphyrin ring. Heme molecules are important elements of the oxygen-binding proteins, hemoglobin and myoglobin, found in erythrocytes and muscle, respectively. Consequently, iron is instrumental in the transport of oxygen around the body and its storage in muscle. Iron is also an important component of many enzymes and cytochromes, and thus has roles in electron transport, respiration, and hormone synthesis.

The maintenance of adequate iron status is essential for optimal health. Status is maintained by the interplay between three key factors, namely iron intake, storage, and loss, and as a result, ID may arise from inadequate dietary intakes, poor absorption, and/or excessive losses. ID is usually caused by inadequate absorption, excessive iron losses (although there is no specific excretory mechanism), or a combination of the two, and is defined as a lack of body iron stores. Iron deficiency erythropoiesis (IDE) is characterized by the absence of iron stores and a reduced level of transferrin saturation, but without a reduction in hemoglobin (Cook, 2005). IDE may lead to iron deficiency anemia (IDA) when hemoglobin concentrations are reduced. Homeostatic mechanisms are key to the body's attempts to maintain appropriate iron status, with adaptive responses aiming to ensure that absorption is up- or downregulated in response to low and high status, respectively. Absorption is upregulated in response to both iron depletion and increased erythropoietic activity as a result of blood loss, e.g., menstrual losses or tissue hypoxia at altitude; whereas iron absorption is downregulated in response to large doses of dietary iron or when stores are high. In contrast with the longer-term systemic control exerted by the iron status of an individual, the causes of short-term (day-to-day) fluctuations in iron absorption are more complex, stemming from both physiological factors that determine iron availability and adaptive mechanisms imposed by enterocytes lining the gastrointestinal tract.

Iron absorption is also influenced by an ever-increasing number of identified genetic polymorphisms in proteins related to iron uptake from the gastrointestinal tract. The principal polymorphisms identified to date include mutations in the *HFE* gene, e.g., C282Y and H63D, which are responsible for specific types of hereditary hemochromatosis, a disorder of excessive iron accumulation. In addition, single-nucleotide polymorphisms (SNPs) in ferroportin genes (*A77D*, *G490D*, etc.) can also result in increased basolateral transport, leading to other types of hemochromatosis (Fairweather-Tait et al., 2007). While most SNPs identified to date relate to iron uptake and potential iron accumulation, much less is known about SNPs related to ID. A polymorphism in the transferrin protein (G277S) has been linked with ID, but the data are inconclusive (Lee et al., 2001).

CURRENT DIETARY RECOMMENDATIONS

Dietary iron requirements vary considerably between population groups, with women and children being most vulnerable to deficiency, particularly those in developing countries. There is often disparity between recommendations set by nutrient recommendation-setting bodies and these inconsistencies have been identified and collated by the EURRECA Network of Excellence (Doets et al., 2008). The variation within the recommendations stems from differences in the scientific evidence base selected and evaluated by committees and also variations in criteria used for determining requirements.

Table 1 provides a brief summary of key recommended daily intakes for iron during various life stages in both males and females. A full summary of dietary iron recommendations can be found in the "Nutri-RecQuest" searchable database developed by the EURRECA Network (www.serbianfood.info/eurreca/index.php) (Cavelaars et al., 2010). Dietary recommendations generally aim to supply sufficient iron to meet the requirements of 97.5% of the relevant population. A notable exception is the European Commission (EC), which made recommendations for menstruating females that only cover 90 or 95% of the population (data for 95% reported in Table 1) (Commission of the European Communities, 1993). This is due to skewed iron requirements in some females due to extremely high menstrual iron losses. The committee felt that to ensure an adequate iron supply for 97.5% of the population, the recommendations would need to be disproportionately high and potentially excessive.

While the majority of nutrient recommendation-setting bodies have taken life stage into account, including menopausal status, pregnancy, and lactation, when determining micronutrient requirements, the World Health Organization/Food and Agriculture Organization (WHO/FAO) are unique in providing a series of recommendations that take into account iron bioavailability for each population group and life stage. A series of recommendations have been made allowing for diets with iron bioavailabilities of 5, 10, 12 and 15% (WHO/FAO, 2002). Table 1 presents FAO/WHO data for diets with a bioavailability of 15%, generally considered to represent the majority of diets consumed by the European population.

CURRENT INTAKES/ADEQUACY

The current European dietary iron intakes in adults and children have recently been detailed in the ILSI Europe Addition of Nutrients to Food Task Force report on upper levels of intake (Flynn et al., 2009). Intakes were derived from nationally representative surveys in several European countries. Mean dietary iron intakes (including fortified foods, but excluding supplements) ranged from 11.2 mg/d in Denmark to 16.7 mg/d in Poland for adult men, and in adult women from 8.4 mg/d in Ireland to 13.4 mg/d in Germany. The European Nutrition and Health Report (ENHR) 2004 (Elmadfa et al., 2005) also specifically assessed dietary iron intake in the elderly European population (Fabian and Elmadfa, 2008).

In the EURRECA Network, the prevalence of inadequate intakes in Europe for several nutrients, including iron, were calculated and estimated using published data from 13 EU countries from the ENHR II by applying the Nordic Nutritional

Table 1 Selected recommended intake levels for iron (mg/d)

			Population group																	
Data source	Gender	Special conditions	Infants		Children		Adolescents				Adults		Elderly		Lactation		Pregnancy			
WHO/FAO (2002)	Male	15% bioavailability	0–6 m	0	1–3 y	3.9	11–14 y		9.7		18–65 y	9.1	>65y	9.1	—		—			
			7–12 m	6.2	4–6 y	4.2	15–17 y		12.5											
					7–10 y	5.9														
	Female	15% bioavailability	0–6 m	0	1–3 y	3.9	Menstruating		Nonmenstruating		18–50 y	19.6	>65 y	7.5		10.0	Null			
			7–12 m	6.2	4–6 y	4.2	11–14 y	21.8	15–17 y	20.7	51–65 y	7.5								
					7–10 y	5.9														
Nordic (Nordic Council of Ministers, 2004)	Male	—	<6 m	Null	1–5 y	8.0	14–17 y		11.0		18–74 y	9.0	≥75 y	9.0	—		—			
			6–11 m	8.0	6–9 y	9.0														
					10–13 y	11.0														
	Female	—	<6 m	Null	1–5 y	8.0	14–17 y		15.0		18–60 y	15.0	≥75 y	9.0		15.0	Null			
			6–11 m	8.0	6–9 y	9.0					61–74 y	9.0								
					10–13 y	11.0														
Australia/New Zealand (National Health and Medical Research Council, 2006)	Male	—	0–6 m	0.2	1–3 y	9.0	14–18 y		11.0		19–70 y	8.0	>70 y	8.0	—		—			
			7–12 m	11.0	4–8 y	10.0														
					9–13 y	8.0														
	Female		0–6 m	0.2	1–3 y	9.0	14–18 y		15.0		19–50 y	18.0	>70 y	8.0	14–18 y	10.0	27.0			
			7–12 m	11.0	4–8 y	10.0					51–70 y	8.0	19–50 y	9.0						
					9–13 y	8.0														
DACH (German Nutrition Society, 2002)	Male	—	0–3 m	0.5	1–3 y	8.0	13–18 y		12.0		19–64 y	10.0	≥65 y	10.0	—		—			
			4–11 m	8.0	4–6 y	8.0														
					7–9 y	10.0														
					10–12 y	12.0														
	Female	—	0–3 m	0.5	1–3 y	8.0	13–18 y		15.0		19–50 y	15.0	≥65 y	10.0		20.0	30.0			
			4–11 m	8.0	4–6 y	8.0					51–64 y	10.0								
					7–9 y	10.0														
					10–12 y	15.0														
EC (Commission of the European Communities, 1993)	Male	—	6–11 m	6.0	1–3 y	4.0	11–14 y		10.0		≥18 y	9.0	≥18 y	9.0	—		—			
					4–6 y	4.0	15–17y		13.0											
					7–10 y	6.0														
	Female	Adolescent and premenopausal adult values cover 95% population	6–11 m	6.0	1–3 y	4.0	11–14 y		22.0		≥18 y	20.0	Null			10.0	Null			
					4–6 y	4.0	15–17 y		21.0		Postmenopausal									
					7–10 y	6.0					8.0									
Institute of Medicine (IOM) (US/Canada) (National Research Council, 2006)	Male	—	0–6 m	0.27	1–3 y	9.0	14–18 y		11.0		19–70 y	8.0	>70 y	8.0	—		—			
			7–12 m	11.0	4–8 y	10.0														
					9–13 y	8.0														
	Female	—	0–6 m	0.27	1–3 y	9.0	14–18 y		15.0		19–50 y	18.0	>70 y	8.0	14–18 y	10.0	27.0			
			7–12 m	11.0	4–8 y	10.0					51–70 y	8.0	19–50 y	9.0						
					9–13 y	8.0														

Recommendations as the standard (Roman-Viñas et al., 2011a). The Nordic data were selected by virtue of being the most recently set European recommendations that target several European countries. The prevalence of iron intake inadequacy was at or below 10% of the population in most of the nutritional surveys. Elderly from Denmark, Finland, Norway, Ireland, and Belgium (only females) and adult males from Finland, the United Kingdom, and Greece had a prevalence of inadequacy between 11% and 21% (Roman-Viñas et al., 2011a). An indication of the effect of applying different recommendations to identify levels of inadequacy may be gained by assessing the disparity in dietary recommendations (Doets et al., 2008).

In order to evaluate micronutrient intake and/or status between European countries and regions, the EURRECA Network collected data for all population groups in Central and Eastern Europe (CEE), Scandinavia, Western Europe, and Mediterranean countries. Studies were identified from electronic databases (PubMed, Embase) and grey literature sources, and the inclusion criteria followed general EURRECA guidelines on dietary intake, status, and study characteristics (see also activities 1 and 3 in Dhonukshe-Rutten et al. (2013)). A key result highlighted no differences between pooled mean iron intakes in European females (range 11–13 mg/d). Based on the Nordic recommendations, all countries reported mean intakes higher than the average requirement (AR), with exception of Hungarian females. For males, the mean estimated intake in CEE (16 mg) was slightly higher than in other regions, which ranged from 13 to 15 mg/d; all countries reported observed mean intakes higher than the AR. Data on iron status were mainly retrieved from the WHO VMNIS (Vitamin and Mineral Nutrition Information System) database. Mean hemoglobin levels in CEE children and adolescents were found to be lower than in other European countries, for which the data were scarce. Mean levels were in general above the cutoff values (hemoglobin level $\leq$ 110 g/L); only infants in Lithuania were at risk of IDA, whereas children in Romania had concentrations bordering on inadequate (Novakovic et al., 2012). Additionally, for Norwegian adults, mean hemoglobin levels were observed to be below the reference values (Novakovic et al., forthcoming).

As not all population groups were represented in the ENHRII or ILSI reports, searches were also conducted by the network to identify European studies and intake data for infants, low-income and immigrant groups, and pregnant and lactating women. It is important to note that many of the data for vulnerable groups were only available in the grey literature. The prevalence of inadequacy for iron was calculated by applying the AR cutpoint method (Beaton, 1994), except for women of childbearing age, where iron requirements are skewed. In this case, the mean intake was compared with the INL98 [European Food Safety Authority (EFSA) equivalent term = Population reference intake (PRI)]. The dietary intake and estimated prevalence of inadequacies based on these sources is reported elsewhere (Ngo et al., in press; Novakovic et al. 2012).

A systematic search was carried out in both Medline and Embase databases to evaluate associations between socioeconomic determinants and micronutrient intake and status in Europe. Studies were considered eligible if they followed EURRECA best practice (see also activities 1 and 3 in Dhonukshe-Rutten et al. (2013)) for assessment of micronutrient intake and/or status. In seven out of the nine relevant studies identified, groups with a low socioeconomic status (SES) had a lower iron intake compared with the remainder of the population, except for adults in Spain. All studies showed a mean iron intake for both SES groups that was above the AR, suggesting a low risk for inadequacy. Data on iron status however were very scarce, with only two studies identified, each reporting higher iron status levels in SES groups.

The results of additional searching and data evaluation demonstrated that overall information for vulnerable groups was sparse, with only Norway, Spain, and the United Kingdom having data on pregnant and lactating women, with 67% of Norwegian pregnant women and 100% of Spanish women deemed to have an inadequate intake. Data on European migrant populations were even sparser, with only four studies focusing on Roma, Afro-Caribbean, Pakistani and Sub-Saharan African minority groups. With the exception of the Sub-Saharan population in Spain, all minority groups had inadequate iron intakes, especially in South Asian and Afro-Caribbean women and in Pakistani males in the United Kingdom (Ngo et al., in press). Data on low-income population groups were only available in the United Kingdom, indicating a prevalence of inadequacy of almost 20% in all male age groups. Data were available from several countries for children and adolescents, but no data were available for infant population groups. However, a recent overview (Mensink et al., 2013) focusing on low micronutrient intakes across Europe that compared recent nationally representative dietary survey data from Belgium, Denmark, France, Germany, the Netherlands, Poland, Serbia, Spain, and the United Kingdom determined that the number of children aged 1–3 years with intakes below the LNRI [equivalent EFSA term = lower threshold intake (LTI)] and EAR [equivalent EFSA term = average requirement (AR)] ranged between 3–27% and 23–50%, respectively. For females aged 4–10 years, the highest proportion of mean intakes below the LRNI (LTI equivalent) and EAR (AR equivalent) was 5.6% and 28%, respectively, while for 11–17 year olds, the percentages were the highest among Danish girls, at 51% and 94%. However, in adult populations, the percentage of males below the LRNI (LTI equivalent) and EAR (AR equivalent) was low in all countries (2.2% and 11%, respectively), but significantly higher in females (approximately 25% and 50%, respectively, in the majority of countries included in the comparison).

ESTABLISHING THE MOST ROBUST METHODOLOGY

Intake Assessment

Accurate assessment of dietary iron intake, particularly in individuals, is hindered by several factors, including the quality

of food composition data, food fortification, supplement use, and inappropriate choice of methodology. One of the initial aims of the EURRECA Network was to evaluate the methodology routinely used to assess dietary intakes of micronutrients in European populations. This was achieved by undertaking a series of systematic reviews covering all aspects of dietary survey methodology (Serra-Majem et al., 2009a). Subsequently, another series of systematic reviews was undertaken that specifically focused on the methodology associated with the EURRECA priority micronutrients and all relevant population groups (Serra-Majem, 2009). One of the reviews concentrated on dietary assessment methods for iron, calcium, selenium, zinc, and iodine intake (Serra-Majem et al., 2009b).

At a workshop of invited experts and EURRECA partners that took place in Leiden, the Netherlands, in February 2011, discussions concluded that assessments of dietary iron intake were not essential for requirement setting, but served as a useful monitoring tool. The consensus was that 7–10 days of weighed food records was the "gold standard" for estimating iron intake, whereas in general food frequency questionnaires (FFQ) were not particularly useful.

Other factors deemed to be problematic for assessing dietary intake were the overall dietary composition, including the heme:non-heme ratio, fortification practice, and the quality of the local food composition databases. Overall, it was concluded that accurately assessing dietary iron intake was problematic.

Status Assessment

The EURRECA Network adopted several complementary approaches for establishing robust methodology in the assessment of iron status. In early 2008, EURRECA partners and international invited experts attended a workshop in Norwich, United Kingdom, with the aim of critically reviewing traditional biomarkers employed in dietary surveys (Zimmermann, 2008). During the workshop, a "Biomarkers of Status Working Party" was formed that produced a quality-rated, eminence-based table, including a brief description of iron biomarkers of status, accompanied by a rating of the methodological limitations and its application in research, i.e., suitability for research and/or fieldwork (http://www.eurreca.org/everyone/8647/5/0/32). At the subsequent Leiden workshop, one of the main themes that emerged centered around the standardization of specific biomarkers, the usefulness of some indicators in association with inflammation, and the difficulties associated with setting cutoff values in different population groups. Inflammation was generally not considered to be a major problem in the European population, except for overweight/obese individuals. Overall, it was concluded that biomarkers of iron status need to be assessed in combination, and an inflammatory marker should be measured simultaneously. However, collation of iron status and anemia prevalence data was deemed essential to inform the DRV setting process.

An assessment of all the latest information concerning measurements of iron status was collated and resulted in the selection of four EURRECA-recommended status biomarkers for adults, namely serum/plasma ferritin, serum/plasma transferrin receptor, body iron [Cook's method (Cook et al., 2003)], and hemoglobin. However, it was recognized that hemoglobin is generally the least sensitive and specific of these markers, and some additional limitations must be considered for infants as reference values, for all indicators are not well developed in this population group (Domellof et al., 2002). Serum/plasma ferritin is generally considered to be the best and most widely used single indicator of iron status in this population group (Hulthen et al., 1998), but it is less useful than in adults partly due to the changes in concentration that continue for the first 18 months of life (Sherriff et al., 1999). While serum/plasma transferrin receptor concentration is considered the single-most sensitive indicator of functional iron depletion (Baynes, 1996), cutoff values are again not well defined (Lozoff et al., 1998).

Relevant Health Outcomes

Currently, there is insufficient evidence to use health outcomes as a basis for establishing dietary iron requirements. Despite this lack of data, there are well-characterized associations between iron status and a range of health outcomes in various population groups. Most DRV panels are guided by health outcomes endpoints, but the derivation of recommendations is dependent on whether the aim is to prevent deficiency or target optimal/adequate health. For adult and elderly populations, relevant health outcomes identified by EURRECA included tiredness, physical performance, immune function, impaired thermoregulation, restless legs syndrome, and cognitive function. It should be noted that while anemia is generally considered to be a health outcome, for the purposes of EURRECA research undertaken in the adult and elderly population groups, anemia was used as a classification of iron status related to other health outcomes rather than being a health outcome in itself. Specific outcomes were identified in relation to pregnancy, namely preeclampsia, postpartum depression, fetal growth, and preterm delivery. Growth and neurodevelopment were acknowledged as relevant outcomes in infants, with immune and cognitive functions and psychomotor development gaining importance in children and adolescents.

Population Groups

An examination of dietary reference values set by various nutrient recommendation-setting bodies highlights disparities in the selection of age ranges for various population groups. Disagreement mostly centers on infants, children, and adolescents, and also on the age at which an individual is deemed to become elderly. At a workshop of invited experts and EURRECA partners held in Leiden, in February 2011, those focusing on iron concluded that population groups for reference values should, where possible, be established using clear

scientific evidence. However, it was agreed that this is not always possible, as for some population groups, there are insufficient data to make a firm decision. As a result, it was felt that further research was needed, particularly on the effects of ageing on requirements, where there is currently no agreement regarding upper-age ranges. For some population groups, there are specific issues related to iron metabolism that need to be taken into consideration when attempting to set DRVs.

Pregnancy and Lactation

Estimating dietary iron requirements during pregnancy is particularly difficult due to the three compartments constituting the pregnant state, namely the mother, placenta, and fetus (Cetin and Alvino, 2009). Increased iron requirements result from an enlarged maternal blood volume and the needs of the developing fetus. Consequently, maternal iron inadequacy may result in pregnancy disorders affecting the mother, fetus, and placenta, such as increased risks of intrauterine growth restriction, preterm delivery, low birth weight, and preeclampsia (Scholl, 2005). But following delivery, women who exclusively breastfeed are usually amenorrhoeic, thereby conserving iron otherwise lost in menses. As iron is secreted in relatively low amounts in breast milk, net iron loss may be lower than in nonlactating women (Dewey et al., 2004).

Infancy and Childhood

Unless born preterm or with low birth weight, most infants are at low risk of ID before 6 months of age as iron stores are usually adequate from the perinatal period. ID commonly develops after 6 months of age if complementary foods provide insufficient absorbable iron or exclusive breastfeeding continues. The iron absorbed from the infant diet is determined by its bioavailability, with iron from breast milk being highly bioavailable compared with other sources.

Adolescents

Older children and adolescents are at high risk of IDA due to the increased iron requirements needed to deal with the associated physiological processes: growth spurt, menarche, and the increase in hemoglobin concentration. In boys, the increase in hemoglobin mass associated with puberty increases iron requirements to a level greater than the average iron requirements in menstruating women. The growth spurt occurs at an earlier stage in girls, which, together with menstrual losses and low iron intake, places them at risk of IDA. The WHO acknowledges additional requirements by setting higher DRVs for menstruating adolescent females.

Adults

As for adolescent girls, there are specific issues for women of child-bearing age related to both menstrual losses and the additional iron requirements of pregnancy. Consideration should also be given to the decrease in requirements in postmenopausal women.

Immigrant Populations

Immigrants and ethnic minority groups constitute a population requiring special considerations in terms of both iron nutrition and status (Tiong et al., 2006; Venters and Gany, 2011). Recent migrants from certain geographic zones are at high risk of IDA due to chronic blood loss resulting from intestinal parasitic infections. Depletion of iron stores depends on the daily absorption of iron, the size of the body's iron stores, and the intensity of infection. Individuals with iron-loading abnormalities, particularly thalassemia, may not be protected by the upper limits set for iron. Bioavailability is a key issue for ethnic minority groups with diets rich in iron-inhibiting components such as phytate, calcium, and polyphenols.

COLLATING, SUMMARIZING, AND INTERPRETING SOURCES OF EVIDENCE [(SYSTEMATIC) DATA COLLECTION, INCLUDING QUALITY ASSESSMENT]

Factorial/Bioavailability Approach

While a factorial approach, accounting for obligatory losses (sweat, cells, hair, menstrual, etc.) and requirements for growth and development, is currently used by those setting recommendations, the data on which these calculations are based are limited and information is generally extrapolated across population groups. In addition, reference values can only be generated from requirements using a bioavailability factor (usually estimated to be in the range 13–18%), as iron is largely poorly absorbed. The host-related factors that influence absorption and utilization are not well characterized, but are likely to explain a significant proportion of the variation in both requirements and absorption.

A review undertaken by the EURRECA Network specifically sought to identify data relevant for the estimation of iron requirements using the factorial approach for all population groups (Vollhardt et al., forthcoming). In addition, reports from various nutrient recommendation-setting bodies were also examined, which included an assessment of data and methods used for the estimation of iron requirements. Data tended to be relatively old and were usually collected in adult male population groups involving a limited number of participants. Both approaches clearly demonstrated that scientific data related to the various components of iron loss are scarce, and this has resulted in significant differences in the estimates of factorial data used by the expert committees in the United States and the EU during the DRV setting process.

The network also undertook specific investigations with respect to factorial data relevant to pregnancy in an attempt to update existing reviews (Widdowson and Spray, 1951; Petry et al., 1992; Faa et al., 1994; Beaton, 2000). During pregnancy,

growth needs may be derived from known changes in blood volume, fetal and placental iron concentration, and increases in total body erythrocyte mass. A standardized systematic search was used to identify recent data on the amounts of iron present in the fetus, placenta, and mother [(Collings et al., 2010) and http://www.eurreca.org/everyone/8567/7/0/32]. A total of 28 relevant studies were identified dealing with the composition of fetal body and/or organs, including the umbilical cord, maternal blood, and cord blood, and placental iron concentration. Iron data measured throughout gestation were limited, with weight and iron content only available for a single fetus in three studies (Iob and Swanson, 1938; Hallberg and Hulthen, 2000; FAO/WHO, 2004). Only one study (Milman, 2006) assessed maternal iron reserves during pregnancy and throughout labor, and another (Nowacka et al., 1997) estimated the total erythrocyte iron content in newborns within 6 days of birth. This lack of data meant that collected data do not allow an updating of the previously used factorial data (Berti 2010) and consequently further research could be undertaken to improve those.

In an attempt to identify relevant data that may be used to derive bioavailability factors for different types of diet, two systematic reviews were undertaken by EURRECA with the aim of quantifying and assessing the efficiency of iron absorption from whole diets, or single/multiple meals where whole-diet data were lacking. The first review was conducted in adults and elderly, and the second focused on infants, children, adolescents, and pregnant women. In each case, the impact of various dietary enhancers, inhibitors, and host-related factors was explored (Collings et al., 2010, 2012; Ngo et al., 2011). Details of the review methodology for collating and evaluating the data can be found elsewhere (Collings et al., 2010). To date, the majority of iron reviews have focused on single-meal studies, as this potentially reduces the complexity of study designs and subsequent analyses. A total of 19 studies measuring iron absorption from whole diets were included in the review of adult data. However, the complexity of these data was highlighted by the diverse nature of study designs, populations, test conditions, and type of diet reported in the included studies. An analysis of the extracted data demonstrated that absorption from diets consumed with a single enhancing factor, such as meat or ascorbic acid, was significantly increased, whereas single inhibiting factors, such as phytate, milk, and calcium, did not significantly reduce absorption. In contrast, a large effect was seen when manipulating multiple dietary factors, i.e., high versus low bioavailable diets.

In the review of data from infants, children, adolescents, and pregnant women, 26 relevant studies were identified, each analyzing the effect of single meals (no whole-diet data were available). Eleven of the studies included infants (up to 1 year old), 13 included children (older than 1 year old) and adolescents, and two studies included pregnant women. Excluding the pregnancy studies, three studies investigated the effect of IDA on the iron absorption and 16 studied the effect of enhancers/inhibitors in the diet, including phytate, ascorbic acid, calcium, meat, and vegetables, on iron absorption. One study investigated the effect of removing lactoferrin from breast milk. Meta-analysis was only possible by type of enhancer in infants, children, and adolescents. The results demonstrated that iron absorption increased with low phytate meals (pooled effect size 3.76, $p < 0.00001$, heterogeneity, $I2 = 0\%$) and by using ascorbic acid as an enhancer (pooled effect size 3.18, $p < 0.0001$, heterogeneity, $I2 = 0\%$). As for the two rather dated studies on pregnant women that were excluded, the results for the study evaluating iron absorption in pregnant women at 12 weeks of gestation and 2 weeks after a legal abortion showed that in early pregnancy, iron absorption was lower (2.5%) than that measured 2 months after abortion (12.5%). In the second study, non-heme iron absorption increased during pregnancy from 1% to 13.5%.

Intake–Status–Health Relationships

A series of systematic reviews was undertaken by network partners to identify potential relationships between iron dietary intake, status, and relevant health outcomes. Reviews were conducted in relevant population groups and meta-analyses conducted where data were appropriate and sufficient. Generally, relationships between dietary intake and specific health outcomes, and potential intake–status relationships were evaluated. All reviews were conducted in accordance with the EURRECA standardized systematic review methodology. Reviews were instigated into all possible relationships between relevant health outcomes, and intake and status in the various population groups, but in the majority of cases, there were insufficient data to conduct meta-analyses. Therefore, only potential relationships where sufficient data were identified are reported here.

Intake–Health Relationships

A systematic review was conducted by the EURRECA Network, summarising current evidence on the relationship between iron intake in infants, children, and adolescents on measures of cognitive development and function. Briefly, randomized controlled trials (RCT) that included an adequate control group in which iron supply was provided by natural food sources, fortified foods, formula, or supplements to infants, children, or adolescents until the age of 18 years were considered for inclusion (full methodological details are reported elsewhere (Hermoso et al., 2011b). Fourteen studies met the selection criteria and 12 were at high or moderate risk of bias. A large degree of heterogeneity between study populations, iron dosages, and outcome measures precluded meta-analysis. Overall, the studies suggested a modest positive effect of iron supplementation on cognition and psychomotor outcomes in anemic infants and children after supplementation periods of at least 2 months' duration (Hermoso et al., 2011b).

A similar review was undertaken to summarize current evidence on the effect of iron intervention on immune function in children and adolescents. Seven RCTs met the selection criteria; six using iron supplements, and one using only fortified food. The majority of studies were at high or moderate risk of

bias, but the large variety of outcomes reported made comparison between studies impossible. Therefore, no evidence-based conclusions could be drawn on the effect of iron intervention on immunity in children and adolescents (Vucic et al. 2011).

In contrast, sufficient data were available to assess the effect of oral iron supply on physical growth in infants, children, and adolescents. The meta-analysis documented no evidence of a beneficial effect of iron supplementation on physical growth, i.e., weight, height and mid-upper arm circumference, or head circumference in infants. Stratification across age, duration of the intervention, and baseline values did not change the results. However, stratification across dosage highlighted a weak but significant effect of 40+ mg iron intake on growth (0.02, 95% CI: 0–0.03, $p = 0.02$), but heterogeneity was high for all analyses. In addition, no significant effect of iron intake on birth weight or length of gestation was identified by a meta-analysis of similar data conducted in pregnant women (Vucic et al. 2013).

A meta-analysis was also undertaken in RCTs to identify data to determine whether prophylactic iron supplementation during pregnancy in iron-sufficient women could reduce the rates of preterm delivery or low birth weight. The systematic search identified six relevant studies on birth weight, and five on length of gestation, which were included in the meta-analysis. Most studies were at moderate risk of bias. For birth weight, the pooled effect estimate was 0.01 (95% CI: −0.01 to 0.03; $p = 0.46$; newborns = 1941); for length of gestation, it was 0.00 (95% CI: −0.00 to 0.00; $p = 0.14$; newborns = 2577). In general, the heterogeneity among trials was high. There was an overall lack of trials supplying low doses of iron but in those identified, iron did not exert any significant effect on fetal growth (Vucic et al. 2013).

Further systematic reviews were undertaken in the adult population in an attempt to investigate potential relationships between iron intake/status and various health outcomes. Standardized EURRECA protocols and search methodology were used to identify 4415 potentially relevant papers; however, relatively few met the inclusion criteria. Twenty studies were eligible for inclusion in an assessment of the relationship between physical performance, as measured by VO_{2max}, and iron supplementation, but inconsistency in data reporting meant that only eight studies could be included in the meta-analysis. All studies were conducted in women, the majority of who were athletes or regularly training and iron-deficient or anemic at baseline. While a significant effect of iron supplementation was identified in this subgroup [weighted mean difference (WMD): 1.99; 95% CI: 0.61–3.37; $n = 134$; $p = 0.005$], with no heterogeneity between studies, this result was not replicated in a sedentary/low-activity group. Differences between the two groups were not significant ($p = 0.25$), thus allowing data to be pooled, resulting in an overall significant effect of iron supplementation on VO_{2max} (WMD: 1.61; 95% CI: 0.39–2.83; $n = 231$; $p = 0.01$). Evaluation of other measures of aerobic capacity, including time to exhaustion, respiratory exchange ratio, and heart and work rates, generally produced inconclusive results due to the paucity of available data resulting from noncomparable outcome measures and disparities between study designs and included population groups. For similar reasons, further analyses also failed to demonstrate relationships between iron supplementation and anaerobic capacity (blood lactate threshold, ventilator threshold). Insufficient data also precluded evaluation of relationships between iron intake and other selected health outcomes, including immune function, cognition, tiredness, and restless legs syndrome.

Intake–Status Relationships

A series of systematic reviews was undertaken investigating the impact of dietary iron intake on status in a range of population groups. The first review was conducted in the healthy adult and elderly population and aimed to assess the impact of type, duration, and dose of iron supplementation on change in iron status (Casgrain et al., 2012). Forty-three RCTs were eligible for inclusion following a standardized search, including iron supplementation or fortification versus placebo studies reporting data for EURRECA-approved iron status biomarkers (see also activity 3 in Dhonukshe-Rutten et al. (2013)). Most were at high risk of bias. Subgrouping, random-effect meta-analysis, and meta-regression were used to describe the dose responsiveness and effects of modifiers with respect to change in status. Meta-analyses determined that iron supplementation significantly improved iron status demonstrated by increases in serum ferritin (SF) and hemoglobin, and a decrease in serum transferrin receptor, although heterogeneity was high. There were obvious effects of length of intervention (0.51 μg/L; 95% CI: 0.02–1.00 μg/L; $p = 0.04$; increase in SF per week), baseline status (0.08 g/dL; 95% CI: 0.15–0.00 g/dL; $p = 0.02$; reduction in serum hemoglobin per 10 mg/L increase in baseline SF), and dose (0.10 μg/L; 95% CI: 0.01–0.2; $p = 0.036$; increase in SF per gram iron as assessed by meta-regression analyses). There was a high degree of heterogeneity in the data. Despite identifying a total of 43 studies, insufficient data were available to assess effects of gender or menopausal status.

In the second review, RCTs assessing the effect of iron intake on hemoglobin and serum/plasma ferritin in women of reproductive age, including pregnant and lactating women, infants, and children under 5 years of age were identified using the EURRECA-standardized methodology. Twenty studies met the inclusion criteria for women, 24 for infants, and 21 for children under 5 years of age. The meta-analyses showed that iron supplementation exerts a significant effect on hemoglobin levels in pregnant women (pooled effect size: 0.03; $p < 0.00001$), in infants (pooled effect size: 0.03; $p < 0.00001$), and children (pooled effect size: 0.05; $p < 0.01$). Similar significant effects were identified for ferritin concentrations in pregnant women (pooled effect size: 0.22; $p < 0.00001$), in infants (pooled effect size: 0.61; $p < 0.00001$), and children (pooled effect size 0.54; $p < 0.00001$) (Berti, forthcoming).

Another review investigated the effect of iron supplementation on iron status in children aged over 5 years and adolescents. All but three of the 31 suitable studies identified were conducted in developing countries, most (in total 22) being located

in mesoendemic, hyperendemic, or holoendemic malaria areas, but most were at high or moderate risk of bias. Full details of the included studies can be found elsewhere (Roman-Viñas et al., 2011a). The effect of total iron intake was analyzed through an intake–status regression coefficient (β) that was based upon the hypothesis that the true intake–status curve for iron would follow a natural logarithmic function, slowly growing to positive infinity as x (intake) increases, and rapidly goes to negative infinity as x (intake) approaches zero. The results of the meta-analysis indicated that the iron supplementation given as supplement or fortificant exerted an effect on hemoglobin (pooled effect size: 0.06; $p < 0.001$) and SF levels (pooled effect size: 0.05; $p < 0.00001$), although the heterogeneity between studies was high (99 and 98%, respectively). The meta-regression analysis indicated that baseline hemoglobin level, malaria endemicity, and the type of iron supplementation (as supplement or as fortificant) had an effect on heterogeneity. The subgroup analysis indicated that the effect of iron was more pronounced among individuals with anemia at baseline, for doses of iron lower than 30 mg/day, for iron given as a fortificant, and for shorter treatment duration.

Multiple Micronutrients (Interactions)

The EURRECA Network did not conduct any specific research into the impact of interactions between iron and other micronutrients in relation to deriving dietary requirements and recommendations. Any significant interactions, including those between iron and calcium and vitamin C, were identified from the literature during the bioavailability reviews reported earlier in this article. However, it is also recognized that other micronutrient interactions may occur; with dietary iron potentially reducing copper absorption (Sandstrom, 2001), and dietary zinc reducing iron absorption (Olivares et al., 2012).

Polymorphisms

Despite the identification of a range of genotypes known to affect various aspects of iron absorption, metabolism, and excretion, the association between the genotype and phenotype is seldom a well-defined relationship. Studies into the effects of SNPs on iron metabolism have reported data demonstrating nonexpression of SNPs, i.e., the phenotype does not reflect the genotype. Therefore, it is likely that additional genetic and/or environmental factors may modify the penetrance and severity of clinical disease. In order to assess current knowledge on the impact of functional gene polymorphisms on iron metabolism, a systematic search was undertaken, as described elsewhere [see also activity 4 in Dhonukshe-Rutten et al. (2013)] to identify pertinent data for inclusion in a specially designed database. Specifically, this involved identifying data assessing the impact of functional polymorphisms (e.g., single nucleotide polymorphisms, or SNPs) on iron status biomarkers and associated health outcomes. Iron status biomarkers considered were hemoglobin, serum/plasma ferritin, serum/plasma transferrin receptor, and body iron [as measured by the Cook method (Cook et al., 2003)]. Due to the large number of references identified in the search, studies that concentrated on hemochromotosis, thalassemia, or sickle-cell anemia were excluded as the focus was on genotypes in the healthy population.

A total of 20 papers were identified that containing relevant data. The more common genes with variants affecting iron status identified during the study search and selection process were haptoglobin and ferroportin. In the former, an association between haptoglobin mutations and iron status biomarkers was reported in four studies (reported as genotype-dependent phenotype, i.e., Hp2-2, Hp2-1, or Hp1-1), while in the latter, statistically significant associations were found for the Q248H mutation in relation to either ferritin or hemoglobin concentrations (King et al., 2011).

INTEGRATING THE EVIDENCE

At the Leiden workshop (in 2011), appraisal of all iron data collated by the EURRECA Network (described previously), in conjunction with expert knowledge, concluded that there was currently insufficient evidence to use health outcomes as a basis for establishing dietary iron requirements. For the duration of the EURRECA Network, partners attempted to identify and evaluate all available sources of information that might provide useful data on the relationship between dietary iron intake or status and a range of selected health outcomes for all population groups. However, the evidence was insufficient to base iron requirements on these relationships, and it was agreed that the data were too sparse to combine into an integrated model with data traditionally used in factorial calculations. Despite this, there is some evidence of associations between iron intake or status and relevant health outcomes in several age groups and life stages, e.g., cognition in infants and children.

Where an intake–status or intake–health relationship cannot be assessed, iron requirements must be derived using factorial estimates. As previously described, current reference values for iron are derived using this approach, but data are limited in many areas and scaling/extrapolation is required to calculate values for nonadult groups. The available data are also old or collected in specific population groups with few volunteers. In general, the group agreed that more data across all population groups and for all types of losses, growth, and development are needed. The research of the EURRECA Network has highlighted the difficulties associated with both identifying existing and generating new data in this area. In addition to the general lack of data on obligatory losses etc., there is also a paucity of relevant iron bioavailability data for whole diets (Collings et al., 2010, 2012; Ngo et al., in press).

Consequently, it was agreed at the Leiden workshop that at present, integrating the available evidence for the derivation of revised reference values would only involve the use of relatively sparse factorial data in association with limited bioavailability

data, in conjunction with a significant contribution based on the opinion of experts. While it was accepted that current recommendations were based on the best data available at the time, workshop attendees suggested that more recent data could be incorporated into the factorial approach to improve the accuracy of physiological requirements. To date, the majority of expert committees have based iron requirements on obligatory loss data generated in the 1960s (Green et al., 1968), but the use of more recent data in both men and women may improve the accuracy of calculated requirements (Hunt et al., 2009). In addition, menstrual iron loss data were also generally taken from the 1960s (Hallberg et al., 1966a; Hallberg et al., 1966b), which pre-dates the common usage of the oral contraceptive pill and therefore overestimates losses. Again, recent and potentially more relevant menstrual loss data are now available (Harvey et al., 2005), which may improve the calculation of dietary requirements. Other factors that should be taken into account when using the factorial approach include the skewness of menstrual loss data and the associated strong genetic component regulating blood losses; the relationship between body size and obligatory losses (pertinent as individuals across Europe are increasing in size).

RESEARCH GAPS AND PRIORITIES

Research gaps and priorities were discussed by partners throughout the duration of the network, but formal discussions took place at two EURRECA-funded expert workshops during the final stages. Both workshops, involving network partners and invited experts, were held to discuss iron (and other micronutrients) nutrition in relation to dietary requirements and recommendations. The first took place in Leiden, in February 2011, with a focus on evaluating the usefulness of the EURRECA "flowchart" (van 't Veer et al., 2013). The workshop identified four key areas where future iron research should be focused. These were (1) the generation of improved absorption and obligatory loss data to improve factorial estimate calculations for all population groups, including the elderly; (2) research into the bioavailability of different types of whole diets for all population groups, which would allow requirements to be converted into reference values; (3) identification of the genetic predeterminants of iron absorption; and (4) information on the effect of obesity and overweight on iron requirements due to raised inflammatory status, and specifically the need to identify appropriate status biomarkers for this population group.

The Early Nutrition Academy (ENA) and EURRECA Network jointly sponsored a scientific workshop on critical micronutrients in pregnancy, lactation, and infancy in Tutzing, Germany, in June 2011 (Hermoso et al., 2011a). In terms of iron nutrition in relation to the derivation of dietary requirements and recommendations, attendees concluded that further research was specifically needed on the effects of perinatal iron intake and status in pregnant women, infants, and toddlers in the European population. Additional data are also required on the impact of dietary choices, iron absorption, and genetic variation. Ideally, long-term RCTs would be undertaken assessing the impact of breast feeding versus formula on outcomes such as motor and cognitive development, and immune function. Additionally, future studies should take advantage of new techniques to assess iron metabolism, including metabolomics, genotyping, and epigenetic effects.

SUMMARY AND CONCLUSIONS

To date, a factorial approach has been used by expert bodies to derive reference values for iron. Calculations include the use of a bioavailability factor to convert the physiological requirement, derived from obligatory losses and requirements for growth and development, into a value for dietary intake. A series of systematic reviews was undertaken by the EURRECA Network of Excellence with the aim of identifying data that may be used to either increase the accuracy of factorial calculations across all population groups or adopt the dose–response approach. The latter would be a novel approach in the setting of DRVs for iron and would require data for relevant intake–status–health relationships. Selection of robust data was guided by the use of standardized review methodology and the evidence-based selection of status biomarkers and dietary intake assessment techniques. Results of the reviews corroborated the dearth of relevant factorial data, in addition to whole-diet bioavailability data, and confirmed the need to continue extrapolating physiological requirements (scaling) across population groups.

Generation of factorial data, particularly in infants and children, is hampered partly by difficulties in measuring iron status. Status biomarkers are generally less reliable due to changes in iron metabolism from birth to 18 months of age and biomarker cutoff values are poorly defined in this population group. Measurements of obligatory iron losses are particularly difficult to achieve often for both practical and ethical reasons, with direct measurements of menstrual blood loss and those specifically associated with lactation and pregnancy being particularly problematic. Consequently, it is not unsurprising that the EURRECA Network was unable to identify sufficient quantities of robust factorial data to modify current DRV setting practice.

Irrespective of whether new factorial data could be identified, the possibility of producing evidence-based bioavailability factors that could be tailored to different types of diet in order to translate requirements into reference values would be of great value. The EURRECA Network adopted a novel systematic review approach, which aimed to identify data from whole-diet studies in adults rather than single-meal or single-food studies. There were several whole-diet studies identified in the adult and elderly review, but in contrast, there was a complete absence of such data for infants, children, adolescents, and pregnant women. However, the complexity of these data meant that it

was difficult to find sufficient information to fully evaluate. The large effects identified in adults when manipulating multiple dietary factors as opposed to single enhancing or inhibiting factors, coupled with the paucity of data in the other population groups, suggests that further research is required to generate data in this area.

Through a series of systematic reviews in all population groups, the EURRECA Network established that suitable data were also unavailable that would currently allow reference values to be based on selected health outcomes associated with iron intake or status, i.e., dose–response relationships. Ideally, a series of observational and RCT studies need to be undertaken across all population groups and life stages to generate robust data for setting dietary reference values for iron.

In summary, while the reviews undertaken by EURRECA have highlighted the dearth of data for setting DRVs, a series of valuable databases have been generated that currently hold the most comprehensive data sets for all elements of the DRV setting process. These databases have the potential to act as a valuable resource for a range of expert bodies and groups. However, key areas for further research include the development of models to assess iron bioavailability from different types of diet across all population groups, the generation of robust dose–response data for relevant health outcomes and investigations into the potential impact of genetic polymorphisms in iron status and metabolism in healthy individuals.

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 preparation of this manuscript was coordinated by Rachel Collings from the University of East Anglia and copy-editing by the European Food Information Council (EUFIC).

The authors would like to acknowledge Professors Michael Zimmermann and Richard Hurrell for helpful discussions during EURRECA workshops on micronutrient bioavailability in Barcelona, Spain; micronutrient biomarkers of status in Norwich, United Kingdom; and the derivation of dietary reference values in Leiden, the Netherlands. We also thank Professor Larry Parnell for helpful discussions during the design stage of the polymorphism database.

ABBREVIATIONS

AR = Average requirement
CEE = Central and Eastern Europe
DRV = Dietary reference value
EAR = Estimated average requirement
EC = European Commission
EFSA = European Food Safety Authority
ENA = Early Nutrition Academy
ENHR = European nutrition health report
EU = European Union
FAO = Food and Agriculture Organization
FFQ = Food frequency questionnaire
ID = Iron deficiency
IDA = Iron deficiency anemia
IDE = Iron deficiency erythropoiesis
ILSI = International Life Sciences Institute
LRNI = Lower reference nutrient intake
LTI = Lower threshold intake
PRI = Population reference intake
RCT = Randomized controlled trial
SES = Socioeconomic status
SF = Serum ferritin
SNP = Single-nucleotide polymorphism
VMNIS = Vitamin and Mineral Nutrition Information Service
WHO = World Health Organization
WMD = Weighted mean difference

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