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Original Article

The nutritional requirements of infants. Towards EU alignment of reference values: the EURRECA network

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Abstract

This paper presents a review of the current knowledge regarding the macro- and micronutrient requirements of infants and discusses issues related to these requirements during the first year of life. The paper also reviews the current reference values used in European countries and the methodological approaches used to derive them by a sample of seven European and international authoritative committees from which background scientific reports are available. Throughout the paper, the main issues contributing to disparities in micronutrient reference values for infants are highlighted. The identification of these issues in relation to the specific physiological aspects of infants is important for informing future initiatives aimed at providing standardized approaches to overcome variability of micronutrient reference values across Europe for this age group.

Keywords: nutrient requirements, nutrient recommendations, recommended intakes, nutrient intake values, infants, EURRECA.

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Background

Different countries and committees have set micronutrient reference values for infancy, i.e. up to 1 year of age. These values vary considerably across Europe. The variability is caused by various factors, e.g. disparities exist between underlying concepts, the terminologies used and the methodologies and assumptions that have been made in the definition of micronutrient requirements and derivation of reference values for intake (Doets *et al*. 2008). Infants are considered a vulnerable group because they have a relatively high requirement of nutrients per unit body weight during a sensitive period of rapid growth and development. The aim of the present paper is to review specific aspects of healthy term infants in relation to micronutrient requirements in early and late infancy, and to critically evaluate the approaches used to determine those requirements and derived reference values for nutrient intake.

1. Nutritional requirements of infants, methodological approaches used for establishing requirements and derived reference values

Infancy is characterized by rapid growth and development. Both are determined by genetic and environmental factors. An important environmental factor is nutrition, because an inadequate diet can compromise growth and the full utilization of an individual's genetic potential (Reyes-Posso 2008). Nutrition is important throughout childhood, but especially during the first 2 years of life, as the growth rate during this period is high and less dependent on growth hormones than in later periods of childhood. The rapid rates of growth and development of infants impose unique nutritional needs upon their already high maintenance needs (Heird 1996). The quantity and quality of nutrient supply during early life modulates the differentiation of tissues and organs and has short- and long-term consequences for health (Koletzko 2008).

The preferred form of nutrition for healthy infants is breastfeeding (Agostoni *et al*. 2009). Current global recommendations, derived from a technical expert committee report commissioned by the World Health Organization (WHO) (Kramer & Kakuma 2002), are that infants should be exclusively breastfed for the first 6 months of life with the introduction of complementary foods thereafter and continued breastfeeding for the first 2 years of the infant's life (WHO 2003b). This report concluded that infants who were exclusively breastfed for 6 months did not differ in growth from those exclusively breastfed for 4 months and experienced less morbidity from gastrointestinal infection. Recent expert committee reports in Europe and in the USA concluded that complementary feeding, in addition to continued breastfeeding, should be introduced not before 17 weeks and not later than 26 weeks of age (Agostoni *et al*. 2008; Greer *et al*. 2008). The comparative benefits of exclusive breastfeeding for six months compared with exclusive breastfeeding for between 4 and 6 months, particularly in infants living in industrialized countries, however, has been challenged (Fewtrell *et al*. 2007). In Kramer & Kakuma's paper (2002), only two of 20 the studies included in the review were randomized intervention trials of different exclusive breastfeeding recommendations, and both were conducted in non-industrialized countries (Cohen *et al*. 1994; Dewey *et al*. 1999). Due, in no small part, to clear ethical and feasibility issues of conducting such trials, the overriding majority of studies in the review were observational and therefore vulnerable to considerable residual confounding and bias. Indeed, other systematic reviews have suggested that breast milk may not meet the full requirements for energy and certain micronutrients of 6-month-old infants (Butte 2002; Reilly *et al*. 2005). Clearly, there is an urgent need for more work in this area.

Despite the multiple benefits of breastfeeding, a significant proportion of mothers of healthy term infants in many industrialized countries chose to formula feed their infants. There is a lack of guidance regarding the appropriate timing of the introduction of complementary foods to formula fed infants because there is virtually no data available to form evidence-based recommendations. It has been argued

Key messages

- Infancy is characterized by growth and development, which impose unique nutritional needs upon the already high maintenance needs of infants.
- Primary data from quality studies linked to functionally relevant outcomes are needed in infants in order to improve the current knowledge on nutritional requirements in this period of life.
- Great disparities exist in established nutrient intake values for infants in Europe. This is mainly due to the different methodological approaches used to define the nutritional requirements of infants. A lack of transparency in the documentation of the decision making by the committees in charge hampers understanding these differences.
- Solid, up-to-date, transparent scientific basis will help committees tasked with setting reference values for nutrients, defining requirements of infant formula, and defining feeding practice.

that, as formula-fed infants receive higher amounts of energy, protein, iron and zinc than breastfed infants, they may not require solid foods until a later age (Fewtrell *et al*. 2007). Despite this, across Europe, complementary feeding is introduced earlier in formula fed than in breastfed infants (Schiess *et al*. 2010). It has been hypothesized that an early introduction of complementary foods to formula fed infants might increase the risk of later overweight and obesity in children and adults. There is evidence to suggest that formula feeding is associated with a more rapid weight gain in early infancy (Dewey 2001; Baker *et al*. 2004) and with an increased risk for obesity in childhood and adolescence (Gillman *et al*. 2001; von Kries *et al*. 2001; Arenz *et al*. 2004; Koletzko *et al*. 2009b). Higher intakes of protein and energy with infant formula compared with breast milk may favour rapid weight gain, adipogenic development of adipocytes and the accumulation of fat (Koletzko *et al*. 2009a). This could lead to increased likelihood of later overweight, but it is as yet unclear whether an earlier introduction of complementary foods plays a relevant role.

1.1 Concepts and use of nutrient intake values

The European Micronutrient Recommendations Aligned (EURRECA) Network of Excellence works similarly towards a general framework including harmonized approaches, methods and key terms to be used for the development of micronutrient reference values (Doets *et al*. 2008). The United Nations University (UNU), in collaboration with the Food and Agricultural Organisation (FAO), World Health Organisation (WHO) and the United Nations Children's Emergency Fund (UNICEF), has previously proposed an international harmonization of nutrient based dietary standards (King & Garza 2007). The term Nutrient Intake Values (NIVs), conceived by UNU, FAO, WHO and UNICEF, encompass all nutrient-based dietary standards derived from primary data and provide estimates on appropriate dietary substrate supply for populations of healthy people (King & Garza 2007). NIVs are used for assessing the adequacy of nutrient intakes and for planning diets of groups and individuals. They are also applied to a number of aspects of food and nutrition policy such as regulatory issues and trade, labelling, planning programmes for alleviating public health nutrition problems, food fortification and dietary guidance (Aggett *et al*. 1997). NIVs are based on physiological requirements, which are defined by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) as the amounts and chemical forms of nutrients needed systematically to maintain normal health and development, without disturbance of the metabolism of any other nutrient and without extreme homeostatic processes and excessive depletion or surplus of bodily reports (Aggett *et al*. 1997). The nutrient requirements of individuals vary markedly, and NIVs do not refer to individuals, but to populations that are defined by age, gender and in some cases additional characteristics relevant for nutrient needs. Existing NIVs for infants are shown and compared in section 2.

The UNU Working Group has defined the following NIVs: average nutrient requirement (ANR), individual nutrient level (INL) and upper nutrient level (UNL). ANR is the estimated average or median requirement of a specific nutrient in a population, derived from a statistical distribution of requirement criterion and for a particular age and sex specific group based on a specific biological endpoint or biochemical measure (King & Garza 2007). It is assumed that individual requirements follow a statistical distribution (symmetrical bell-shaped curve). INL is the individual nutrient level and INL_{97} is the nutrient intake considered adequate to meet the known nutrient needs of practically all healthy individuals in a particular age and sex-specific group (King & Garza 2007). Equivalent terms are population reference intakes and recommended dietary allowance. This value, set at a level of intake that meets the needs of the majority of the population (mean + 2SD), is generally used as the target for provision of essential nutrients to populations and as the reference point for nutrient labelling of foods. The exception is energy, for which the ANR is used because the use of INL_{97} or equivalents would lead to overfeeding. UNL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals of a particular life-stage group (King & Garza 2007).

1.2 Methods used to estimate the nutritional requirements of infants and derived NIVs

Indicators of function provide information to target requirements for health protection and not just to prevent clinical deficiencies. However, there are a limited number of functionally relevant outcome measures for infants that reflect the response to dietary intake (IOM 2000b). The first months of life pose particular challenges with regards to clinical research, and few quality studies have been performed in this age group. The paucity of available data for estimating nutrient requirements of infants hampers the establishment of adequate NIVs (Pombo *et al*. 2001). Usual intakes of presumably healthy populations, factorial approaches and balance techniques are the methods used most often to estimate nutrient needs of infants. None are fully satisfactory because they seldom adequately address the issue of nutrient intake supporting long-term health and optimal functional capacities rather than just avoiding acute deficiency states (Butte 2002).

NIVs for infants during the first 6 months of life are usually derived from estimated intakes of fully breastfed infants. For older infants (7–12 months), estimates of intakes from both human milk and complementary foods are used as a reference. However, the actual intakes of breastfed infants are difficult to determine due to the variability of milk volume and composition between women, as well as the changing composition of the milk during the course of lactation, during the day and even during a feeding. Moreover, the bioavailability of substrates and their metabolism differ between infants fed human milk, those fed infant formula and infants given complementary feeds. Therefore, the composition of human milk and the nutrient intake of breastfed infants do not always provide useful guidance for infants who are not exclusively breastfed (Aggett *et al*. 1997).

Factorial approaches are generally based on estimates of maintenance needs, nutrient accretion that accompanies growth, measures of digestibility and/or absorption (bioavailability), and utilization efficiency. The requirements for growth are derived from estimates of body composition at different ages, from which the nutrient accretion over time (increase in the total body content of that nutrient from one age to another) can be calculated, taking into account the metabolic cost of accretion. However, very limited direct analytical information on body composition is available, which cannot be reliably extrapolated between age groups. Maintenance needs are derived from estimates of losses related to cellular turnover and unavoidable metabolic inefficiency. Data on inevitable losses in newborns, toddlers and infants are scant. Given that in adults such information is best gained under circumstances of negligible intakes of the nutrient of interest when homeostatic conservation is maximal, it is unlikely that such data could be acquired ethically in infants (Aggett *et al*. 1997).

Balance studies at known intakes provide information about net whole retention and net intestinal absorption or secretion and whole-body retention of nutrients. These studies are difficult to perform in infants, although some studies have been performed in term and pre-term infants. One limitation is that they tend to overestimate net retention and thus underestimate requirements due to technical difficulties in sampling. To extrapolate nutrient requirements from balance studies, subjects should be in equilibrium at the intake of the nutrient in question, which is difficult to determine in periods of fast growth. The intake has to be manipulated so that it balances losses. The length of the study period also depends on the size of the body stores of the nutrient and the rate at which the stores are mobilized (Prentice *et al*. 2004). The interpretation of balance studies often relies heavily on estimates derived by factorial approaches, that is, the appropriateness of retained quantities of target nutrients is determined by comparison with expected retention based on estimates derived by factorial methods. Thus, estimates of growth velocity and tissue composition are key to interpreting balance results (Butte 2002). The use of isotopic labels of endogenous or exogenous (dietary) pools of nutrients can enable better characterization of the flux and pool sizes underlying homeostasis. Thus, the balance-study approach, with these refinements, is likely to remain a key method in investigating requirements until new methods become established (Aggett *et al*. 1997).

Extrapolation and interpolation methods are often employed to derive NIVs for infants, especially from 7 months of age. Values for nutrient needs are extrapolated from one life stage to another using weighting for body size, energy requirement and other metabolic differences. These approaches have several limitations, as outlined elsewhere (Atkinson & Koletzko 2007). The rationale for the method chosen for extrapolating NIVs should be completely transparent and described in detail for each nutrient (Atkinson & Koletzko 2007).

1.3 Nutrient requirements of infants for energy, macro- and micronutrients

1.3.1 Energy and macronutrients requirements

Energy

During infancy, energy requirements are defined as the amount of energy needed to balance total energy expenditure at a desirable level of physical activity, and to support optimal growth and development consistent with long-term health (FAO/WHO/UNU 2004). Energy requirements during growth and development can be partitioned into components of basal metabolism, thermogenesis, physical activity and energy cost of growth (Butte 2005). The energy needed for growth is estimated to be around 35% of the total energy requirement in the first month of life, and this requirement declines continuously to about 3% at 12 months, remaining low until the onset of the pubertal growth spurt (Butte 2005).

Protein

The protein requirement of infants can be defined as the minimum intake that will allow nitrogen equilibrium at an appropriate body composition during energy balance at moderate physical activity, plus the needs associated with the deposition of tissues consistent with good health (WHO/FAO/UNU 2007). The nine essential amino acids (leucine, isoleucine, valine, tryptophan, phenylalanine, methionine, threonine and histidine) need to be obtained from the diet. The conditionally essential amino acids (arginine, cysteine, glutamine, glycine, proline and tyrosine) are those that the infant in unable to produce in sufficient amounts and hence all or part of the daily needs for those amino acids must be provided through the diet (Pencharz & Elango 2008). The average protein content of human milk is 11.7 g/L^{-1} (Pencharz & Elango 2008). Exclusive breastfeeding meets the protein and amino acid requirements during the first 4–6 months of life. During the second 6 months of life, solid foods contribute a significant amount of protein to the infant diet. The biological value of a protein refers to its ability, when it is the sole dietary source of protein, to support protein synthesis and therefore body maintenance and growth. On this scale, breast milk proteins and egg have the highest value (1.0). All animal proteins (with the exception of gelatin) are complete, that is they contain all the essential amino acids and are of high biological value. Most vegetable proteins, except soya, are incomplete because they offer an unbalanced assortment of amino acids that cannot alone satisfy the body's needs (Michaelsen *et al*. 2000).

Lipids

Fats are the main source of energy for infants, and n-6 and n-3 long-chain polyunsaturated fatty acids (LCPUFAs) are essential for normal growth and development and maturation of numerous organ systems, most importantly the brain and eye. Moreover, lipid-soluble vitamins (A, D, E, K) require dietary lipids for absorption (Mena & Uauy 2008). Exclusively breastfed infants receive a dietary fat supply usually in the range of 40–55% of total dietary energy intake (Michaelsen *et al*. 1990). The introduction of complementary feeding that is rich in carbohydrates may reduce fat intake to 30–40% of energy intake. For infant formula a fat content in the range of 40–60% of total energy content has been recommended (Scientific Committee on Food 2003). This corresponds to a fat content of 4 to 6 g/100 kcal as established by the European Commission Directive on Infant Formulae and Follow on Formulae (European Commission 2006). Human milk provides linoleic acid (LA), alpha-linoleic acid (ALA), docosahexaenoic acid (DHA), arachidonic acid (AA), and other LCPUFAs to breastfed infants. The level of AA is relatively constant on a worldwide basis whereas the level of DHA is more variable and depends on maternal diet and lifestyle (Koletzko *et al*. 2008). Recent consensus recommendations support that pregnant and lactating women should achieve a DHA intake of at least 200 mg/d (Koletzko *et al.* 2007). The ESPGHAN recommends the following content of essential fatty acids in infant formula: 0.3–1.2 g/100 kcal (2.7–10.8% total energy) of LA and 0.5–2.4 g/100 kcal (0.54–2.59% total energy) of ALA, with a minimum LA/ALA ratio of 5:1 and a maximum of 15:1 (Koletzko *et al.* 2005). The authors of a recent review conclude that the available evidence supports the addition of DHA to infant formula: the addition of at least 0.2% of fatty acids as DHA appears necessary for achieving a benefit on functional endpoints, but DHA levels should not exceed 0.5% of fatty acids because systematic evaluation of higher levels of intake have not been published (Koletzko *et al.* 2008). Based on current knowledge, infant formula contents of AA should be at least those of added DHA, and eicosapentaenoic acid (EPA) should not exceed levels of DHA (Koletzko *et al.* 2008).

Examples of reference values used in European countries for average daily energy, protein, fat and essential fatty acids intakes in populations of healthy infants set by different European and international committees is presented for comparison in Table 1.

Digestible and indigestible carbohydrates

Lactose is the main digestible carbohydrate in human milk, providing about 40% of the energy content (Koletzko *et al.* 2005). In addition to lactose, mature breast milk contains a large variety of oligosaccharides in concentrations of approximately 5–10 g/L^{-1} (Kunz *et al.* 2000). Human milk oligosaccharides may prevent bacterial adhesion by interfering with the docking of bacteria on the intestinal cell surface and with the expression of certain enzymes in the intestine required for bacterial adhesion (Bode 2006). The total digestible carbohydrate content of infant formula and follow-on formula is set between 9 and 14 g/kcal, which is based on the calculated glucose consumption of the central nervous system (Scientific Committee on Food 2003; European Commission 2006). Non-digestible carbohydrates such as fructooligosaccharides, galactooligosaccharides, inulin, soy polysaccharide, resistant starch, and gums are added to dietary products, enteral formulas and breast milk substitutes consumed by infants. Additionally, some resistant starches and non digestible carbohydrates are formed during processing (Aggett *et al.* 2003). The overall benefits to health of supplementing infant formula or infant solid foods with fibre, inulin (probiotics) or prebiotic oligosaccharides remain unclear (Agostoni *et al.* 2004; Kien 2008).

1.3.2 Micronutrient requirements

Iron

During the first year of life, the body iron content increases markedly. In healthy term infants, iron stores at birth comprise most of the iron requirements during the first 4–6 months. From the 4th month, the requirement for dietary iron increases to an estimated 0.78 mg/day due to the stepwise depletion of endogenous stores and rapid growth with an expansion of blood volume and increased tissue and storage iron (AAP 1999; Fisher *et al.* 2000; IOM 2000b). Iron deficiency in humans is most prevalent in the late infancy period, which is characterized by peak hippocampal and cortical regional development, as well as myelogenesis, dendritogenesis and synaptogenesis in the brain where iron availability may play a role (Lozoff & Georgieff 2006). Although the iron content of breast milk is low, its bioavailability is high and needs of dietary iron are limited due to the large iron stores of newborn infants born at term, therefore iron deficiency at 6 months is uncommon in exclusively breastfed, term infants in industrialized countries (Yang *et al.* 2009). It has been shown that the same is true for healthy full-term born infants fed exclusively an infant formula with only 1.6 mg iron/L^{-1} (Hernell & Lönnerdal 2002); despite this most modern infant formulae are fortified with iron. A recent study has shown that while iron supplementation of breastfed infants caused some preservation of the iron endowment, the effect was modest and did not extend beyond the period of supplementation (Ziegler *et al.* 2009). The study was underpowered to investigate any adverse affects of supplementation. However, other studies have reported adverse effects of iron supplementation in iron replete infants, for example on length growth (Domellof 2007). Due to the low prevalence of iron

Table 1. Comparison of reference values for average daily energy, protein, fat and essential fatty acids intakes by different countries and committees in populations of healthy infants

	Age		Energy	Protein	Fat	Essential fatty acids	
			Male/female	Male/female	Male/female	n-6	n-3
DACH[1]	Month		kcal/d	g/d	% of energy	% of energy	
	0–<4	0–1	500 / 450	12	45–50	4.0	0.5
		1–2	700 / 700	10			
		2–4		10			
	4–<12	4–6	95	10	35–45	3.5	0.5
		6–12		10			
NNR[2]	Month		MJ/d	% of energy	% of energy	% of energy	
	<6	0–1	1.3 / 1.4	–	–	–	–
		3	2.1 / 2.2				
	6–11	6	2.6 / 2.7	7–15	30–45	4	1
		12	3.4 / 3.7				
UK[3]	Month		kcal/d	g/d			
	0–<3		545 / 515	12.5	–	–	
	4–<6		690 / 645	12.7	–	–	
	7–<9		825 / 765	13.7	–	–	
	10–<12		920 / 865	14.9	–	–	
USA/Canada[4]	Month		kcal/d	g/d	g/d	g/d	
	0-<6	1	472 / 438	9.1	31	4.4	0.5
		2	567 / 500				
		3	572 / 521				
		4	548 / 508				
		5	596 / 553				
		6	645 / 593				
	7-<12	7	668 / 608	11	30	4.6	0.5
		8	710 / 643				
		9	746 / 678				
		10	793 / 717				
		11	817 / 742				
WHO/FAO/UNU[5a, 5b]	Month		kcal/d	g/d	% of energy		
	3–6		700	13			
	6–9		810	14	30–40		
	9–12		950	14			
The Netherlands[6]	Month		MJ/[kg.d]	g/d	% of energy	g/day	
	0–2		0.39	9/8	45–50	0.64	–
	3–5		0.35	10/9	45–50	0.64	–
	6–11		0.35	10/10	40		0.15–0.2

[1]German Nutrition Society (DGE), Austrian Nutrition Society (OGE), Swiss Society for Nutrition Research (SGE), Swiss Nutrition Association (SVE) (2000) Referenzwerte für die Nahrstoffzufuhr/Reference Values for Nutrient Intake, 1st edition, 3 vollständig durchgesehener und korrigierter Nachdruck 2008. Frankfurt am Main: Umschau/Braus.

[2]Nordic Council of Ministers (2004) Nordic Nutrition Recommendations 2004, 4th edition: Integrating nutrition and physical activity. Copenhagen.

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[4]Food and Nutrition Board, Institute of Medicine (2005) Dietary Reference Intakes for Energy, Carbohydrate, Fibre, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). National Academy Press: Washington DC.

[5a]Joint FAO/WHO/UNU Expert Consultation on Human Energy Requirements (2004) Human energy requirements: report of a Joint FAO/WHO/UNU Expert Consultation. (FAO Food and Nutrition Technical Report Series, no. 1) Rome.

[5b]Joint WHO/FAO/UNU Expert Consultation on Protein and Amino Acid Requirements in Human Nutrition (2007) Protein and amino acid requirements in human nutrition: report of a joint FAO/WHO/UNU expert consultation. (WHO technical report series; no. 935) Geneva.

[6]Health Council of the Netherlands (2001) Dietary Reference Intakes: energy, proteins, fats and digestible carbohydrates. The Hague: Health Council of the Netherlands; publication no. 2001/19R (corrected edition: June 2002).

deficiency in infants in affluent populations, universal iron supplementation appears unjustified. The ESPGHAN Committee on Nutrition recommends an iron content ranging from 0.3 to 1.3 mg/100 kcal in infant formulae (Koletzko *et al*. 2005). Substantial evidence indicates that some indictors of iron status, particularly ferritin and haemoglobin concentrations, are lower in boys than in girls (Domellof *et al*. 2002). It has been suggested that boys may have lower body iron stores at birth or higher intestinal iron losses than girls (Yang *et al*. 2009). Other possible explanations for the reported gender difference could be due to genetic or hormonal factors, but further research is warranted (Domellof *et al*. 2002).

Zinc

Both iron and zinc are critical for normal growth, haematopoiesis, immune function and neurologic development during infancy. The young infant has a relatively high zinc requirement to support his very rapid growth. Zinc and protein intakes have been shown to be predictors of head growth (Krebs 2000, 2007). Some studies show that zinc intakes are lower than recommendations established for this age group, but it has been proposed that some current recommendations are higher than actual needs (García-Ramos Estarriol *et al*. 2000).

About 40% of the breast milk zinc content is absorbed, which is considered to be sufficient to meet the requirements of zinc in the first 6 months. To date there is no marker of zinc deficiency that is sensitive and specific. This explains why there is considerable variability in the requirements and recommendations of various international agencies. A committee of experts convened by the WHO proposed that the recommendations should be based on the metabolic requirements of each age, including a factor that represents the interference of phytates in the absorption. These recommendations (lower limits of consumption of zinc) were adjusted to diets with low bioavailability of zinc (phytate content >15 mg/day), median bioavailability (10–15 mg phytate/day) and high bioavailability (<15 mg phytate/day) (Gil Hernandez *et al*. 2006). It has been concluded that complementary feeding should provide 84–89% of the zinc requirements between 6 and 24 months of life (Dewey 2001). Animal products are the best source of zinc, both in their content and bioavailability.

Calcium

Calcium is the most abundant mineral in the human body (Perez-Lopez 2007). Over 99% of total body calcium is found in teeth and bones. The remainder is present in blood, extracellular fluid, muscle and other tissues, where it plays a role in mediating vascular contraction and vasodilatation, muscle contraction, nerve transmission and glandular secretion. The calcium content of infant formulae is often greater than breast milk to account for a lower fractional calcium absorption in order to achieve a comparable calcium retention (IOM 1997).

Iodine

Iodine is a trace element required for the production of the thyroid hormones, triiodothyronine and thyroxine. These hormones play a vital role in the early growth and development of most organs, especially the brain (Perez-Lopez 2007). Monitoring of iodine status during infancy is difficult as there are no established reference criteria for urinary iodine concentration for this age group (Zimmermann 2007). The iodine content of breast milk and the infant's small iodine pool in the thyroid turns over very rapidly and is highly sensitive to variations in dietary iodine intake. Studies from France, Germany, Belgium, Sweden, Spain, Italy, Denmark, Thailand and Zaire have shown that breast milk concentrations of iodine are lower than recommended levels, suggesting a less than optimal maternal and infant iodine nutrition in many countries (Azizi & Smyth 2009).

Sodium

Infants are less efficient in excreting excess dietary sodium than adults (Michaelsen *et al*. 2000). High sodium intakes during infancy carry both short- and long-term risks. Short-term effects include hypernatraemia, tissue dehydration, renal dysfunction and increased blood pressure. A possible life threatening acute complication is severe hypernatriaemic dehydration, which occurs at high sodium intakes without sufficiently rehydrating a child to compensate for past and ongoing losses, and can lead to renal insufficiency and failure to excrete sodium (Fomon 1993). The role of salt intake during complementary feeding has not been extensively explored. Investigations demonstrating that an excess of dietary sodium may raise blood pressure in newborns and young infants have suggested that infancy may be a period of greater salt sensitivity than later in life (Agostoni *et al*. 2008). There is evidence that early life factors are important determinants of adult blood pressure (Lawlor & Smith 2005). The long-term effects of high salt intake in infancy on blood pressure are possible, but so far not proven (Brion *et al*. 2007).

Copper

Copper concentrations in human milk decrease during the course of lactation and appear to be unrelated to maternal serum levels (Dorea 2000). Based on the copper concentration of human milk, the Institute of Medicine (IOM) estimated that intakes of 200 μg/day were adequate for the first 6 months of life increasing to 220 μg/day for the second 6 months (IOM 2000b). For formula fed infants, the United States Food and Drugs Administration (FDA), Codex Alimentarius and the American Academy of Pediatrics (AAP) recommend a minimum level of an artificial formula for copper of 0.6 mg/kcal, whereas the ESPGHAN Committee on Nutrition recommends 35 to 80 μg/100 kcal (Koletzko *et al*. 2005). There has been concern about the potential risks of excess copper supply in infants fed powered infant formula mixed with tap water with a high copper content. Copper in drinking water contributes 0.1–1 mg/day in most situations, but water obtained from unprotected copper pipes or fittings can considerably increase total daily copper exposure (WHO 2003a). The WHO has proposed that a copper content of drinking water not exceeding 2 mg/L^{-1} would provide an adequate margin of safety in populations with normal copper homeostasis (WHO 2003a); whereas it has been proposed that infants fed powdered formula prepared with tap water containing >2 mg/L^{-1} copper may pose a risk for liver damage particularly in young infants (Uauy *et al*. 2008). A controlled study of 100 healthy infants consuming water with 2 mg of copper per litre from 3 months onwards did not show biochemical or clinical evidence of health problems (Olivares *et al*. 1998), but the intervention was only started after the age considered most sensitive for copper toxicity. An epidemiological survey in Germany did not demonstrate a link between high copper exposure from water and evidence of liver abnormalities in infants, but there was no systematic health assessment for markers of copper toxicity in the infant population studied (Zietz *et al*. 2003).

Vitamin A is a group of compounds, the precursor of which is *trans*-retinol. Vitamin A is essential for growth and differentiation of a number of cells and tissues. It is one of the most critical vitamins during the breastfeeding period because it has an important role in the healthy development of the newborn, with lung development and maturation being particularly important. Insufficient intake of vitamin A by infants may have serious consequences, especially regarding susceptibility to infections, the development and function of respiratory organs and the integrity of mucous membranes (Strobel *et al*. 2007). Vitamin A deficiencies are uncommon in breastfed infants in Europe, although retinol and retinyl esters content in breast milk varies widely depending on maternal intake. β-carotene is found in plants and is considered a provitamin of vitamin A because humans are able to convert it into retinol. However, its bioequivalence to retinol in infants is not known. For this reason, the Scientific Committee on Food of the European Commission advised that vitamin A activity in infant formula should be provided by retinol or retinyl esters, while any carotene content should not be included in the calculation and declaration of vitamin A activity (SCF 2003).

Vitamin D is required to maintain adequate calcium metabolism and bone health at all ages. Many countries recommend vitamin D supplementation during infancy to avoid rickets resulting from its low content in human milk (Molgaard & Michaelsen 2003). For prevention of rickets, the Committee on Nutrition of the AAP recommends supplementing breastfed infants, whether consuming formula or not, with 400 IU (10 μg) of vitamin D per day from birth (Wagner & Greer 2008). In addition to dietary supply, the infant's vitamin D status is also modified by sunlight exposure and hence the season of the year and the geographical latitude. Dark-skinned children or children whose clothing obscures the skin may be at greatest risk of vitamin D deficiency. Ziegler *et al*. (2006) reported that 10% of breastfed infants living in Iowa (41 degrees N) were deficient in vitamin D as determined by low serum 25-OH-D levels; most were dark-skinned (Ziegler *et al*. 2006). Sunlight exposure is critical for vitamin D synthesis because cutaneous biosynthesis upon exposure of skin to ultraviolet B light is the major source of vitamin D for most people, which influences vitamin D status and calcium absorption. Thus, there is an increased reliance on dietary sources during winter months to help maintain adequate vitamin D status (Cashman 2007; Kimlin 2008).

Vitamin C

The biological functions of vitamin C are based on its ability to provide reducing equivalents for a variety of biochemical reactions (IOM 2000a). Ascorbic acid is important in facilitating iron absorption and a good ascorbic acid status in the newborn is important for collagen synthesis and may contribute to protecting cells against oxidative insults (Jain *et al*. 2008). Breastfed infants of well nourished mothers do not require vitamin C supplementation.

Vitamin E

This vitamin serves as a non-specific chain-breaking antioxidant and protects cell membranes in the retina and lungs against oxidant-induced injury (IOM 2000a). Breast milk concentrations of tocopherol (~3 IU/100 kcal) appear adequate for meeting infant requirements and particularly high levels are found in colostrum. A study in the USA observed that infants and children had low intakes of vitamin E compared with the requirements established by the IOM (IOM 2000a), but there is some concern that those reference values may be too high (Briefel *et al*. 2006).

Folate and cobalamin are necessary cofactors in the synthesis of RNA and DNA, and cobalamin is required for maintaining the nervous system. Both vitamins are therefore critical to the rapid growth and development during the early years of life (Hay *et al*. 2008). Reports of severe neurodevelopmental damage and long-term neurologic sequelae due to infantile cobalamin deficiency demonstrate the importance of adequate cobalamin status during the first months of life (von Schenck *et al*. 1997; Bjorke-Monsen *et al*. 2008). However, reference values for indices of cobalamin and folate status in infants are lacking (Hay *et al*. 2008).

Several factors may affect dietary intake of micronutrients such as the composition of foods (e.g. iron and calcium absorption depends on vitamin C and vitamin D intakes, respectively) (Sandstrom 2001; Cashman 2007) and the iodine concentration in the soil that is determined by geographical location (Aston & Brazier 1979).

Nutritional status of infants depends on micronutrient supply with human milk that is modified by maternal micronutrient intake and lifestyle, such us tobacco smoking, alcohol intake or drug consumption. Moreover, micronutrient content and bioavailability of infant formula and complementary foods and variability of nutrient absorption are of importance (IOM 2000a).

2. Current European nutrient intake values for infants

Previous EURRECA research activities collated and compared current micronutrient reference values from 35 countries and committees, by means of a questionnaire and background documents (Doets *et al*. 2008). There follows a summary of the specific characteristics that concern the infant population group, together with a comparison of reference values used in European countries and discussion of the methodological approaches to set them.

2.1 Characteristics of the infant population group in currently used micronutrient intake values

The definition of age groups within infancy, each considered as relatively homogenous with regard to nutrient requirement, differ between countries and committees that have set reference values for intake. This may be due to differences in reasoning in defining population groups, but in most publications these arguments are not clearly described (Doets *et al*. 2008). Most European countries have set reference values for one or two age groups during infancy: 13 of the 30 countries investigated by Doets and colleagues and the WHO/FAO defined two age groups, while 12 countries and the European Commission (EC) defined only one age group. Four countries defined four different age groups, and one country, the Russian Federation, set three age groups. Serbia did not set reference values for infants under the age of 1 year. The five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden), Croatia, Estonia, Italy and the EC, do not give values for infants under 6 months. France did not set reference values for minerals under 1 year of age, but they did for vitamins. None of the countries or committees set different values for male and female infants.

Specific subpopulation groups within the infant group are specified for particular micronutrients by some countries. Groups recognized are bottle and formula fed infants, respectively (the Netherlands: calcium, phosphorus, zinc and vitamin B6; WHO/FAO: zinc and magnesium), and cows' milk fed infants (WHO/FAO: calcium).

The infant population group is one of the populations recognized as a 'vulnerable' group (defined as a population group in a healthy population having a higher nutrient requirement) by 8 of the 35 countries and committees questioned in the scoping exercise for collecting reference values (Doets *et al*. 2008). The most commonly cited micronutrients thought to be related to infant vulnerability were vitamin D (in three countries), vitamin A ($n = 2$), iodine ($n = 2$), copper ($n = 2$) and iron ($n = 2$).

For the purposes of EURRECA, a list of terms and definitions that are relevant to the infancy period and to infant feeding have been agreed for use within the network (Table 2).

2.2 Comparison of nutrient intake values for infants

Micronutrient reference values for infants vary considerably across Europe; for some micronutrients there is a great difference between the highest and the lowest values. Table 3a and b show the differences between reference values used in Europe that have been set by the different European countries and European and international committees for each micronutrient at 3 and 9 months of age (lowest and highest values for each micronutrient, mean value, 25th and 75th percentile). As reference values are expressed as single values, multiple values, ranges and so on, Doets and colleagues defined standardization procedures to enable comparison (Doets *et al*. 2008).

Table 4a–d give an overview of the level of reference values set by each country/committee for vitamins, minerals and trace elements at two points of time (3 and 9 months), defined as 'high level' when they exceed the 75th percentile or 'low level' when they fall below the 25th percentile.

Twenty-two countries, WHO/FAO and the EC have their own background reports on the setting of nutrient reference values; 13 countries based their reference values on those of other countries or organizations; Germany, Austria and Switzerland (DACH) and the Nordic countries cooperated in setting reference values. The Nordic countries, the DACH countries, France, Latvia, the Netherlands and the United Kingdom, WHO/FAO and the EC, defined their own reference values (Doets *et al*. 2008). Table 5 gives an overview of the European countries and international working groups with published micronutrient reference values used in Europe. From those countries and committees setting their own reference values, only a small number of documents provided detailed information of the evaluation of evidence supporting the reference values (United Kingdom 1991; EC 1993; DACH 2000; the Netherlands 1992, 2000 and 2003; France 2001; NNR 2004; WHO/FAO 2004). We will solely refer to these documents when examining the methodological approaches for setting their micronutrient reference values in detail (see tables in section 2.2.1 to 2.2.4).

2.2.1 Water soluble vitamins (Table 6)

2.2.2 Fat soluble vitamins (Table 7)

2.2.3 Minerals (Table 8)

2.2.4 Trace elements (Table 9)

Table 2. List of terms and definitions related to the infant population group and adopted by EURRECA Research Activity 'infant nutrition'

Term	Definition
Infant	A person in the first year of life. The first 12 months of life have been defined as an age group to set reference values by national and international committees. Within this age group, reference values are set for one to four different age subgroups. Most European countries defined one or two age subgroups. For the purposes of EURRECA, the infant group is defined from birth up to 12 months of age.
Young infant	An infant up to the 6th month of life (completed 180 days).
Older infant	An infant from about the 6th month of life up to 1 year of age.
Newborn	An infant from birth to 28 completed days. The term newborn includes premature infants, post-mature infants and full term newborns.[1]
Pre-term birth	Delivery before 37 completed weeks of gestation.[1]
Full-term	Infant born between 37 completed weeks of gestation and less than 42 weeks.
Post-mature neonate	Infant born after 42 weeks gestation.
Gestational age	Time elapsed between the first day of the last menstrual period and the day of delivery. Measured in completed weeks. [Note: If pregnancy was achieved using assisted reproductive technology, is calculated by adding 2 weeks to conceptional age (time elapsed after conception)].[2]
Chronological age	Time elapsed since birth. Measured in days, weeks, months or years.[2]
Post-menstrual age	Gestational age + chronological age. Measured in days, weeks, months or years.[2]
Corrected age (similar term: adjusted age)	Chronological age reduced by the number of weeks born before 40 weeks of gestation. Measured in weeks or months used for preterm children until 3 years old.[2]
Toddler	Young child who is of the age of learning to walk between infancy and childhood. Toddling usually begins between age 12 and 24 months
Low birthweight (LBW) infant	A neonate weighing less than 2500 g at birth (up to and including 2499 g), irrespective the gestational age.[1]
Very low birthweight (VLBW) infant	A neonate weighing less than 1500 g at birth.[1]
Extremely low birthweight (EXLW)	A neonate weighing less than 1000 g at birth.[1]
Small for gestational age (SGA) infant	Neonates with birthweight and/or length at least 2 standard deviations (SDs) below the mean for gestational age (≤–2 SD) based on the data derived from a reference population.[3]
Exclusive breast-feeding	Exclusive breast-feeding implies that the infant receives only breast milk (including milk expressed or from a wet nurse) and no other liquids or solids except for Oral Rehydration Solution (ORS) drops or syrups consisting of vitamins, mineral supplements, or medicines.[4]
Predominant breastfeeding	Predominant breastfeeding implies that breast milk (including milk expressed or from a wet nurse) is the predominant source of nourishment, in combination with the supply of certain liquids (water and water-based drinks, fruit juice) ritual fluids and ORS, drops or syrups (vitamins, mineral, medicines).[4]
Full breastfeeding	Exclusive breastfeeding and predominant breastfeeding together.[5]
Breastfeeding	Breastfeeding implies that the infant receives breast milk (including milk expressed or from a wet nurse) and can also receive any food or liquid including non-human milk and formula.[4]
No breastfeeding	The infant receives no breast milk.[5]
Complementary feeding (similar terms: weaning, weaning foods, Beikost)	The term 'complementary feeding' should embrace all solid and liquid foods other than breast milk or infant formula and follow-on formula.[6]
Bottle-feeding	Any liquid (including breast milk) or semi-solid food from a bottle with nipple/teat.[4]
Infant formulae	Foodstuffs intended for particular nutritional use by infants during the first months of life and satisfying by themselves the nutritional requirements of such infants until the introduction of appropriate complementary feeding.[7]
Follow-on formulae	Foodstuffs intended for particular nutritional use by infants when appropriate complementary feeding is introduced and constituting the principal liquid element in a progressively diversified diet of such infants.[7]
Breast milk substitutes	Any food being marketed or otherwise presented as a partial or total replacement for breast milk, whether or not suitable for that purpose.[8]

[1]WHOSIS (WHO statistical information system).
[2]American Academy of Pediatrics. Age Terminology During the Perinatal Period. Pediatrics 2004;114:1362–1364.
[3]International Small for Gestational Age Advisory Board consensus. Development conference statement: management of short children born small for gestational age, April 24–October 1, 2001. Pediatrics. 2003 June;111(6 Pt 1):1253–61.
[4]Indicators for assessing infant and young child feeding practices: conclusions of a consensus meeting held 6–8 November 2007 in Washington D.C., USA. WHO 2008.
[5]Indicators for assessing breastfeeding practices. Report of an informal meeting in June 1991, Geneva. World Health Organization, Geneva.
[6]Agostoni *et al*. Complementary Feeding: A Commentary by the ESPGHAN Committee on Nutrition Journal of Pediatric Gastroenterology and Nutrition 2008, 46:99–110.
[7]Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC.
[8]International Code of Marketing of Breast-milk Substitutes. World Health Organization Geneva, 1981.

Table 3. Comparison of micronutrient recommendations for infants at 3 and 9 months of age

Micronutrient (Unit)	Lowest reference value	Highest reference value	Median	P25[†]	P75[‡]
a. Comparison of micronutrient recommendations for infants at 3 months of age					
Thiamin (mg)	0.2	0.5	0.3	0.2	0.3
Rivoflavin (mg)	0.3	0.6	0.4	0.4	0.4
Niacin (mg)	2	8	4	2.3	5
Vitamin B12 (μg)	0.3	0.5	0.4	0.3	0.5
Folate (μg)	24	80	50	40	64
Vitamin C (mg)	25	50	35	29	40
Vitamin B6 (mg)	0.1	0.5	0.3	0.2	0.3
Vitamin A (μg)	350	500	400	375	435
Vitamin D (μg)	5	22.5	10	6.3	10
Vitamin E (mg)	2.7	6	3	3	4
Calcium (mg)	210	800	400	360	500
Phosphorus (mg)	100	400	300	141	300
Potassium (mg)	233	800	600	400	800
Sodium (mg)	100	638	210	200	250
Magnesium (mg)	24	70	50	39	55
Iodine (μg)	15	110	40	40	50
Iron (mg)	0.3	12.5	5	1.7	7
Zinc (mg)	1	5	3,5	2	4
Selenium (mg)	6	25	10	10	10
Copper (mg)	0.2	1.5	0.4	0.2	0.5
b. Comparison of micronutrient recommendations for infants at 9 months of age					
Thiamin (mg)	0.2	0.6	0.4	0.3	0.4
Rivoflavin (mg)	0.4	0.7	0.4	0.4	0.5
Niacin (mg)	2	8	5	4	6
Vitamin B12 (μg)	0.3	1.5	0.5	0.5	0.5
Folate (μg)	32	80	50	50	66
Vitamin C (mg)	20	55	35	30	40
Vitamin B6 (mg)	0.2	0.6	0.4	0.3	0.6
Vitamin A (μg)	300	600	388	350	400
Vitamin D (μg)	5	22.5	10	7	10
Vitamin E (mg)	2.7	6	4	3	4
Calcium (mg)	270	800	540	438	600
Phosphorus (mg)	200	500	400	300	500
Potassium (mg)	425	1110	750	700	800
Sodium (mg)	180	850	370	320	500
Magnesium (mg)	48	100	70	60	75
Iodine (μg)	40	135	50	50	63
Iron (mg)	6	15	9	7.8	10
Zinc (mg)	2	5	4.5	3.8	5
Selenium (mg)	8	40	15	10	19.3
Copper (mg)	0.2	1.5	0.4	0.3	0.7

[†]25th percentile; [‡]75th percentile.

Table 4. Overview of the level of reference values between countries for vitamins, minerals and trace elements

Country	Year	Ref.	Vitamin C		Vitamin B6		Vitamin A		Vitamin D		Vitamin E	
			3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months
a. Overview of the level of reference values between countries for vitamins												
Albania	2005	[1]		High				High	Low	Low		High
EC	1993	[2]	–	Low	–		–		–	High	–	–
Croatia	2004	[3]	–		–		–		–		–	
the Netherlands	1992	[4a]					High		Low	Low	–	–
	2000	[4b]										
	2003	[4c]										
	2008#	[4d]										
Ireland	1999	[5]	Low	Low			Low				–	–
DACH	2000	[6]	High	High			High	High				
Belgium	2006	[7]			High		Low		High	High	–	–
Romania	1990	[8]			High		High	High			–	–
Latvia	2001	[9]										
France	2001	[10]	High	High			Low		High	High		
The former Yugoslav Republic of Macedonia	2001	[11]										
Slovakia	1997	[12]	High	High							High	High
Lithuania	1999	[13]										
Bulgaria	2005	[14]	Low						Low	Low	Low	Low
Nordic countries	2005	[15]	–	Low	–		–	Low	–		–	
United Kingdom	1991	[16]	Low	Low			Low				–	–
Bosnia and Herzegovina	2005	[17]	Low	Low					Low	Low	Low	Low
Spain	2007	[18]	High	High			High	High			High	High
Serbia	1994	[19]	–	–	–		–	–	–	–	–	–
Italy	1996	[20]	–		–		–		–	High	–	–
Russian Federation	1991	[21]			High							
Estonia	2006	[22]	–		–		–	Low	–		–	
WHO/FAO	2004	[23]	Low						Low	Low	Low	Low
Poland	1996	[24]			High		High	High				
Iceland	2006	[25]	–	Low	–		–	Low	–		–	
Hungary	2005	[26]		High								High

b. Overview of the level of recommendations between countries for vitamins

			Thiamin		Riboflavin		Niacin		Vitamin B12		Folate	
			3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months
Albania	2005	[1]					Low				High	High
EC	1993	[2]	–		–		–		–		–	
Croatia	2004	[3]	–		–		–		–		–	Low
the Netherlands	2000	[4b]					Low	Low				
	2003	[4c]										
Ireland	1999	[5]					–	–				
DACH	2000	[6]					Low			High		High
Belgium	2006	[7]					High	High				
Romania	1990	[8]	High		High		High		–	–	–	–
Latvia	2001	[9]						High		High	Low	Low
France	2001	[10]						Low			High	High
The former Yugoslav Republic of Macedonia	2001	[11]					High				Low	Low
Slovakia	1997	[12]		High		High						
Lithuania	1999	[13]		High		High		High		High	Low	Low
Bulgaria	2005	[14]					Low				High	High
Nordic countries	2005	[15]	–		–		–		–		–	
United Kingdom	1991	[16]										
Bosnia and Herzegovina	2005	[17]						Low			High	High
Spain	progr	[18]				High				Low		
Serbia	1994	[19]	–	–		–	–	–	–	–	–	–
Italy	1996	[20]	–				–		–		–	
Russian Federation	1991	[21]		High		High		High				
Estonia	2006	[22]	–		–		–		–		–	
WHO/FAO	2004	[23]					Low			High	High	High
Poland	1996	[24]	High	High	High	High	High	High			Low	
Iceland	2006	[25]	–		–		–		–		–	
Hungary	2005	[26]										

Table 4. Continued

Country	Year	Ref.	Vitamin C		Vitamin B6		Vitamin A		Vitamin D		Vitamin E	
			3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months
c. Overview of the level of recommendations between countries for minerals												
			Calcium		Phosphorus		Potassium		Sodium		Magnesium	
			3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months
Albania	2005	[1]	Low	Low	Low	Low			Low		Low	
EC	1993	[2]	–	Low	–		–		–	–	–	–
Croatia	2004	[3]	–		–		–	–	–	–	–	
the Netherlands	1992	[4a]	Low		–	Low	–	–	–	–		Low
	2000	[4b]										
Ireland	1999	[5]	High		–	–						
DACH	2000	[6]	Low	Low	Low			Low	Low	Low	Low	
Belgium	2006	[7]					–	–	–	–		
Romania	1990	[8]	High	High	High		–	–	–	–	High	
Latvia	2001	[9]										
France	2001	[10]	–	–	–	–	–	–	–	–	–	
The former Yugoslav Republic of Macedonia	2001	[11]		High	High							
Slovakia	1997	[12]					–	–	–	–		High
Lithuania	1999	[13]					–	–	–	–		
Bulgaria	2005	[14]	Low	Low	Low	Low	–	–	–	–	Low	Low
Nordic countries	2005	[15]	–		–		–	High	–	–	–	High
United Kingdom	1991	[16]	High		High							
Bosnia and Herzegovina	2005	[17]		Low			–	–	High		Low	Low
Spain	progr	[18]			Low	Low			–	–	High	High
Serbia	1994	[19]	–	–	–	–	–	–			–	–
Italy	1996	[20]	–			–	–				–	–
Russian Federation	1991	[21]					–	–				
Estonia	2006	[22]	–		–		–	High			–	High
WHO/FAO	2004	[23]	Low (cow milk)	Low	–	–	–	–			Low	Low
Poland	1996	[24]	High	High			Low	Low	High	High		
Iceland	2006	[25]	–		–		–	High			–	High
Hungary	2005	[26]				Low						

d. Overview of the level of recommendations between countries for trace elements

			Iodine		Iron		Zinc		Selenium		Copper	
			3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months	3 months	9 months
Albania	2005	[1]	High	High	Low	High		Low	High	High	–	
EC	1993	[2]	–		–	Low	–		–	Low	–	
Croatia	2004	[3]	–		–		–		–			
the Netherlands	1992	[4a]	–	–		Low		Low	High			
Ireland	1999	[5]										
DACH	2000	[6]		High (no Switz)	Low		Low	Low		High		
Belgium	2006	[7]	High	High			–					
Romania	1990	[8]		Low		Low			–	–	–	–
Latvia	2001	[9]					High					
France	2001	[10]	–	–	–	–	–	–	–	–	–	–
The former Yugoslav Republic of Macedonia	2001	[11]					High		High	High	High	High
Slovakia	1997	[12]			High		High					
Lithuania	1999	[13]						Low	–	–	–	–
Bulgaria	2005	[14]	High	High	Low	High		Low				
Nordic countries	2005	[15]	–		–		–		–		–	
United Kingdom	1991	[16]										
Bosnia and Herzegovina	2005	[17]	Low	High	High	High	Low	Low	Low		High	High
Spain	progr	[18]	Low	Low		Low					–	–
Serbia	1994	[19]	–	–	–	–	–	–	–	–	–	–
Italy	1996	[20]			–	Low	–		–	Low	–	
Russian Federation	1991	[21]							–	–		
Estonia	2006	[22]	–		–		–		–		–	
WHO/FAO	2004	[23]	High	High	–	High			Low		–	
Poland	1996	[24]			High	High	High					
Iceland	2006	[25]	–		–		–		–	–		
Hungary	2005	[26]										

'High' means reference value is above the 75th percentile; 'low' means reference value is below the 25th percentile. Blank cells indicate that the reference value is between the 25th and 75th percentile.

Table 5. List of European countries and international working groups with published reference values for vitamins and minerals.

Albania 2005 [1]	Adopted from the literature (especially Linus Pauling Institute)
European Community (EC) 1993 [2]*	Own
Croatia 2004 [3]	Aligned with EU legislation
the Netherlands 1992, 2000, 2003 [4a] [4b] [4c]	Own
Ireland 1999 [5]	Adopted from EC and United Kingdom. Own recommendations for calcium, iron (and folate and vitamin C)
Germany, Austria, Switzerland 2000 [6]*	Own
Belgium 2006 [7]**	Based on WHO/FAO, EC and European countries culturally and geographically related to Belgium (United Kingdom, the Netherlands, France)
Romania 1990 [8]	Own
Latvia 2001 [9]	Own
France 2001 [10]	Own
The former Yugoslav Republic of Macedonia 2001 [11]	Based on WHO/FAO and United Kingdom
Slovakia 1997 [12]	Adopted from unknown source
Lithuania 1999 [13]	Own
Bulgaria 2005 [14]	Based on WHO/FAO and IOM
Denmark, Finland, Norway, Sweden 2005 [15]*	Own
United Kingdom 1991 [16]*	Own
Bosnia and Herzegovina, entity: Republic of Srpska 2005 [17]	Adopted from unknown source
Spain [18]	Own
Serbia 1994 [19]	Adopted from unknown source
Italy 1996 [20]	Based on EC and FNB
Russian Federation 1991 [21]	Own
Estonia 2006 [22]	Based on Nordic Council of Ministers
WHO/FAO 2004 [23]*	Own
Poland 1996 [24]**	Based on United Kingdom, EC and FNB
Iceland 2006 [25]	Shared with Nordic countries. Own recommendations on calcium and vitamin D
Hungary 2005 [26]	Based on EC and IOM

*Background scientific report available in English language; **Polish and Belgian reference values have been revised in 2008.

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Table 6. Comparison of reference values for water soluble vitamins for infants and methods used to estimate requirements

	Range between countries		Method on which the estimated requirements is based			
	3 m	9 m	Younger infants		Older infants	
			Method	Country	Method	Country
Thiamine	0.2–0.5 mg/d	0.2–0.6 mg/d	Adequate intake from human milk	DACH, WHO/FAO, United Kingdom, the Netherlands	Adequate intake from human milk	DACH, WHO/FAO, United Kingdom
					Interpolated between values for young infants and for adults	the Netherlands
					Derived from adult values on the basis of energy expenditure	EC, NNR
Riboflavin	0.3–0.6 mg/d	0.4–0.7 mg/d	Adequate intake from human milk	DACH, WHO/FAO, the Netherlands	Adequate intakes from human milk	DACH, WHO/FAO
			Intake related to a satisfactory riboflavin status using erythrocyte glutathione reductase activation coefficient according to a study on Gambian infants (Bates *et al*. 1982)	United Kingdom	Necessary intake to restore the erythrocyte glutathione reductase activation coefficient	EC, United Kingdom
					Derived from adult values on the basis of energy expenditure	NNR
					Interpolated between values for young infants and for adults	the Netherlands
Niacin	2.0–8.0 mg/d	2.0–8.0 mg/d	Adequate intake from human milk	DACH, WHO/FAO, the Netherlands	Derived from adult values on the basis of energy expenditure	United Kingdom, EC, NNR
					Interpolated between values for young infants and for adults	the Netherlands
VitB12	0.3–0.5 μg/d	0.3–1.5 μg/d	Adequate intake from human milk	DACH, WHO/FAO, the Netherlands	Adequate intake from human milk	WHO/FAO
			Intake required to normalize methyl malonic acid excretion according to a study carried out in infants of vegan mothers (Specker *et al* 1990)	United Kingdom	Intake seen to correct biochemical deficiency as evidenced by methylmalonic acid excretion	EC, United Kingdom, NNR
					Interpolated from young infants on the basis of weight increase	DACH
					Or interpolated between values for young infants and for adults	the Netherlands

Table 6. Continued

	Range between countries		Method on which the estimated requirements is based			
	3 m	9 m	Younger infants		Older infants	
			Method	Country	Method	Country
Folate	24–80 μg/d	32–80 μg/d	Adequate folate intakes from human milk	DACH, WHO/FAO, United Kingdom, the Netherlands	Adequate intake from human milk	WHO/FAO
					Interpolated from young infants on the basis of weight increase	DACH
					Interpolated between values for young infants and for adults	the Netherlands
					Based on an intake of 3.6 mcg/kg body weight appeared to maintain plasma levels and showed maintained growth, heamopoiesis and clinical well being of the 20 infants involved in a trial (Asfour *et al.* 1977)	NNR, EC
					Set a value for formula fed infants based on the adequate intake from human milk plus intake from formula that produced lower red cell folate levels than breast milk does but no differences in haemoglobin concentration, weight gain or growth rate according to a supplementation study in infants (Foged *et al.* 1989)	United Kingdom
Vitamin C	25–50 mg/d	20–55 mg/d	Based on vitamin C content of breast milk considering maternal intake	DACH, WHO/FAO, United Kingdom, the Netherlands, FR	Based on vitamin C content of breast milk considering maternal intake	DACH, EC and United Kingdom
					From the reference value estimated for young infants	WHO/FAO
					Extrapolated from adult requirements by assuming a growth factor of 1.3	NNR
					From those for adults based on square heights	France
					Interpolated between values for young infants and for adults	the Netherlands
Vitamin B6	0.1–0.5 mg/d	0.2–0.6 mg/d	Usual vitamin B6 intakes from human milk	DACH, WHO/FAO, United Kingdom, the Netherlands	Usual intakes from human milk	DACH, United Kingdom
					Derived from adult values on the basis of dietary protein intake, assuming that 15% of energy is provided from protein as for adult values and then using values set for energy expenditures	DACH, United Kingdom
					Extrapolated from values for young infants on the basis of metabolic size, weight and growth, considering vitamin B6 content of breast milk, with consideration of average maternal intakes and average plasma pyridoxal phosphate (PLP) of nursing infants	EC
					Interpolated between values for young infants and for adults	the Netherlands
					Extrapolated values for adults using an adjustment for body height	France

Table 7. Comparison of reference values for fat soluble vitamins for infants and methods used to estimate requirements

	Range between countries		Method on which estimated requirements is based			
	3 m	9 m	Younger infants		Older infants	
			Method	Country	Method	Country
Vitamin A	350–500 mcg/d	300–600 mcg/d	Usual intakes from breast milk	DACH, WHO/FAO, the Netherlands	Based on usual intakes from breast milk	DACH
			Intakes considered sufficient to build and maintain sufficient liver stores	United Kingdom	Extrapolated from adult requirements by using metabolic body weight and growth factors	NNR
					Considered sufficient to build and maintain sufficient liver stores	WHO/FAO, United Kingdom, EC
Vitamin D	5–22.5 mcg/d	5–22.5 mcg/d	Vitamin D intakes sufficient to maintain plasma 25-OHD levels within a range considered to support adequate bone health	DACH, WHO/FAO, United Kingdom, the Netherlands	Vitamin D intakes sufficient to maintain plasma 25-OHD levels within a range considered to support adequate bone health	DACH, WHO/FAO, United Kingdom, EC, the Netherlands
					Took into account additional intakes showing to have maximal effect in linear growth according to supplementation studies in infants	NNR
Vitamin E	2.7–6 mg/d	2.7–6 mg/d	Based on vitamin E content of breast milk Consider vitamin E intake in relation to PUFA intake		Derived from adult values on an energy allowance basis	France

Table 8. Comparison of reference values for minerals for infants and methods used to estimate requirements

	Range between countries		Method on which estimated requirements is based			
	3 m	9 m	Younger infants		Older infants	
			Method	Country	Method	Country
Calcium	210–800 mg/d	270–800 mg/d	Usual calcium intakes from breast milk	the Netherlands, DACH, France	Based on usual intake from formula or food	DACH
			Based on calcium retention (factorial method for calcium needed for growth, including skeleton, urinary excretion and insensible losses) followed by absorption studies	WHO/FAO, United Kingdom	Based on calcium retention	the Netherlands, WHO/FAO, NNR, EC, United Kingdom
Phosphorus	100–400 mg/d	200–500 mg/d	Based on breast milk content	DACH, France	Based on the infant formulae content	DACH
			On the basic principle of an equimolar relationship in the body between calcium and phosphorus	United Kingdom	On the equimolar relationship with calcium	the Netherlands, United Kingdom, EC, NNR
			The minimum level based on a relation of Ca/P of 1.7 molar, to lower the risk on tetany	the Netherlands	On the amount required for growth derived from the values for calcium with the Ca/P ratio for weight gain of about 1.7 molar	France
Potassium[†]	233–800 mg/d	425–1100 mg/d	Based on the need to maintain electrolyte homeostasis and for growth of cellular mass based on factorial estimation of the urinary excretion, the amount needed for growth and lean tissue synthesis, the integumental and faecal losses (although the latter may represent homeostatic excretion of excessive intakes or losses incurred in maintaining sodium homeostasis)	DACH United Kingdom	Factorial estimation	United Kingdom, EC
					Extrapolated values from adult requirements by using metabolic body weight and growth factors (the values of the adults are set by considering the effect on blood pressure)	NNR
Sodium[‡]	100–638 mg/d	180–850 mg/d	Based on the requirement for maintenance and growth, according to balance studies and body analysis	DACH	Based on the requirement for maintenance and growth, according to balance studies and body analysis	DACH
			On breast milk content of sodium	United Kingdom	On the daily increments in total sodium body content allowing for the declining proportion with age of extracellular fluid in body mass with an allowance for dermal, faecal and urinary losses	United Kingdom
Magnesium[§]	24–70 mg/d	48–100 mg/d	On the basis of magnesium usual intake from breast milk	DACH, WHO/FAO, United Kingdom, France	On the basis of magnesium usual intake from breast milk	DACH, WHO/FAO, NNR, United Kingdom, France
					Extrapolated from the19–21 year age group, whose values are estimated on the basis of balance studies and taking the body weight into account	the Netherlands

[†]Out of 26 countries, only 14 have recommendations for potassium (Albania, EC, Ireland, DACH, Latvia, the former Yugoslav Republic of Macedonia, Nordic countries, United Kingdom, Spain, Italy, Estonia, Poland, Iceland, Hungary).
[‡]Out of 26 countries, only 9 (Albania, Ireland, DACH, Latvia, the former Yugoslav Republic of Macedonia, United Kingdom, Bosnia and Herzegovina, Poland, Hungary) have recommendations for sodium for infants.
[§]According to WHO/FAO, the magnesium in human milk is absorbed with substantially greater efficiency (about 80–90%) than that of formula milks (about 55–75%) or solid foods (about 50%).

Table 9. Comparison of reference values for trace elements for infants and methods used to estimate requirements

	Range between countries		Method on which estimated requirements is based			
			Younger infants		Older infants	
	3 m	9 m	Method	Country	Method	Country
Iodine	15–110 μg/d	40–135 μg/d	Based on the iodine concentration in breast milk, which depends on the mother's iodine intake	DACH, WHO/FAO, United Kingdom	Balance studies were used to estimate the adequate mother's intake, and these are valid also for old infants	WHO/FAO
			Balance studies were used to estimate the adequate mother's intake, and these are valid also for old infants	WHO/FAO	Extrapolated from adults aged 19–24 y, considering the iodine status in balance studies, the connection between iodine status and goitre frequency in epidemiological studies, the relation between long-term iodine intake and iodine content of the thyroid gland, and inactivation of active autonomous thyroid adaptation mechanisms once a certain level of iodine intake has been exceeded.	DACH[†]
					Derived values for older infants from adult values, making a rough estimate on the basis of energy requirements and body weight	EC
					Based on data on goitre prevalence and urinary iodine excretion in European children and extrapolation from adult values based on energy and growth requirement	NNR
					Extrapolated from adult values using EARs for energy, which being based on basal metabolic rate have a weight component	United Kingdom
Iron[‡]	0.3–12.5 mg/d	6–15 mg/d	A requirement for dietary iron exists only from the 4th month due to the newborn's reserve of placental iron (Hb iron)	DACH, WHO/FAO	Based on iron requirements for growth and on iron basal losses	DACH, NNR, United Kingdom
			Extrapolation based on metabolic weight	the Netherlands	Extrapolation based on metabolic weight	the Netherlands
					Based on the amount of body stores of iron and by the properties of the diet (iron content and bioavailability)	WHO/FAO
					Considers body weight and energy expenditure	EC
Zinc	1–5 mg/d	2–5 mg/d	Based on zinc content in breast milk	DACH	Based on zinc content in breast milk	DACH
			Extrapolation from adult values of losses and need for growth estimated with factorial methods and balance studies	United Kingdom, the Netherlands, WHO/FAO	Extrapolation from adult values of losses and need for growth estimated with factorial methods and balance studies	United Kingdom, the Netherlands, WHO/FAO
			Based on metabolic weight	the Netherlands	Based on metabolic weight	the Netherlands
			Basal metabolic rates and considering 3 different bioavailabilities	WHO/FAO	Basal metabolic rates and considering 3 different bioavailabilities	WHO/FAO
					Factorial method	EC, NNR

Table 9. Continued

	Range between countries		Method on which estimated requirements is based			
	3 m	9 m	Younger infants		Older infants	
			Method	Country	Method	Country
Selenium	6–25 mg/d	8–40 mg/d	During the first months of life low selenium intake is sufficient as selenium has been stored in the liver before birth; then, recommendations for younger infants are based on breast milk content of selenium	the Netherlands, DACH	It valid also for older infants, with an allowance for growth taken into account	United Kingdom
			Interpolation of the estimates for 65 Kg adult males of average normative requirement + 2SD deviation assumed of 12.5%; nonetheless these values are compatible with estimates of the selenium intake from breast milk and formula	WHO/FAO	Interpolation of the estimates for 65 Kg adult males of average normative requirement + 2SD deviation assumed of 12.5%; nonetheless these values are compatible with estimates of the selenium intake from breast milk and formula	WHO/FAO
					Based on extrapolation from adult values of the values of plasma glutathione peroxidase activity on the basis of body weight	DACH, the Netherlands, EC, NNR, WHO/FAO
Copper	0.2–1.5 mg/d	0.2–1.5 mg/d	Based on the amount of copper in breast milk, due to fetal copper stores in the liver and to the high absorption rate	the Netherlands, DACH, United Kingdom, France	Extrapolated from adult levels based on body weight	the Netherlands, NNR
					Based on the copper tissue content and an adjustment for loss of endogenous copper, assuming an absorption of 50%	United Kingdom, EC
					Based on the liver stores	France

[†]Germany/Austria and Switzerland adopted two different values: Switzerland adopted those from the former WHO/FAO.
[‡]Different bioavailabilities (EC, UK: 15%), WHO/FAO's value is the average of 4 different bioavailabilities, DACH does not take into account bioavailability.

3. Concluding remarks

The summary in section 2 reflects great disparities in the established current micronutrient reference values for infants between European countries. Environmental and life-style factors can justify national or regional differences only to a limited extent. In most cases, the large variation of reference values is the result of different methodological approaches used to establish requirements and derived NIVs. This is illustrated in section 2 by the comparison of approaches followed by seven committees to establish reference values based on their published scientific reports. Further discrepancies are found when converting requirements to intake reference values on the basis of body weight or of energy intake, for which the selected normative data used are often not explained. Similarly, different extrapolation methods used result in different reference values. Furthermore, up to four different age groups are defined within the first year of life within which reference values are set. Other than the transition from milk to complementary foods, no clear explanations are given for the establishment of reference values for different age groups in the first 12 months of life.

Thus, a major issue in understanding the existing disparities of reference values is the lack of transparency in the documentation of the decision making by the committees in charge. As an example, only 7 of 30 committees have published scientific reports that we could use for comparing the approaches used to establish reference values. Even in the available reports, clear explanations on assumptions, decision criteria and reference data are often lacking. Improving transparency in the process of setting micronutrient reference values has major implications for nutritional policy (e.g. development of nutritional guidelines for infant feeding and regulation of infant formula and follow-on formula composition), and feeding practice.

Reference values need to be translated in nutritional guidelines. When attempting to apply any future guidelines to the infant population group, attention should also be placed upon the social, cultural and structural determinants of infant feeding practices. Factors such as socio-economic and political contexts, gender relationships, food availability, local cultural practices, lifestyles, attitudes and beliefs are known to play a role in child health and nutrition (Pelto 1987). Poverty may be used as an example of such a factor,for example in some Western countries the lower the socio-economic group of the parents the less likely the woman is to breastfeed or give complementary foods at the appropriate time (e.g. Ponza *et al*. 2004; Heinig *et al*. 2006; Bolling *et al*. 2007; Schiess *et al*. 2010), for a wide range of socio-cultural reasons and embedded cultural norms (Sellen 2001; Dykes 2005a,b, 2006; Spiro 2006; Scavenius *et al*. 2007; Bhutta *et al*. 2008), placing the infant under considerable nutritional disadvantage. Low income mothers and their infants are also more likely to eat an 'unhealthy' diet (high in fat, sugar and salt and low in fruit and vegetables) than those on a higher income (Attree 2005). Despite various initiatives aimed at improving diet in poor households, evidence suggests they have limited effectiveness among lower socio-economic groups who are their prime target (Lynch *et al*. 2007). Instead interventions should be multi-faceted and include measures to improve families' socio-economic circumstances (Attree 2005). It is therefore essential to recognize any socio-cultural, political and economic constraints upon women and families in securing optimum nutritional standards for their infants.

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Conflict of interest

The authors have declared no conflict of interest.

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