The Impact of Micronutrient Deficiencies in Agricultural Soils and Crops on the Nutritional Health of Humans

22

Marija Knez and Robin D. Graham

Contents

22.1 Introduction – Micronutrient Deficiencies

You can trace every sickness, every disease and every ailment to a mineral deficiency

(Dr. Linus Pauling, Nobel Laureate 1954)

Cereal crops underpin the food supply for peasant farmers in developing countries, a situation that has persisted since the green revolution of the decades of the 1960s and 1970s greatly increased their productivity; indeed yields more than doubled. Ever since, the modern high-yielding, disease-resistant cereals that also show greater tolerance to environmental stresses like drought and heat have dominated the diets of subsistence farmers and urban poor alike. It was known that cereals are less dense in some nutrients important to health and vigour than crops they in part replaced, like pulses, but the consequences of that were not immediately apparent. However, the incidence of iron deficiency in humans grew through the 1980s and by 1990 was becoming a matter of real concern to nutritionists (Graham et al. 2007). Throughout this period the international consortium of agricultural scientists was naturally concentrated on increasing the yield, with little attention being devoted to the issue of nutritional quality (micronutrient density) of produced crops. Exhausted from the years of cultivation, soils slowly become more deficient in most essential nutrients, including micronutrients. Consequently, more and more people in developing country populations, who were entirely dependent on these soils for their food production, began to have inadequate mineral and vitamin intakes, leading to malnutrition and poor health. Later still, we became aware that a large number of people was affected by four other micronutrient deficiencies, those of iodine, vitamin A, zinc and selenium (WHO 1995).

Micronutrient deficiencies still remain a major public health problem in many countries worldwide, with more than two billion people suffering from one or more micronutrient deficiencies (WHO 2012).

M. Knez (✉) • R.D. Graham
School of Biological Sciences, Flinders University of South Australia, Adelaide 5001, Australia
e-mail: knez0004@flinders.edu.au

O. Selinus et al. (eds.), *Essentials of Medical Geology: Revised Edition*,
DOI 10.1007/978-94-007-4375-5_22, © Springer Science+Business Media Dordrecht 2013

As anticipated, deficiencies of micronutrients are highly prevalent in places where cereals with low nutritional quality are the main diet (Cakmak 2009; Subramanian and Jagan 2008).

The World Health Organization (WHO 2011) has estimated that nearly 3.7 billion people are Fe deficient, with two billion of these so severely deficient in Fe that they can be described as being anemic. In addition, it is estimated that two billion people globally are at high risk of I deficiency (WHO 2009); 35 % of all children (1–5 years old) suffer from Zn or Fe deficiencies, 190 million preschool-aged children and 19 million pregnant women are at risk of subclinical vitamin A deficiency (WHO 2009). In many areas of the world, poor dietary quality and micronutrient deficiencies are more widespread problems than low energy intake (Stewart et al. 2010), with devastating consequences: 19 % of all deaths before the age of 5 years can be attributed to vitamin A, Zn, Fe and/or I deficiency (Prentice et al. 2008).

Micronutrient deficiencies are currently identified as the main contributors to the global burden of disease. The human and economic costs are enormous, falling hardest on the very poor, especially women and children (Bryce et al. 2008). The interaction of poverty, poor health and poor nutrition has a multiplier effect on the general wellbeing of the population and also adds significantly towards keeping a population in a downward trend of poverty and nutritional insecurity (Stewart et al. 2010). Therefore, the problem of resolving the micronutrient deficiencies becomes a major challenge for the entire scientific community.

This chapter addresses the impact of micronutrient deficiencies in agricultural soils and crops on the nutritional health of humans. Initially, the most common mineral deficiencies of soils and crops are discussed. The second part gives an explanation of the biological roles of most important micronutrients in humans, with particular emphasis on the impact of micronutrient deficiencies on human health. Finally, the last part of this chapter discusses the agricultural interventions that could be deployed to decrease the number of people suffering from micronutrient deficiencies, both in developing and developed countries.

22.2 Micronutrient Deficiencies in Soils and Crops

The micronutrients of most practical interest here are iron, zinc, copper, manganese, boron, molybdenum, nickel, cobalt and selenium, there being a second group (chlorine, sodium, aluminium, silicon, vanadium) that may be essential or beneficial in some particular situations. We will concentrate on the first group as those in the second group are only rarely deficient in agriculturally important soils to an extent that is of economic significance.

Unlike humans and animals, plants can synthesize all the organic molecules, such as amino acids and vitamins that they require; that is they need only minerals, air and water. We include boron in our priority group because it is so widely deficient in agricultural soils and so highly effective as a remedial fertilizer. It is important to production in its own right; its requirements for humans become secondary because its essentiality is still under investigation and deemed by some to be not fully proven. The comprehensive work of Sillanpaa (1990), that not only used soil and plant analysis but field experiments with several crops, has given us an appreciation of the extent of these micronutrient deficiencies in agriculturally important soils, especially in developing countries: while he found Zn was deficient in half of the major agricultural soils and boron deficient in a third, the deficiencies of copper, molybdenum and manganese were all of small and similar extent (10–15 %), and all three together adversely affected a total of ~40 % of all soils in the study (Sillanpaa 1990). Most curiously, although Fe deficiency is widespread in humans (on one occasion estimated by WHO in 2005 to affect five billion people, at least to some degree) it is deficient in only about 3 % of all productive soils of the survey. As a broad generalization, a deficiency of at least one micronutrient is probable for most soils and multiple deficiencies are not uncommon because of the similar soil-pH effects on the availability of most of the cations.

Whereas we can generalize that micronutrient concentrations in plants reflect those in the soils they are growing in, this does not take us very far. In reality, plant species differ dramatically in their inherent abilities to extract each nutrient from a given soil. These and varietal differences operate within each target species such that plant breeding within a species can greatly increase the adaptation to a deficient soil (Graham 1984). Whether plant breeding is focused on a specific trait or simply on pursuing potential yield empirically, a nutrient efficiency trait is a common basis for yield improvement, especially providing a capacity to extract nutrient from deeper soil horizons that cannot be economically treated with fertilizers.

Formal studies of micronutrient efficiency traits have shown that copper efficiency appears in cereals to be due to a single major gene (Graham et al. 1987); in Mn deficient soils growing durum wheat breeders' lines, we found the trait involved one gene with major effect operative per genome (Khabaz-Saberi et al. 2002), whereas in Zn-deficient cereal growing soils, the trait was polygenic, yet it can be usefully manipulated in breeding programs using molecular markers that have been developed (Blair et al. 2009; Genc et al. 2009; Lonergan et al. 2009).

Further, these micronutrient efficiency traits are composed of both uptake efficiency traits and seed loading traits (Wissuwa et al. 2008; Genc et al. 2009). Grains with high micronutrient concentrations produce more vigorous seedlings when planted in deficient soils and this early advantage almost invariably manifests itself in significantly higher grain yield. In an example from Bangladesh, micronutrient-enhanced seeds from fertilizer-treated mother plants resulted in 24 % higher grain yields averaged over 4 years (Duxbury et al. 2009).

The chemistry of the micronutrient cations Fe, Cu, Mn, Ni and Co in soils is largely dominated by pH and texture: the lower the pH, the more soluble and available they are to plant roots, but below pH 4.5–5, the effect of H^+ ions on plant membrane integrity counters the advantage of higher solubility of micronutrient cations in soil, so deficiencies in the plant are more likely under extreme soil acidity. The higher the content of clay, the more strongly micronutrient cations are held by soil colloids, countering leaching, but on the other hand, decreasing by adsorption the movement laterally towards the roots for absorption into the plant. All these and many other soil factors make assessing the availability of micronutrients in soil for plant growth quite difficult to the extent that in the writer's opinion, nutrient availability, and fertilizer requirements, are best assessed by analysing the growing plant, especially actively growing leaves, and comparing the results to plant analysis standards that have been set by exhaustive experimentation (see Reuter and Robinson 1997). This approach usually identifies the most limiting nutrient and when treated, other limitations may be explored. At pH 5 and lower, root activity is itself adversely affected so the optimal pH for availability of these nutrients to plants is commonly in the intermediate range around 5.5–7. Acidity in soil can be decreased with application of lime or dolomite. On the other hand if salinity is not severe, many cereal crops can obtain sufficient of these micronutrients from soils in the alkaline range, a common condition in cereal cropping soils of lower rainfall regions.

22.2.1 Remediation of Soils by Fertilizer Use

Micronutrients can be used as fertilizers to increase soil concentrations to a level that results in adequate uptake by plant roots, so removing this constraint to productivity. Micronutrients can be applied separately or combined with organic manures or one or more macronutrients such as nitrogen, phosphorus, potassium, calcium, magnesium and sulphur. Fertilizers may be applied to the soil or in aqueous solution, much diluted and often repeated, to the leaves of the plants themselves.

The use of fertilizers containing some combination of macronutrients and micronutrients is standard practice in highly productive agriculture but most competent studies in subsistence farming systems show they can be equally highly effective. The limitation for poor farmers is the cost. This can be addressed to some extent by first diagnosing the limiting nutrients in order to decrease the overall cost of the optimal fertilizer mix. This is a complicated task for the experienced professional agronomist. Diagnosis of nutrient needs is therefore more often than not prohibitive in cost or availability of expertise to subsistence agriculture. Consequently, the best compromise may be a complete nutrient mix containing macronutrients and micronutrients in ratios derived from an extensive literature of agronomic experience in comparable environments, crops and soils. Small areas should be treated with small amounts of a complete mixture (at small cost) and the results assessed for the economic advantage of scaling up the area treated for the following crop. If promising, professional support should be found to help in fine-tuning the mixture for maximal returns on the investment.

22.3 Biological Functions of Micronutrients

UNICEF (1998) defined micronutrients as nutrients (dominantly vitamins and minerals) that are only needed by the human body in minute amounts. Micronutrients are required by humans for a vast range of physiological functions; they play leading roles in the production of enzymes, hormones and other substances, helping to regulate growth, development and the functioning of the immune and reproductive systems. While it is argued that at least 51 different nutrients are needed in adequate amounts by human beings (Welch 2008), only a few of these elements are needed in such small amounts that they are known as micronutrients (chromium, manganese, iron, cobalt, copper, zinc, selenium, molybdenum, and fluorine). For some other elements, clinical symptoms have been observed with low concentrations in the diet, but the possible essential function is not known. On the other hand, micronutrients defined as nutrients with public health importance include the following: zinc, iodine, iron, selenium, copper, vitamins A, E, C, D, B2, B6, B12 and folate. Humans suffer primarily from deficiencies of iron, zinc, iodine, selenium and Vitamin A (WHO 2009).

The text below provides a concise review of the main biological functions of some of the essential micronutrients in humans. More information on the issue can be found in Chaps. 6 and 7.

22.3.1 Zinc (Zn)

Zinc (Zn) is one of the most important trace elements in the human body, with an average amount in the adult body

between 1.4 and 2.3 g Zn (Calesnick and Dinan 1988). Zinc is found in all body tissues and fluids in relatively high concentrations, with 85 % of the whole body Zn in muscle and bone, 11 % in the skin and the liver and the remaining in all the other tissues (Kawashima et al. 2001).

Zinc has been identified to bind with 925 proteins in humans, and as such, it can be deemed the most important metabolic promoter among the known essential nutrients. It is involved in almost all processes and metabolic pathways, and is necessary for a wide range of biochemical, immunological and clinical functions (Hotz and Brown 2004). Zinc is needed for nucleic acid metabolism and protein synthesis, cellular differentiation and replication as well as glucose metabolism and insulin secretion (Vallee and Falchuk 1993). Additionally, Zn promotes the synthesis of metallothionenin, a protein found in intestinal mucosa, liver, and kidneys that is necessary for normal heavy metal metabolism (Hotz and Brown 2004). Metallothioneins play a key role in Zn-related cell homeostasis due to their high affinity for Zn, which is in turn relevant against oxidative stress and immune responses, including natural killer (NK) cell activity and ageing.

Zinc is essential as a catalytic, structural and regulatory ion. Several genes have been recognised as potential candidates for regulation by Zn: genes involved in the regulation of redox state, fatty acid metabolism, signal transduction and platelet activation.

Zinc serves as a structural component that allows for the coordinate binding of amino acids, mainly cysteine and histidine residues in the protein chain, to form a finger like structure.

Zinc is an important element in preventing free radical formation, in protecting biological structures from damage and in regulating the immune functions. More specifically, Zn is an essential element for thymic functions by means of a Zn-dependent thymic hormone called thymulin required for T-cell maturation and differentiation (Mocchegiani et al. 2000).

22.3.2 Iron (Fe)

The human body contains approximately 3–5 g of Fe (45–55 mg/kg of body weight in adult women and men, respectively). The majority of body Fe (~60–70 %) is utilized within hemoglobin in circulating red blood cells (Andrews 1999). Approximately 20–30 % of body Fe is stored in hepatocytes and in reticuloendothelial macrophages, to a large extent within ferritin and its degradation product hemosiderin. The remaining body Fe is primarily localized in myoglobin, cytochromes, and Fe containing enzymes. A healthy individual absorbs daily 1–2 mg of Fe from the diet.

Iron is a key element in the creation of hemoglobin and myoglobin in humans; necessary for various biochemical pathways and enzyme systems including energy metabolism, cell division, neurotransmitter production, collagen formation and immune system function (Edison et al. 2008). Iron plays an essential role in oxygen transport, oxidative metabolism, and cellular growth. On the other hand, too much of it can be toxic to cells, as it can catalyse the creation of reactive oxygen species through the Fenton reaction. Therefore, it is essential that Fe uptake and storage at both cellular and whole body levels are precisely regulated. For the maintenance of body Fe homeostasis, there must be effective communication between the main sites of Fe utilization (e.g., the erythroid marrow), storage (e.g., the liver and reticuloendothelial system) and the primary site of absorption in the small intestine (Steele et al. 2005). Due to the different Fe requirements within the body, a number of 'regulators' of Fe homeostasis has been hypothesized: dietary regulator (or mucosal block regulator), stores regulator, erythropoietic regulator, inflammatory regulator, etc. (Edison et al. 2008). However, the latest data are showing that the various regulators may not be necessarily different and could represent differential responses mediated by the same molecules (Hentze et al. 2004). A molecule that could have a central regulatory role in Fe metabolism, secreted by the liver and excreted by the kidneys is hepcidin. It is a small peptide, which acts as a functional target for all other regulators (Edison et al. 2008).

In order to better understand how systemic Fe homeostasis is maintained, it is necessary to look at the movement of Fe among various tissues and organs of the human body (Fig. 22.1).

The bloodstream carries Fe bound to transferrin around the body; most of it is integrated into hemoglobin by developing erythrocytes in the bone marrow. Old or damaged erythrocytes are removed from the bloodstream by the macrophages, and the Fe is recycled back to plasma transferrin. Iron is needed in all tissues for their metabolic needs, and as it is not actively excreted, the amount of Fe in the body must be controlled at the point of absorption in the small intestine.

Dietary Fe is absorbed by the body through the small intestine in quantities equal to the amounts of lost Fe from the body, so establishing the body's Fe homeostasis. Iron flux from intestinal enterocyte to the bloodstream is modulated by a liver-derived peptide, hepcidin. Hepcidin expression is influenced by systemic stimuli such as the rate of erythropoiesis, Fe stores, hypoxia, oxidative stress and inflammation.

Hepcidin is the major regulatory point of Fe homeostasis and its expression is determined by the complex interplay of various factors, and depending on the specific situation, one of several stimuli will predominate (Prasad 1991).

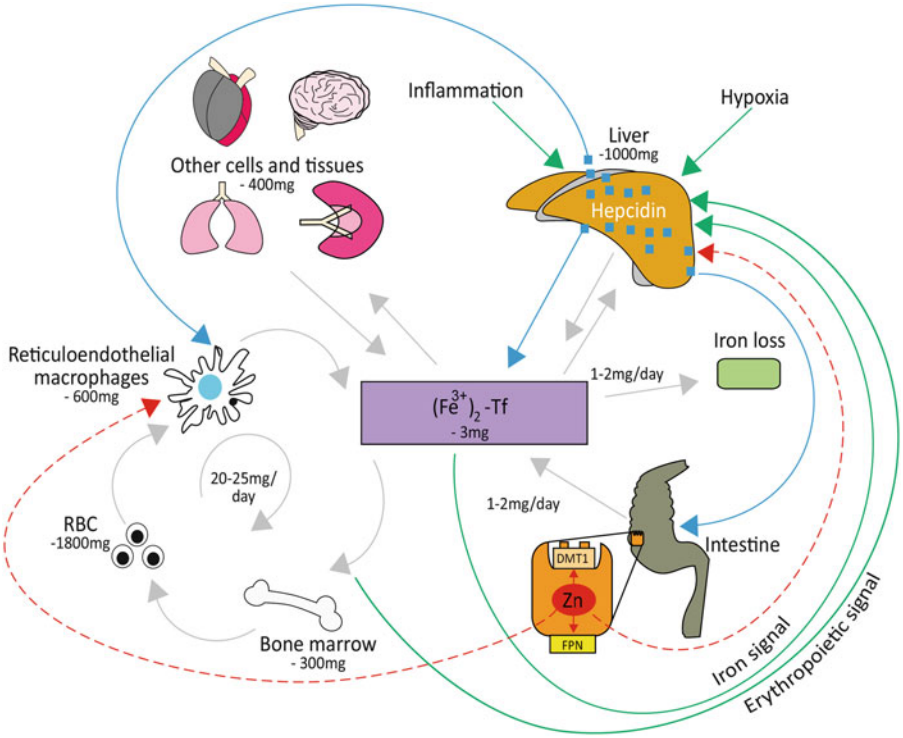

Fig. 22.1 Main routes of iron transport between various tissues and organs including the likely role of zinc in iron homeostasis. *Tf* transferrin, *RBC* red blood cells, *DMT1* divalent metal transporter 1, *FPN* – ferroportin

Stimuli can signal through multiple pathways to regulate hepcidin expression, and the interaction between positive and negative stimuli is critical in determining the net hepcidin level (Darshan and Anderson 2009). Since hepcidin expression is mostly restricted to the liver, it is highly likely that the hepatocyte is the site of action of the regulatory stimulus. Current data would suggest that Fe levels as such do not play a primary role in this process, but rather that an additional signal is involved. Recent research, summarized in Graham et al. (2012) provides evidence that Zn concentrations in the body may have a crucial role in Fe homeostasis (more about Fe uptake in the human body, Fe transporters and Fe homeostasis mechanism can be found in Chaps. 6 and 7).

22.3.3 Selenium (Se)

Selenium was first discovered in 1817; however it was not until 1957 that Schwarz and Foltz confirmed Se as an essential nutrient necessary for normal growth and reproduction in animals and humans. There is less than 1 mg of Se in the human body, most of it in the liver, kidneys and pancreas (Haas 2001). At least 25 different selenoproteins and a variety of subsequent isoforms exist in the human body (Gromer et al. 2005) and they exert multiple actions on endocrine, immune, and inflammatory functions. Of particular importance to reproduction and pregnancy are the six antioxidant glutathione peroxidases (GPxs), which play a pivotal role in reducing hydrogen peroxide (H_2O_2) and lipid peroxides to harmless products thus reducing the propagation of damaging reactive oxygen species (ROS) (Gromer et al. 2005). As antioxidants, the GPxs help maintain membrane integrity, protect prostacylin production, and limit the propagation of oxidative damage to lipids, lipoproteins, and deoxyribonucleic acid (DNA). Selenium is essential for testosterone biosynthesis and the formation and normal development of spermatozoa. Evidence is accumulating that elevated dietary levels of Se may be protective against colorectal and prostate cancer (Clark et al. 1996) and against heart disease (Liu 2003). It also appears that Se may reverse the accelerated decline in immune response in the elderly (Rayman 2000). Besides antioxidant and anti-cancer action, Se also has a positive role in detoxification of heavy metals (Rayman 2000).

22.3.4 Copper (Cu)

Copper is a relatively scarce metal in humans with an average concentration of 1.4–2.1 mg/kg in healthy individuals (Milne 1998). It is normally bound to proteins or to organic compounds and is not found as free Cu ions. Nearly two thirds of the body's Cu is found in the skeleton and muscles (Turnlund et al. 1998).

Most enzymes employ Cu in electron transfer reactions; enzymes involved in energy production (cytochrome oxidase) and in the protection of cells from free radical

damage (superoxide dismutase). Copper in ceruloplasmin has a well documented role in oxidising Fe before it is transported in the plasma (Lonnerdal and Uauy 1998).

Copper is also involved with an enzyme that strengthens connective tissue (lysyl oxidase) and in brain neurotransmitters (dopamine hydroxylase and peptidyl alpha amidating monoxygenase).

The few Cu containing proteins found in the cytoplasm are involved in protection and detoxification of Cu and in the cellular response to Cu levels. Most features of severe Cu deficiency can be explained by a failure of one or more of these Cu dependent enzymes.

22.3.5 Iodine (I)

Iodine is an essential element found in trace amounts in the human body (15–20 mg). It is stored almost entirely within the thyroid gland (Zimmermann 2011). According to Australian Nutrition Foundation (2003), I is defined as a chemical element that is required for growth and survival.

Iodine functions as a component of thyroid hormones (triiodothyronine, T3 and thyroxine, T4) which play a vital role in the regulation of metabolic processes such as growth and energy expenditure (Zimmermann 2011). Iodine is also essential to the normal development of the foetal nervous system. It regulates the effect of oestrogen on breast tissue, and it may protect against the effects of radioactivity. Additionally, the extra-thyroidal I has other functions; it removes toxic chemicals and biological toxins, suppresses autoimmunity, strengthens the T-cell adaptive immune system and protects against abnormal growth of bacteria in the stomach, *Helicobacter pylori* in particular (Miller 2006).

22.3.6 Vitamin B12 – Cobalt (Co)

The importance of cobalt (in the form of vitamin B12) for humans was discovered in 1948 (Rickes et al. 1948), while the full chemical structure of B12 was not identified until the 1960s. Vitamin B12 is the only vitamin synthesized solely by certain microorganisms (algae, yeast), many of which are abundant in soils, and the only vitamin containing a metal ion, Co (Carmel 2007).

B12 owes its chemical name ‘cobalamin’ to the Co at the centre of its molecular structure. Vitamin B12 can be stored in the body for extended amounts of time, even for years. It is primarily stored in the liver; other places are the heart, spleen, brain, kidneys, bones, and muscles (Seatharam and Alpers 1982).

Two forms of vitamin B12 are used in the human body, methylcobalamin and 5-deoxyadenosyl cobalamin.

Cobalamin is a cofactor for only two enzymes, methionine synthase and L-methylmalonyl-CoA mutase (Carmel 2007). Proper functioning of methionine synthase is needed for methylation of DNA which is important in cancer prevention. Inadequate function of methionine synthase can lead to an accumulation of homocysteine, which has been associated with increased risk of cardiovascular diseases. 5-deoxyadenosylcobalamin is required by the enzyme that catalyzes the conversion of L-methylmalonyl-CoA to succinyl-CoA, a substance required for the synthesis of haemoglobin, which is perhaps the most well known function of vitamin B12. Additionally, vitamin B12 is involved in the development of nerve cells; it is required for growth and repair of cells and for the proper movement of carbohydrates and fats through the body (Seatharam and Alpers 1982).

22.3.7 Vitamin B9 (Folic Acid)

Folic acid is named after the Latin word, “folium” for leaf. Synonyms for folic acid are vitamin B9, folacin, pteroylglutamate, pteroylmonoglutamate, and folate. Folic acid is composed of three parts; pteridine connected to para-aminobenzoic acid (PABA), which forms pteroic acid. Finally, pteroic acid is connected to glutamic acid to form folic acid. These compounds must be present for activation of folic acid (Hathcock 1997). Folic acid helps in the metabolism of several amino acids such as histidine, glycine, serine, and methionine. This vitamin is essential for cell division, production of DNA and RNA, and assists in the prevention of changes in DNA. Folate is essential for the formation of red and white blood cells in the bone marrow and for their maturation and is a single carbon carrier in the formation of heme. Folic acid is also involved in the synthesis of neuromediators which play a key role in the metabolism of the brain and nerve tissues (De Walle and De Jong-Van Den Berg 2002).

22.3.8 Manganese (Mn)

Manganese is essential for life. The human body contains approximately 20 mg of Mn most of which is found in the liver, bones, and kidneys. Manganese serves two primary biochemical functions in the body, it activates specific enzymes, and it is a constituent of several metalloenzymes (Davis and Greger 1992). The enzymes Mn activates include hydrolases, decarboxylases, kinases, and transferases.

The manganese metalloenzymes include arginase, pyruvate carboxylase, glutamine synthetase, and Mn superoxide dismutase. Manganese functions with vitamin K in the formation of prothrombin. It participates in numerous

biochemical functions in the body including steroid and sulfomucopolysacchride biosynthesis, carbohydrate and lipid metabolism, and bone, blood clot, and protein formation (Friedman et al. 1987). Manganese is also essential for normal brain function, possibly through its role in biogenic amine metabolism (Bowman 2011).

22.4 Impact of Micronutrient Deficiencies on Human Health

22.4.1 Development of a Micronutrient Deficiency

Micronutrient deficiency occurs when needs and losses exceed dietary intake. A number of factors contribute to needs including normal metabolism, growth and development, pregnancy and lactation, and disease state (Gibson 2005). Loss of nutrients can also be part of normal physiological processes (e.g. menstruation, skin exfoliation) and it can be highly accelerated during disease and infections (Gibson 2005). Before we discuss the negative effects associated with deficits of individual micronutrients, it is important to identify various ways by which a mineral deficiency can arise.

Primarily, a micronutrient deficiency occurs as a consequence of an insufficient dietary intake of an essential nutrient. Diets of people living in developing countries are mostly based on plant foods with low concentrations of important micronutrients. Consumption of animal-protein foods such as meat, poultry and fish is often small, because of economic, cultural and/or religious constraints. As a result, the amount of micronutrients accessible for absorption from such diets is low, and is probably the main cause of micronutrient deficiencies.

A secondary, or conditioned, deficiency may occur even if the dietary content of the essential nutrient appears to be adequate (Keen et al. 2003). Conditioned deficiencies occur through several mechanisms (Fig. 22.2).

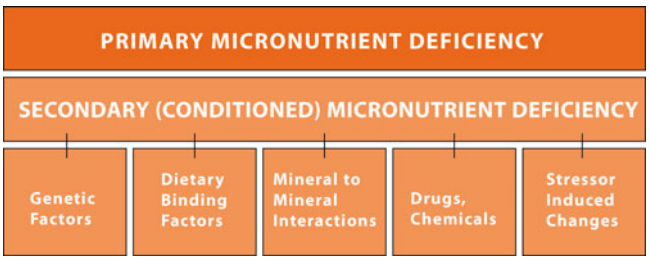

Fig. 22.2 Factors contributing to the development of a nutritional deficiency. Primary micronutrient deficiency is due to the inadequate dietary intake of a particular nutrient, while secondary micronutrient deficiency is caused by various factors

1. Genetic factors may be responsible for increased requirements of particular nutrients. For example, individuals with acrodermatitis enteropathica require a large amount of Zn in their diet because of a genetic defect in Zn absorption (Wang et al. 2002), whereas people with Menkes disease suffer from copper deficiency resulting from defects in the intracellular trafficking of this element (Keen 1998).
2. Interactions between the essential nutrients may also result in conditioned deficiencies. For example, dietary binding factors, including phytate and polyphenols, can create a complex with essential nutrients in the gut and consequently limit their absorption.

It is well known that Fe and Zn deficiencies occur in individuals who consume phytate-rich diets (Hambidge 2000).

In the research literature phytic acid and phytate are terms that are often used as synonyms, which can lead to misunderstandings. To explain, phytic acid is a free acid, a hexa phosphorous acid ester of the 6-hydroxyl group cyclic alcohol myo-inositol that has an essential characteristic for certain microorganisms. The correct chemical term for phytic acid is myo-inositol 1,2,3,4,5,6 hexakis dihydrogen phosphate. Phytates are the salts of phytic acid. The international abbreviation PA stands for both phytic acid and for phytate. The antinutritive effect of phytic acid is based on its molecular structure. At complete dissociation, the six phosphate groups of phytic acid carry twelve negative charges which, in weak acidic to neutral pH conditions, bind various di- and tri-valent cations (Ca, Mg, Fe, Zn, Cu, Mn) into a stable complex (Fig. 22.3).

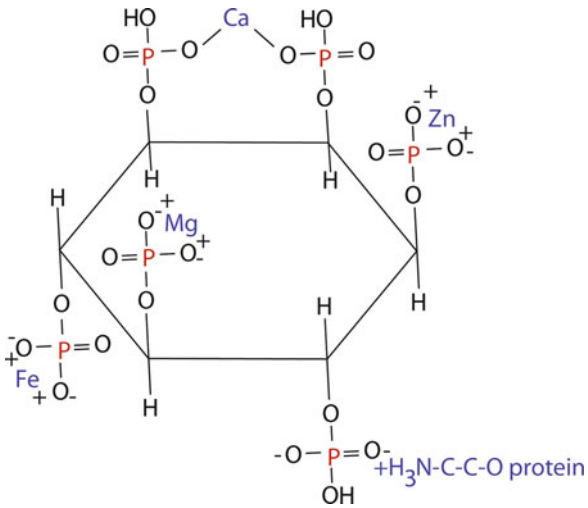

Fig. 22.3 Structure of phytic acid showing six phosphorous acid molecules bound to a phytic acid molecule, with negative charges binding divalent cations (Modified from Sohail and Roland 1999)

The formation of insoluble phytate mineral complexes in the intestinal tract prevents mineral absorption, and thus reduces the bioavailability of essential minerals (Elkhalil et al. 2011).

Zinc appears to be the trace element whose availability is the most influenced by phytic acid (Rimbach et al. 2008). Similarly, non-heme Fe is poorly absorbed in presence of phytates which irreversibly bind Fe in the gastrointestinal lumen, making it unavailable for absorption.

In addition, a number of studies over the years showed a 12–15 fold decrease in the absorption of Fe and Zn in the presence of phytate (Egli et al. 2004; Bohn et al. 2004).

A negative effect of phytate on absorption of other nutrients (manganese, calcium, copper) has also been observed (Lonnerdal et al. 1989).

Polyphenols, mostly present in the outer layer of the cereal grain, have also been shown to have inhibitory effect on absorption of certain micronutrients. Polyphenols are thought to act through the formation of complexes between the hydroxyl groups of the phenolic compounds and mineral molecules. Generally, the extent of inhibition varies inversely with the condensed polyphenol content (Elkhalil et al. 2011).

3. Mineral-mineral interaction can happen in a variety of ways. If the metabolism of one nutrient is dependent on the metabolism of another, a deficit of one may influence the availability of the other. Another interaction may occur when minerals share a common transport site or transport ligand (e.g. the absorption of Fe and metals close to Fe).

   The presence of competing metals in the diet can have a marked effect on their absorption.

   For example, zinc and cadmium are very strong antagonists of copper absorption (Danzeisen, et al. 2002). A number of studies over the years showed that absorption of metals close to Fe (e.g. cobalt, nickel, manganese and cadmium) is enhanced in Fe deficient subjects (Lynch 1997). Lead absorption is increased in Fe-deficient human subjects (Lynch 1997). The enhanced absorption of Mn and Co in Fe deficient rats can be inhibited competitively by Fe, and vice versa. Prolonged or excessive supplementation of the diet with zinc can lead to copper deficiency, very probably due to the Zn stimulated induction in the intestinal mucosa, mechanism not clear (Lynch 1997). Large doses of Fe may also reduce copper absorption, which has been demonstrated in children suffering from severe protein malnutrition (Kwashiokor) in Peru (Anderson 1981).
4. A fourth mechanism by which a conditioned deficiency can arise is through an effect of drugs or chemicals on the metabolism of the nutrient. Examples are diuretics that increase urinary loss of some nutrients. The increased turnover of folic and ascorbic acid, which occurs via oxidative damage secondary to smoking, is an example of how one toxin can induce essential nutrient deficiencies (Van Wersch et al. 2002).
5. A fifth mechanism by which a conditioned deficiency arises is through stressor-induced physiological changes in micronutrient metabolism. For instance, diabetes, renal diseases, hypertension modify the metabolism of some minerals, including Zn, Fe and copper (Keen 1996), possibly because of the induction by stress of an acute phase response. Inflammatory bowel disease often leads to deficiencies of vitamin A, K, D, Zn and Fe, while patients with asthma have lower concentrations of Zn and Se; higher Cu concentrations, and higher Cu/Zn and Cu/Se ratios (Goh and Morain 2003).

22.4.2 The Consequences of Deficiency of Individual Micronutrients on Human Health

22.4.2.1 Zinc Deficiency in Humans

The first cases of human Zn deficiency were described in early 1960s, in male adolescent dwarfs from the Middle East consuming plant-based diets (Prasad et al. 1963). Since that time, Zn deficiency has been identified in many other regions of the world. During the past 50 years, it has become evident that deficiency of Zn in humans is quite prevalent, and today it affects over two billion people in the developing world (WHO 2011). In 2002 Zn deficiency was incorporated as a major risk factor to the global and regional burden of disease, along with Fe, vitamin A and I deficiency (WHO 2002).

Zinc binds with 925 proteins in humans. Because Zn interacts with so many proteins Zn deficiency in humans is manifested in a wide range of symptoms, from acute, life-threatening problems to mild subclinical or marginal disorders which may only vaguely disturb well being (Walsh et al. 1994). The acute problems are often seen in profoundly ill patients treated in hospitals, whereas subclinical problems may be so indistinct that they often stay unrecognised (Prasad 2003).

The clinical manifestations of severely Zn deficient subjects include bullous pustular dermatitis, diarrhoea, alopecia, mental disturbances, and intercurrent infections due to cell-mediated immune disorders. Growth retardation, male hypo-gonadism, skin changes, poor appetite, anorexia, mental lethargy, abnormal dark adaptation, and delayed wound healing are usual manifestations of moderate deficiency of Zn (Barceloux, 1999). Systemic intestinal inflammation associated with Zn deficiency can lead to Fe deficiency anemia (Roy 2010).

Most recently, mild Zn deficiency has been shown to cause colitis in rats via impairment in the immune response (Iwaya et al. 2011), which shows a critical role of Zn in controlling inflammatory reactions in the intestine.

Additionally, a mild or marginal deficiency of Zn in humans is characterized by neurosensory changes, oligospermia in males, decreased serum testosterone in males, hyperammonemia, decreased serum thymulin activity, decreased IL-2 production, decreased natural killer cell activity, alterations in T cell subpopulations (Beck et al. 1997), impaired neuropsychological functions, and decreased ethanol clearance (Prasad 2002).

Zinc deficiency is associated with many diseases, for example, malabsorption syndrome, chronic liver disease, chronic renal disease, sickle cell disease, diabetes, malignancy, and other chronic illnesses (Prasad 2003). In these conditions, deficiencies of other micronutrients such as vitamins and other trace elements are often seen, which means that deficiency of one micronutrient rarely occurs in isolation.

22.4.2.2 Iron Deficiency in Humans

The human population is surprisingly Fe-deficient despite the earth and its rocks and soils being quite rich in Fe. The World Health Organisation (1995, 2005, 2011) on its website estimated in 2005 the global incidence of Fe deficiency to be between four and five billion people, and the current website identifies two billion severely deficient, that is, anemic. It appears that more than half the total problem is dietary in origin.

Total body Fe (measured by ferritin), transport Fe (measured by transferrin saturation), serum Fe, and other hematologic and biochemical markers are used to describe the degrees of Fe deficiency. Iron depletion refers to the earliest stage of diminishing Fe stores in the setting of insufficient Fe supply. Iron deficiency (without anemia) develops as these Fe stores are depleted further and begin to impair hemoglobin synthesis. Finally, Fe deficiency anemia results when the Fe supply is insufficient to maintain normal levels of hemoglobin.

Iron deficiency anemia is most severe and widespread among growing children and pre-menopausal women, because adult males even in old age resist anemia despite poor diets in resource-poor countries (Markle et al. 2007). Common symptoms of Fe deficiency are: tiredness, lethargy, shortness of breath (dyspnoea) and palpitations (irregular heartbeat).

Most Fe-deficient women and children are debilitated to some degree in both physical and mental work capacity.

Iron deficiency anemia results in increased child and maternal mortality, slower child development, delayed cognitive development in children and adolescents and decreased work productivity (Andrews 1999).

22.4.2.3 Selenium Deficiency in Humans

Selenium is an important trace element that has heightened interest because of its antioxidant and anticancer properties. Selenium deficiency has been mainly identified in people inhabiting geographical regions notable for low soil selenium content, such as volcanic regions (Poland, former Yugoslavia, China, and Russia). Deficiency symptoms for Se are difficult to determine and controversial in the research literature. Intake of Se that is borderline or only mildly deficient has not been connected with specific symptoms. With prolonged and severe deficiency, symptoms usually centre around two of the body areas, the heart and the joints (Diplock 1992). Keshan disease is a well known example of an endemic cardiomyopathy that has been observed in children, adolescents and pregnant women in the Keshan region of China, a place where Se levels in soil and food are extremely low (Lederer 1986). Similarly, Kachin-Beck disease is an osteoarthropathy reported to occur in Se-deficient populations (Navarro-Alarcon and Lopez-Martinez 2008). Deficient Se intake may also contribute to carcinogenesis, possibly due to the failure of GSH-Px to scavenge free radicals efficiently (Rayman 2000). Finally, numerous reports associate Se deficiency with several reproductive and obstetric complications including male and female infertility, miscarriage, preeclampsia, foetal growth restriction, preterm labor, gestational diabetes, and obstetric cholestasis (Sager 2006).

22.4.3 Copper (Cu) Deficiency in Humans

Copper has been recognized as an essential nutrient since the 1920s; however the first good evidence of a nutritional Cu deficiency was provided by studies on malnourished Peruvian children (6 months to 3 years) in the 1960s (Cartwright and Wintrobe 1964).

Disruptions in Cu homeostasis have implications in a number of diseases, and deficiencies in Cu absorption have a number of negative effects.

Unfortunately, most research into Cu deficiency has focused on acute, severe deficiency, which is relatively rare in humans on typical, varied diets. Marginal, chronic deficiency, however, is much more common. The determination of Cu needs and symptoms of marginal deficiency are complicated by the fact that while Cu deficiency doesn't necessarily lower the level of Cu-dependent enzymes, it does significantly lower their activity (Turnlund 1998).

Copper enzymes are widely distributed within the body; they perform several diverse functions (Cartwright and Wintrobe 1964) including transport of oxygen and electrons, catalysis in oxidation-reduction reactions and the protection of the cell against damaging oxygen radicals. At least ten enzymes are known to be dependent upon Cu for their

function. Inadequate Cu uptake during development interferes with the activity of cuproenzymes that leads to increased oxidative stress, decreased availability of nitric oxide, abnormal Fe metabolism, problems with cross linking in the extracellular matrix and altered cell signalling; in turn, these reactions affect a variety of tissues and organs including the brain, heart, lungs and skin (Uriu-Adams et al. 2010). Abnormalities associated with Cu deficiency include: anemia, neurological damage, hypercolesterolaemia, cardiomyopathy, osteoporosis and impaired immune function (Cordano 1998). Other changes may also develop, including subperiosteal haemorrhages, hair and skin depigmentation, and defective elastin formation (Lonnerdal 1998).

Despite the scarcity of Cu in the environment, overt Cu deficiency is rare in humans (Cordano 1998). Deficiency has been observed in individuals with restricted diets and in premature infants fed cow's milk formulas (Cordano 1998). Chronic ingestion of large quantities of Zn may reduce the efficiency of Cu absorption and has been reported to cause deficiency (Bertinato et al. 2003). Also, individuals suffering from malnutrition and severe malabsorption syndromes as well as patients undergoing chelation therapies are at increased risk of deficiency (Bleackley and MacGillivray 2011).

22.4.3.1 Iodine Deficiency in Humans

Current calculations by the International Council for Control of Iodine Deficiency Disorders have suggested that 29 % of the world's population, or approximately 1.6 billion people, live in areas of I deficiency and are at risk for IDD. Nearly 30 % of the world's 241 million school-age children remain I-deficient (ICCIDD 2011).

Those people at highest risk for IDD are located primarily in mountainous regions far from the sea such as the Himalayas, the European Alps, the Andes, and the mountains of China.

Population effects of severe I deficiency include endemic goiter (enlarged thyroid gland), decreased fertility rate, increased infant mortality, and mental retardation. If iodine deficiency is extremely severe, thyroid hormone production falls, and patients become hypothyroid.

Hypothyroidism in the fetus, neonates, and in young children prevents central nervous system maturation, especially neuronal myelination, leading to permanent mental retardation. In the most severe form, the constellation of mental retardation and growth abnormalities is called cretinism. Cretenism is rare, but is still seen in regions of severe I deficiency in Southern and Eastern Europe, Asia, Africa, and Latin America.

22.4.3.2 Vitamin B12 and Folate Deficiencies

B12 and folate are B complex vitamins that are necessary for normal red blood cell formation, tissue and cellular repair, and DNA synthesis. A vitamin B12 and/or folate deficiency reflects a chronic shortage of one or both of these vitamins. Since the body stores 3–6 years worth of vitamin B12 and about a 3 month's supply of folate in the liver, deficiencies and their associated symptoms can take months to years to manifest in adults (Seatharam and Alpers 1982). Infants and children will show signs of deficiency more rapidly because they have not yet established extensive reserves.

A cobalt deficiency has never been produced in humans. Signs and symptoms of one are actually those of a vitamin B12 deficiency. Untreated vitamin B12 deficiency can lead to serious complications, such as micrositic anemia, nerve damage, and growth abnormalities. Indications of a deficiency of vitamin B12, when they do reach a stage where they have shown up, can be quite severe: fatigue, paleness, anorexia, mental confusion, delusions, paranoia, weight loss, etc. Vitamin B12 deficiency is estimated to affect 10–15 % of individuals over the age of 60 (Baik and Russell 1999).

Folic acid deficiency causes cell multiplication to slow down, particularly regarding cells with a high renewal rate such as blood cells and cells in the intestine, liver and skin.

Signs of this hypovitaminosis are therefore anaemia, depression, dementia, increased rate of heart disease, digestive and neurological problems and mucous membrane problems (gums, for example) (Flood and Mitchell 2007). In pregnant women, the consequences of folic acid deficiency are even more dramatic: anomalies with the development of maternal tissue (placenta, blood circulation), anomalies with foetal development (spina bifida, anencephalia), delayed growth of the foetus, increase in the risk of premature birth and low folate reserves in the baby (Van Wersch et al. 2002).

22.4.3.3 Manganese Deficiency in Humans

The requirements of Mn for plants are generally higher than those for animals owing to its high requirement in the synthesis of cell wall materials which animal cells do not have (Graham and Stangoulis 2001). Consequently, plant-based diets should generally be adequate in Mn for humans, except in areas of severe Mn deficiency in the soil itself. While an outright Mn deficiency has not been observed in the general human population, suboptimal Mn status may be more of a concern. As reviewed by Freeland-Graves and Lianis (1994), several disease states have been associated with low levels of serum Mn. These include epilepsy, exocrine pancreatic insufficiency, multiple sclerosis, cataracts, and osteoporosis. In addition, several inborn errors of metabolism have been associated with poor Mn status (e.g. phenylketonuria, maple syrup urine disease). Impaired fertility, growth retardation, birth defects, bone malformations, seizures, and general weakness may also result from Mn deficiencies (Friedman et al. 1987).

22.5 Interaction Between Micronutrient Deficiencies

It is now well recognised that many population groups in developing countries do not suffer from single but rather from multiple nutrient deficiencies. Multiple deficiencies are a consequence of a range of common factors, including diets lacking in adequate nutritional quality mainly related to poverty, seasonal variation in food availability, and cultural food practices. Low bioavailability of nutrients, especially from plant sources, illness or infection, further intensify deficiency due to poor nutrient utilization. Existing public health strategies mostly focus on one micronutrient, for example, the National Nutritional Anaemia Control Programme and the National IDD Control Programme.

Major intervention programs address mostly Fe, I and vitamin A deficiencies, mostly as single nutrient interventions, with fewer programs operating for other limiting essential trace elements (Gibson 2003).

It cannot be said with certainty that there is a common underlying cause of multiple micronutrient deficiencies, or that one micronutrient deficiency specifically leads to another deficiency. However, it is obvious that micronutrient deficiencies are occurring simultaneously in many regions of the world (Fig. 22.4). A diet rich in phyate and low in animal proteins, common in many developing countries, can lead to insufficient intake and absorption of both Fe and Zn (Kennedy et al. 2003). Dijkhuizen et al. (2001) observed concurrent occurrence of vitamin A, Fe, and Zn deficiencies in lactating mothers and their infants in rural villages in West Java, Indonesia. In addition, Anderson et al. (2008) demonstrated a high prevalence of co-existing micronutrient deficiencies in Cambodian children, with Zn (73 %) and Fe (71 %) being the most prevalent deficiencies. Vitamin A, Zn, Fe, and I have been mentioned, but there are many more significant overlaps. For example, according to Singh (2004) selenium deficiency may impair utilization of I because it is a key component of the enzyme required to convert thyroxine to triidothyronine.

Vitamin A deficiency can aggravate both Fe and Zn deficiencies (Welch 1986). Similarly, vitamin B12 deficiency can cause anemia (Fe-resistant or pernicious anemia).

More importantly, newly published mechanisms of the regulation of Fe uptake by dietary Zn in humans (Graham et al. 2012) show that Zn deficiency could be the cause of up to half of the global burden of Fe deficiency anemia.

It is important to treat concurrent micronutrient deficiencies together, as the positive effects of this approach have been reported in number of studies. For example, Shoham and Youdim (2002) investigated the effect of 4-week Fe and/or Zn treatments on neurotransmission in the hippocampal region in rats. Iron or Zn alone was not effective whereas together they caused a significant increase in ferritin-containing mossy fiber cells (cells important for memory and learning). This is the classical response to the addition of two limiting essential nutrients acting together on a physiological or developmental pathway.

Ramakrishnan et al. (2004) undertook meta-analyses of such randomized controlled interventions to assess the effects of single vitamin A, Fe, and multi-micronutrient (Fe, Zn, vitamin A, vitamin B and folic acid) interventions on the growth of toddler children. In their summary of around 40 different studies, they clearly found greater

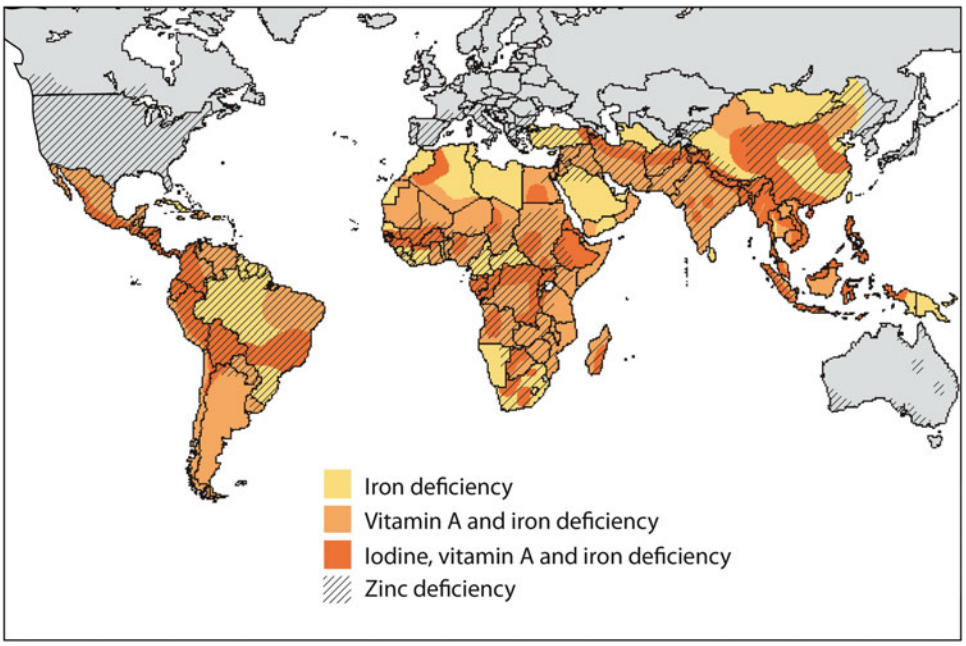

Fig. 22.4 Prevalence of common micronutrient deficiencies in developing countries. (Modified from Welch and Graham 1999)

benefits from multi-micronutrient interventions that they explained by the high prevalence of concurrent micronutrient deficiencies and the positive synergistic effects between these nutrients at the level of absorption and/or metabolism (for example, vitamin A and Fe, vitamin A and Zn, Fe and Zn, all three) (Ramakrishnan et al. 2004).

To sum up, micronutrient deficiencies often coexist in the same at-risk individuals owing to poor quality diets and recurring illnesses. Therefore, multiple, rather than single, micronutrient interventions are needed to positively affect various health and nutrition outcomes.

22.6 Agricultural Interventions for Reducing Micronutrient Deficiencies in Humans

Traditionally, agricultural programs have not been designed to promote human health, but are mainly focused on increasing yields, productivity and general food availability. For many years, the agriculture, nutrition and health sectors have operated as separate entities, and policies and government structures have been planned without looking at the interactions among these sectors (Bouis and Welch 2010).

Nowadays, more and more people realise that agricultural interventions may have a positive impact on nutritional status of humans, particularly if they are clearly implemented with that objective. Collaboration among health, agriculture and nutrition sectors is essential in the development of programs that can reduce the number of people suffering from micronutrient deficiencies in a most effective way.

Plant foods can serve as dietary sources of all essential minerals required by humans. Unfortunately, mineral concentrations of some plants are very low. This problem of low mineral density is particularly important in staple foods, such as cereal grains and tuber crops, which make up a large proportion of daily food intake in the developing world (Calloway 1995 in Grusak 2002). Thus, various agricultural interventions are used to increase the mineral content of these foods in order to ensure adequate intake of dietary minerals in all individuals. One well known agricultural strategy is crop mineral biofortification which is achieved by agronomic fertilisation with metal salts. Nutrient concentrations can be increased greatly, from less than double for Zn in rice to a 100 times in an example of selenium in wheat (Lyons et al. 2004). However, this approach involves some technology and costs. On the other hand, crop biofortification by breeding or by genetic modification offers a sustainable and low-cost way to provide essential micronutrients to people in both developing and developed countries (Graham et al. 2007).

Biofortification refers to the use of traditional crop breeding practices to increase the micronutrient concentrations in crops, in order to target the specific micronutrient deficiency of a target population (Nestel et al. 2006). It involves classical breeding approaches designed to characterize and exploit genetic variation for mineral content as well as new approaches involving gene discovery and directed genetic modification for creating new plant lines with improved mineral qualities (Graham and Welch 1996).

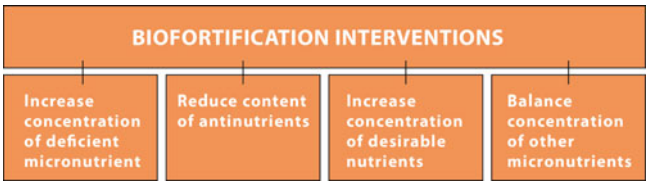

Fig. 22.5 The biofortification strategies for improving absorption of micronutrients in humans

The ultimate aim of each biofortification intervention is to increase the absorption of a certain micronutrient from a human diet. In this instance, four main biofortification strategies can be applied to crops (Fig. 22.5).

1. Increase the concentration of a deficient micronutrient

   Due to genotypic variation, the concentrations of micronutrients in grains of major crops can be quite diverse. For example, Fe concentration in the edible parts of differing varieties of maize (*Zea mays*), wheat (*Triticum* spp.), rice (*Oryza sativa*) and common beans (*Phaseolus vulgaris*) falls between 6 and 70 mg/kg dry weight. Similarly, higher concentrations of both Fe and Zn have been measured in emmer wheat (*Triticum turgidum* ssp. *dicoccoides*), a progenitor of domesticated wheat, than in a modern durum wheat cultivar (Grusak 2002). Plant mineral concentrations do also vary among plant tissues (e.g. leafy structures versus seeds) (Abbo et al. 2000).

   One way of increasing the concentrations of a deficient micronutrient through breeding processes is by identification and reintroduction of functional genes (responsible for higher concentrations of a particular micronutrient/group of nutrients) from wild relatives to domesticated varieties (Grusak 2002). In recent years, plant scientists have begun to identify genes which encode proteins of relevance to the membrane transport of various mineral nutrients. These protein products include membrane transporters, as well as proteins that facilitate the availability of minerals at the root-soil interface (Grusak 2002).

   The data are now available for genes encoding various divalent metal transporters (e.g. for Fe^{2+} Zn^2, Mn^2, Cu^2, Ni^2, and others) (Elde et al.1996; Grotz et al. 1998). The overexpression of a Ca^{2+}/H^+ antiporter in the model plant, *Arabidopsis thaliana*, has led to a moderate increase in leaf Ca concentration (Hirsch 1999) which demonstrates the potential usefulness of this approach. Similarly, the

genes for ferric reductases have been identified (Robinson et al. 1999).

Overexpression of the Fe-storage protein ferritin in rice grains has also been reported to result in a threefold (Lucca et al. 2001) increase in Fe concentrations. New discoveries clearly show that improvement of mineral content of plants by transgenic manipulation is a feasible option; however much more work is required before this technology can have a widespread use.

2. Reduce the content of substances ('antinutrients') that hinder the absorption of micronutrients (phytate and polyphenols)

   Phytic acid and polyphenols are considered as antinutrients because by mixing with minerals, they reduce the absorption of micronutrients in the human gut. The presence of high levels of phytic acid in cereals contributes to reduced absorption of micronutrients (particularly of Fe and Zn). One of the approaches for improved absorption of minerals in humans is the isolation of 'low phytate' cereals and legume genotypes and reduction of phytate in specific seed tissues (Joyce et al. 2005). Phytic acid fulfils essential biological functions in plants; it represents an important metal cation reserve; it also acts in the leaves in the signalling cascade triggered by drought/osmotic stress; maintain basal resistance against a wide range of pathogens, etc. (Guttierit et al. 2006). In addition, phytic acid and polyphenols possess diverse biologically beneficial properties for humans (antineoplastic, antioxidant and anti-inflammatory) (Trowel 1973; Welch 2008).

   Reduction of phytic acid and polyphenol concentrations should be done with caution as there is an obvious need for a careful balance between the beneficial and antinutritive properties of these nutrients. Therefore, the first priority of breeding programs should be to increase the content of a particular micronutrient rather than to decrease phytate concentrations of major crops (Bouis and Welch 2010).

3. Increase the concentration of substances favouring absorption of a certain desirable micronutrients (e.g. ascorbate, prebiotics)

   Prebiotics (fructans and arabinoxylans) are nutrients naturally present in cereal grains, resistant to digestion and absorption in the human upper gastrointestinal tract but selectively fermented in the colon by gut microflora (Roberfroid 2005). This favorable fermentation stimulates the production of short chain fatty acids (SCFAs) that confer several health benefits to humans, one of them being increased absorption of certain micronutrients.

   In recent years, there has been more and more efforts put towards increasing fructan and arabinoxylan levels in grains by genetic manipulation. Two quantitative trait loci (QTLs) for increased wheat fructan content have been identified (QGfc.awww-6D.2 on chromosome 6D and QCfc.aww-7A.1 on chromosome 7A (Huynh et al. 2008). Lines having alleles at these loci had 17–27 % higher fructan content.

   Furthermore, two major QTLs (QGax.aww-2A.1and QGax.aww-4D.1 on chromosome 6B) that influence grain arabinoxylan concentration has been identified (Nguyen et al. 2011). Wheat lines carrying the favourable alleles at these loci have higher arabinoxylan content of up to 19 %. These new findings are important as they can help in breeding grains with higher fructan and arabinoxylan content, which consequently may mean improved absorption of certain micronutrients. However, the entire efficacy of these interventions is yet to be confirmed.

   It is suggested that ascorbic acid promotes Fe absorption from the diet by reducing the negative effect on Fe absorption of certain ligands such as phytates and tannins present in the diet. In recent years, more and more research is devoted towards understanding the pathways leading to ascorbic acid biosynthesis in plants. The overexpression of GalUR gene enhanced vitamin C content of certain plants (Agius et al. 2003).

   Similarly, overexpression of the enzyme DHAR (dehydroascorbate reductase) responsible for recycling ascorbate has also been shown as an effective way in increasing the concentration of this vitamin in wheat plants (Khan et al. 2012).

4. Balance the concentrations of other micronutrients

   Increasing the concentrations of individual micronutrients through biofortification approaches is important and could significantly contribute to the nutritional enhancement of the species of interest; however, this strategy can be successful only if the concentrations of other essential nutrients are taken into account and balanced appropriately. The increase of a particular micronutrient by more than what brings the deficient nutrient up to a relative abundance roughly matching that of the other nutrients in the system should be avoided because replacing one imbalance (e.g. Zn too low) with another (e.g. Zn too high) will induce a deficiency of another micronutrient and so give little progress in health (Graham et al. 2012). Additionally, nutritional enhancement of crops should be achieved without a reduction in other major traits, such as agronomic performance, crop yield and protein concentration.

   Breeding of nutrient-rich staple food crops is the main goal of a number of international organisations. The Consultative Group on International Agricultural Research (CGIAR) Global Challenge Program,

HarvestPlus (http://www.harvestplus.org/), aims to reduce micronutrient malnutrition, mainly provitamin A, Zn, Fe, Se and I, through various biofortification programs. AgroSalud (www.agrosalud.org) is another international consortium supporting the production and dissemination of Fe and Zn-rich bean and rice varieties in Latin America.

Delivery of more micronutrients into staple food crops through plant breading is a huge task and the challenge is to minimize the number of genes involved to accomplish this end. It is feasible to help meet this challenge by use of supplemental fertilizers especially on soils inherently low in these nutrients. So far, little prospect of breeding for high Se or I content has been seen (Welch 1986) so fertilizer strategies are still the most appropriate for these (Welch 1996; Cao et al. 1994).

In the same way, the improvement of mineral content of plants by transgenic manipulation is also a viable option; however many of the molecular elements relevant to mineral transport still need to be identified before this technology can have a widespread utility. Our knowledge base is most lacking in the area of mineral loading into the phloem pathway, which is a critical process in the delivery of mineral nutrients to developing seeds (Grusak 2002). Due to simpler genetics, it may prove more effective to breed for increased bioavailability promoting substances (e.g. prebiotics) to enhance the absorbability in the human gut of minerals in staples than to increase mineral concentrations in staple food grains (Graham et al. 2007). However, further research is required to delineate positive and negative health effects of reduced phytic acid concentrations, important for the health of both plants and humans, in plant tissues.

Of other challenges more related to the human nutrition field, there is a need for the development of sensitive and specific biomarkers that can be used with confidence across a range of applications and conditions (Raiten et al. 2011). Similarly, large-scale trials of efficacy of biofortification programs in human populations still need to be performed.

Ideally, in the future, programs would be greatly improved with the inclusion of biomarkers that could simultaneously reveal the status of multiple micronutrients, going beyond the usual big four (i.e., vitamin A, Fe, Zn, I) and in line with assessment of status associated with optimal health (Wasantwisut and Neufeld 2012). Furthermore, extending our understanding of absorption mechanisms of individual/multiple micronutrients in humans will help to maximise the benefits of various biofortification approaches and to reduce any possible drawbacks.

In the end, the control of micronutrient deficiencies is a major goal of the whole scientific community. A successful strategy requires strong collaboration among scientists of several disciplines (plant physiology, biotechnology, human nutrition, epidemiology and medical care) and is therefore crucial for offering the most effective solutions. Improving the status in one micronutrient or even several micronutrients simultaneously in the case of multiple deficiencies can have wider benefits to health of people in developing countries. Multiple micronutrient interventions will help not only to accelerate progress in reducing micronutrient deficiencies but also to address several of the underlying drivers, poverty, food insecurity, gender inequity, and lack of access to basic services. The largest effect of well designed biofortification interventions will undoubtedly be observed in developing countries, but measurable and cost-effective outcomes should also occur in developed countries, even in populations characterised by appropriate diets, given that secondary micronutrient deficiencies can occur by multiple means.

See Also the Following Chapters. Chapter 3 (Natural Distribution and Abundance of Elements), Chapter 6 (Uptake of Elements from a Biological Point of View), Chapter 7 (Biological Functions of the Elements), Chapter 12 (Arsenic in Groundwater and the Environment), Chapter 15 (Bioavailability of elements in soil), Chapter 17 (Soils and Iodine Deficiency), Chapter 18 (Geophagy and the Involuntary Ingestion of Soil), Chapter 19 (Natural Aerosolic Mineral Dusts and Human Health), Chapter 20 (The Ecology of Soil-Borne Human Pathogens), Chapter 23 (Environmental Medicine), Chapter 24 (Environmental Pathology)

References

Abbo S, Grusak MA, Tzuk T, Reifen R (2000) Genetic control of seed weight and calcium concentration in chickpea seed. Plant Breed 119:427–431

Agius F et al (2003) Engineering increased vitamin C levels in plants by overexpression of a D-galacturonic acid reductase. Nature 21:177–181

Anderson A (1981) Nat Food Inst 52 (Soberg, Denmark)

Anderson VP, Jack S, Monchy D, Hem N, Hok P, Bailey KB, Gibson RS (2008) Co-existing micronutrient deficiencies among stunted Cambodian infants and toddlers. Asia Pac J Clin Nutr 17(1):72–9

Andrews N (1999) Disorders of iron metabolism. N Engl J Med 341:1986–1995

Baik H, Russell RM (1999) Vitamin B12 deficiency and elderly. Annu Rev Nutr 19:357–377

Barceloux DG (1999) Zinc. Clin Toxicol 37:279–292

Beck FW, Kaplan J, Fitzgerald JT, Brewer GJ (1997) Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. Am J Physiol 272:E1002–E1007

Bertinato J, Iskandar M, L'Abbe RM (2003) Copper deficiency induces the upragulation of the copper chaperone for Cu/Zn superoxide dismutase in weaning male rats. J Nutr 133(1):28–31

Blair MW, Astudillo C, Grusak M, Graham R, Beebe S (2009) Inheritance of seed iron and zinc content in common bean (*Phaseolus vulgaris* L.). Mol Breed 23:197–207
Bleackley R, MacGillivray RT (2011) Transition metal homeostasis: from yeast to human disease. Biometals 24:785–809
Bohn T, Davidsson T, Walczyk T, Hurrell RF (2004) Phytic acid added to white-wheat bread inhibits fractional apparent magnesium absorption in humans. Am J Clin Nutr Rev 79:418–423
Bouis HE, Welch RM (2010) Biofortification—a sustainable agricultural strategy for reducing micronutrient malnutrition in the global South. Crop Sci 50:S20–S32
Bowman B, Kwakye GF, Hernandez HE, Aschner M (2011) Role of manganese in neurogenerative diseases. J Trace Elem Med Biol 25(4):191–203
Bryce J et al (2008) Maternal and child undernutrition 4: effective action at the national level. The Lancet 371:510–526
Cakmak I (2009) Enrichment of fertilizers with zinc: an excellent investment for humanity and crop production in India. J Trace Elem Med Biol 23(4):281–289
Calesnick B, Dinan AM (1988) Zinc deficiency and zinc toxicity. Am Fam Physician 37:267–270
Cao X-Y et al (1994) Iodination of irrigation water as a method of supplying iodine to a severely iodine-deficient population in XinJiang, China. Lancet 344(8915):107–110
Calloway DH (1995) Human nutrition: food and micronutrient relationships. International Food Policy Research Institute, Washington, DC
Carmel R (2007) Haptocorrin (transcobalamin I) and cobalamin deficiencies. Clin Chem 53(2):367–368
Cartwright G, Wintrobe MM (1964) Copper metabolism in normal subjects. Am J Clin Nutr Rev 14:224–232
Clark LC, Combs GF, Turnbull BW, Slate EH, Chalker DK, Chow J et al (1996) Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. JAMA 276:1957–1963
Cordano A (1998) Clinical manifestation of nutritional copper deficiency in infants and children. Am J Clin Nutr 67:1012S–1016S
Danzeisen R, Fosset C, Chariana Z, Page K, David S, McArdle HJ (2002) Placental ceruloplasmin homolog is regulated by iron and copper and is implicated in iron metabolism. Am J Physiol Cell Physiol 282:C472–C478
Darshan D, Anderson GJ (2009) Interacting signals in the control of hepcidin expression. Biometals 22:77–87
Davis C, Greger JL (1992) Longitudinal changes of manganese-dependent superoxide dismutase and other indexes of manganese and iron status in women. Am J Clin Nutr 55:747–752
De Walle H, De Jong-Van Den Berg LT (2002) Insufficient folic acid intake in the Netherlands: what about the future? Teratology 66 (1):40–43
Dijkhuizen MA, Wieringa FT, West CE, Martuti S, Muhilal (2001) Effects of iron and zinc supplementation in Indonesian infants on micronutrient status and growth. J Nutr 131:2860–5
Diplock A (1992) Selenium, antioxidant nutritions, and human diseases. Biol Trace Elem Res 33:155–156
Duxbury MA, Bodruzzaman M, Lauren JM, Sadat RM, Welch N, E-Elahi, Meisner CA (2005) Increasing wheat and rice productivity in the sub-tropics using micronutrient enriched seed. In: Andersen P. et al (ed) Micronutrients in South and South East Asia. Proceedings of international workshop, Kathmandu, Nepal. 8-11 Sept 2004. International Centre for Integrated Mountain Development (ICIMOD), Kathmandu, pp 187–198
Edison S, Bajel A, Chandy M (2008) Iron homeostasis: new players, newer insights. Eur J Haemotol 81:411–424
Egli I, Davidsson L, Zeder C, Walczyk T, Hurrell R (2004) Dephytinization of a complementary food based on wheat and soy increases zinc, but not copper, apparent absorption in adults. J Nutr 134:1077–1080
Eide D, Broderius M, Fett J, Guerinot ML (1996) A novel iron-regulated metal transporter from plants identified by functional expression in yeast. Proc Natl Acad Sci USA 93:5624–5628
Elkhalil A, Osman HA, Osman O (2011) Phytic acid analysis by different bacterial phytases. Aust J Basic Appl Sci 5(11):2295–2302
Flood V, Mitchell P (2007) Folate and vitamin B12 in older Australians. Med J Aus 186:321–322
Freeland-Graves J, Lianis C (1994) Models to study manganese deficiency. In: Klimis-Tavantzis DJ (ed) Manganese in health and disease. CRC Press, Boca Raton, pp 59–86
Friedman BJ, Freeland-Graves J, Bales CA et al (1987) Manganese balance and clinical observations in young men fed a manganese-deficient die. J Nutr 117(1):133–143
Genc C, Verbyla AP, Torun AA, Cakmak I, Willsmore K, Wallwork H, McDonald GK (2009) Quantitative trait loci analysis of zinc efficiency and grain zinc concentration in wheat using whole genome average interval mapping. Plant Soil 314:49–66
Gibson RS (2003) Concurrent micronutrient deficiencies in developing countries: problems and solutions. Proc Nutr Soc 28:21–34
Gibson R (2005) Principles of nutritional assessment, 2nd edn. Oxford University Press, Oxford
Goh J, Morain CA (2003) Nutrition and adult inflammatory bowel disease. Aliment Pharmacol Ther 17(3):307–320
Graham RD (1984) Breeding for nutritional characteristics in cereals. Adv Plant Nutr 1:57–102
Graham RD (2008) Micronutrient deficiencies in crops and their global significance Chapter 2. In: Alloway BJ (ed) Micronutrient deficiencies in global crop production
Graham CG, Cardano A (1939) Copper depletion and deficiency in the malnourished infant. John Hopkins Med J 124:139–150
Graham RD, Stangoulis JCR (2001) Trace element uptake and distribution in plants. J Nutr 133(5):1502S–1505S
Graham RD, Welch RM (1996) Breeding for staple food crops with high micronutrient density. International Food Policy Research Institute, Washington, DC
Graham RD, Ascher JS, Ellis PAE, Shepherd KW (1987) Transfer to wheat of the copper efficiency factor carried on rye chromosome arm 5RL. Plant Soil 99:107–114
Graham RD, Welch RM, Saunders DA, Ortiz-Monasterio I, Bouis HE, Bonierbale M, de Haan S, Burgos G, Thiele G, Liria R, Meisner CA, Beebe SE, Potts MJ, Kadian M, Hobbs PR, Gupta RK, Twomlow S (2007) Nutritious subsistence food systems. Adv Agron 92:1–74
Graham RD (2008) Micronutrient deficiencies in crops and their global significance. Chapter 2 in Alloway BJ (ed) Micronutrient deficiencies in global crop production (pp. 41–61), Dordrecht, Springer
Graham RD, Knez M, Welch RM (2012) How much nutritional iron deficiency in humans globally is due to an underlying zinc deficiency? Adv Agron 115:1–40
Gromer S, Eubel JK, Lee BL, Jacob J (2005) Human selenoproteins at a glance. Cell Mol Life Sci 62(21):2414–2437
Grotz N, Fox T, Connolly E, Park W, Guerinot ML, Eide D (1998) Identification of a family of zinc transporter genes from Arabidopsis that respond to zinc deficiency. Proc Natl Acad Sci USA 95:7220–7224
Grusak M (2002) Enhancing mineral content in plant food products. J Am Coll Nutr 21(3):178S–183S
Guttieri MJ et al (2006) Agronomic performance of low phytic acid wheat. Crop Sci 46:2623–2629
Haas E (2001) Selenium. Health world on-line available at: http://www.healthy.net/scr/article.aspx?ID=2068
Hambidge M (2000) Human zinc deficiency. J Nutr 130:1344S–1349S

Hathcock J (1997) Vitamins and minerals: efficacy and safety. Am J Clin Nutr 66:427–437
Hentze M, Muckenthaler MU, Andrews NC (2004) Balancing acts: molecular control of mammalian iron metabolism. Cell 117 (3):285–297
Hirsch IK (1999) Expression of Arabidopsis CAX1 in tobacco: altered calcium homeostasis and increased stress sensitivity. Plant Cell 11:2113–2122
Hotz C, Brown KM (2004) Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull 25: S99–S199
Huynh B, Mather DE, Wallwork H, Graham RD, Welch RM, Stangoulis JCR (2008) Genotypic variation in wheat grain fructan content revealed by a simplified HPLC method. J Cereal Sci 48:369–378
ICCIDD (2011) International council for the control of iodine deficiency disorders. http://www.iccidd.org/
Iwaya H, Kashiwaya M, Shinoki A, Lee JS, Hayashi K, Hara H, Ishizuka S (2011) Marginal zinc deficiency exacerbates experimental colitis induced by dextran sulfate sodium in rats. J Nutr 141 (6):1077–1082
Joyce C, Deneau A, Peterson K, Ockenden I, Raboy V, Lott JNA (2005) The concentrations and distributions of phytic acid phosphorus and other mineral nutrients in wild-type and low phytic acid Js-12-LPA wheat (Triticum aestivum) grain parts. Can J Bot 83(12):1599–1607
Kawashima Y et al (2001) Dietary zinc-deficiency and its recovery responses in rat liver cytosolic alcohol dehydrogenase activities. J Toxicol Sci 36:101–108
Keen CL (1996) Teratogenic effects of essential trace metals: Deficiencies and excesses. In: Chang L, Magos L, Suzuki T (eds) Toxicology of metals. CRC Press Inc, New York, pp 997–1001
Keen CL, Uriu-Hare JY, Hawk SN, Jankowski MA, Daston GP, Kwik-Uribe CL, Rucker RB (1998) Effect of copper deficiency on prenatal development and pregnancy outcome. Am J Clin Nutr 67:1003S–1011S
Keen C et al (2003) The plausability of micronutrient deficiencies being a significant contributing factor to the occurrence of pregnancy complications. J Nutr 133(5):1597S–1605S
Kennedy C, Nantel G, Shetty P (2003) The scourge of hidden hunger: global dimensions of micronutrient deficiencies. FAO Food, Nutr Agric 32:15–16
Khabaz-Saberi H, Graham RD, Pallotta MA, Rathjen AJ, Williams KJ (2002). Genetic markers for manganese efficiency in durum wheat (*Triticum turgidum* L. var. *durum*). Plant Breed 121:224–22
Khan A et al (2012) Ascorbic acid: an enigmatic molecule to development and enviromental stress in plants. Int J Appl Technol 2 (3):97–111
Lederer J (1986) Sélenium et Vitamine E, Jouvence, France
Liu T (2003) Selenium. Chem Eng News 81(36):94
Lonnerdal B, Uauy R (1998) Genetic and environmental determinants of copper metabolism. Am J Clin Nutr 67:951
Lonnerdal B, Sandberg AS, Sandstrom B, Kunz C (1989) Inhibitory effects of phytic acid and other inositol phosphates on zinc and calcium absorption in suckling rats. J Nutr 119:211–214
Lonergan PF, Pallotta MA, Lorimer M, Paull JG, Barker SJ, Graham RD (2009) Multiple genetic loci for zinc uptake and distribution in barley (*Hordeum vulgare*). New Phytol 184:168–179
Lucca P, Hurrell R, Potrykus I (2001) Genetic engineering approaches to improve the bioavailability and the level of iron in rice grains. Theor Appl Genet 102:392–397
Lynch S (1997) Interaction of iron with other nutrients. Nutr Rev 55(4):102–110
Lyons GL, Stangoulis JCR, Graham RD (2004) Exploiting micronutrient interaction to optimize biofortification programs: the case for inclusion of selenium and iodine in the harvest plus program. Nutr Rev 62:247–252
Markle W, Fisher MA, Smego RA (2007) Understanding global health. McGraw-Hill Medicall, New York
Miller W (2006) Extrathyroidal benefits of iodine. J Am Physician Surg 11(4):106–110
Milne D (1998) Copper intake and assessment of copper status. Am J Clin Nutr 67:1041S–1045S
Mocchegiani E, Giacconi R, Muzzioli M, Cipriano C (2000) Zinc, infections and immunosenescence. Mech Ageing Dev 121 (1–3):21–35
Navarro-Alarcon M, Cabrera-Vique C (2008) Selenium in food and the human body: a review. Sci Total Environ 400:115–141
Nestel P, Bouis HE, Meenakshi JV, Wolfgang P (2006) Biofortification of staple food crops. Am Soc Nutr 136(4):1064–1067
Nguyen Van Lam H, Wallwork H, Stangoulis CRJ (2011) Identification of quantitative trait loci for grain arabinoxylan concentration in bread wheat. Crop Sci 51(3):1143–1150
Prasad AS (1963) Zinc and iron deficiencies in male subjects with dwarfism and hypogonadism but without ancylostomiasia, schistosomiasis or severe anemia. Am J Clin Nutr 12:437–444
Prasad AS (1991) Discovery of human zinc deficiency and studies in an experimental human model. Am J Clin Nutr 53:403–412
Prasad AS (2002) Zinc deficiency in patients with sickle cell disease. Am J Clin Nutr 75:181–182
Prasad AS (2003) Zinc deficiency. BMJ 326:409–410
Prentice AM et al (2008) New challenges in studying nutrition disease interactions in the developing world. J Clin Invest 118:1322–1329
Raiten J et al (2011) Executive summary—biomarkers of nutrition for development: building a consensus. The Am Clin Nutr 94(2): 633S–650S
Ramakrishnan U, Cossio GT, Neufeld ML, Rivera J, Martorell R (2004) Multimicronutrient interventions but not vitamin A or iron interventions alone can improve child growth: results of 3 meta analyses. J Nutr 134:2592–2602
Rayman M (2000) The importance of selenium for human health. Lancet 356:233–241
Reuter DJ, Robinson JB (1997) Plant analysis: an interpretation manual 2nd edn CSIRO Publishing, Melbourne
Rickes EL, Brink NG, Koniuszy FR, Wood TR, Folkers K (1948) Crystalline vitamin B12. Sci Total Environ 107:396
Rimbach G, Pallauf J, Moehring J, Kraemer K, Minihane MA (2008) Effect of dietary phytate and microbial phytase on mineral and trace element bioavailability, a literature review. Curr Top Nutraceutical Res 6(3):131–144
Robertfoid M (2005) Introducing inulin-type fructans. Br J Nutr 9: S13–S25
Robinson N, Procter CM, Connolly EL, Guerinot ML (1999) A ferricchelate reductase for iron uptake from soils. Nature 397:694–697
Roy C (2010) Anemia of inflammation. Hematology 30:276–280
Sager M (2006) Selenium in agriculture, food and nutrition. Pure Appl Chem 78:111–133
Schwarz K, Foltz CM (1957) Selenium as an integral part of factor-3 against dietary necrotic liver degeneration. J Am Chem Soc 79: 3292–3293
Seatharam B, Alpers DH (1982) Absorption and transport of cobalamin (vitamin B12). Ann Rev Nutr 2:343–349
Shoham S, Youdim MB (2002) The effect of iron deficiency and iron and zinc supplementation on rat hippocampus ferritin. J Neural Transm 109:1241–1256
Singh M (2004) Role of micronutrients for physical growth and mental development. Indian J Pediatr 71(1):59–62
Sillanpaa (1990) Micronutient assessment at country level: an international study. FAO Soils Bulletin No.63 FAO, Rome

Sohail S, Roland AD (1999) Fabulous phytase: phytase enzyme proving helpful to poultry producers and environment. Highlight Agric Res 1(46)
Steele M, Frazer DM, Anderson AJ (2005) Systematic regulation of intestinal iron absorption. Life 57:499–503
Stewart CP et al (2010) The undernutrition epidemic: an urgent health priority. Lancet 375:282
Subramanian KB, Bharathi C, Jegan A (2008) Response of maize to mycorrhizal colonization at varying levels of zinc and phosphorus. Biol Fertil Soils 45(2):133–144
Trowel L (1973) Definition of dietary fiber and hypotheses that it is a protective factor in certain diseases. Am J Clin Nutr 26:417–427
Turnlund J (1998) Human whole-body copper metabolism. Am J Clin Nutr 67:960S–964S
Turnlund JR, Keyes WR, Peiffer GL, Scott KC (1998) Copper absorption, excretion and retention by young men consuming low dietary copper determined by using the stable isotope 65Cu. Am J Clin Nutr 67:1219–1225
United Nations (1998) WHO, UNICEF, UNU (1998) IDA: Prevention, assessment and control. Report of a joint WHO/UNICEF/UNU consultation, Geneva. World Health Organization, Geneva
Uriu-Adams JY, Scherr RE, Lanoue L, Keen CL (2010) Influence of copper on early development: prenatal and postnatal considerations. Biofactors 36(2):136–152
Vallee B, Falchuk KH (1993) The biochemical basis of zinc physiology. Physiol Rev 73:79–118
Van Wersch JW, Janssens Y, Zandvoort JA (2002) Folic acid, vitamin B(12), and homocysteine in smoking and non-smoking pregnant women. Eur J Obstet Gynecol Reprod Biol 103:18–21
Walsh T et al (1994) Zinc: health effects and research priorities for the 1990's. Environ Health Perspect 102:5–46
Wang K, Zhou B, Kuo YM, Zemansky J, Gitschier J (2002) A novel member of a zinc transporter family is defective in acrodermatitis enteropathica. Am J Hum Genet 71:66–73
Wasantwisut E, Neufeld (2012) Use of nutritional biomarkers in program evaluation in the context of developing countries. J Nutr 142(1):186S–90S
Welch RM (1986) Effects of nutrient deficiencies on seed production and quality. Adv Plant Nutr 2:205–247
Welch RM (1996) The optimal breeding strategy is to increase the density of promoter compounds and micronutrient minerals in seeds: caution should be used in reducing anti-nutrients in staple food crops. Micronutr Agric 1:20–22
Welch RM (2008) Linkages between trace elements in food crops and human health. Micronutr Defic Glob Crop Prod 287–309
Welch RM, Graham RD (1999) A new paradigm for world agriculture: meeting human needs: productive, sustainable, nutritious. Field Crop Res 60(1):1–10
Wissuwa M, Ismail AM, Graham RD (2008) Rice grain zinc concentrationsas affected by genotype, native soil-zinc availability, and zincfertilization. Plant Soil 306:37–48
World Health Organization (1995) http://www.who.int/nut/malnutrition_worldwide.htm Malnutrition Worldwide. World Health Organization, Geneva
The World Health Report 2002: reducing risks, promoting healthy life. Geneva
WHO (2009) Trace elements in human nutrition and health. World Health Organization, Geneva
WHO (2011) World Health Statistics. World Health Organization, Geneva
WHO (2012) The World Health Report 2012, World Health Organization, Geneva
Zimmermann B (2011) The role of iodine in human growth and development. Semin Cells Dev Biol 22:645–652