Approaches to reduce zinc and iron deficits in food systems

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Abstract

There is a deficit of mineral micronutrients in global food systems, known as ‘hidden hunger’, especially in the global south. This review focuses on zinc (Zn) and iron (Fe), whose entry into food systems depends primarily on soil and crop factors. Approaches to increase dietary supplies of Zn and Fe include: (1) supplementation, (2) food fortification, (3) dietary diversification, and (4) crop biofortification, including breeding and fertilizer-based approaches. Supply-based estimates indicate that Zn deficiency might be more widespread than Fe deficiency in sub-Saharan Africa, although there are major knowledge gaps at an individual biomarker level. Recent analytical advances, including the use of stable isotopes of Zn and Fe, can play an increasing role in improving our understanding of the movement of micronutrients in food systems, and thereby help to reduce the immense human cost of ‘hidden hunger’.

Keywords: biofortification, diet, food supply, micronutrient deficiency, micronutrients, stable isotopes

1. Introduction

1.1 Scope of Review

Micronutrient deficiencies (MNDs) can occur due to inadequate dietary intakes of vitamins and mineral elements, excessive losses, or malabsorption. Also known as ‘hidden hunger’, the consequences of MNDs are often less apparent than energy or protein deficiencies. However, their prevalence is likely to be more widespread than energy/protein malnutrition, with at least 1.5 billion (GBD, 2016), and potentially more than 3 billion (Kumssa et al. 2015a,b), people likely to be affected by one or more MNDs. Micronutrients is a term often used to include any of the >20 essential elements required by humans; the elements most commonly studied are calcium (Ca), copper (Cu), iron (Fe), iodine (I), magnesium (Mg), selenium (Se) and zinc (Zn)

(Black et al., 2008; Broadley and White, 2010; Bouis et al., 2011; Muthayya et al., 2013). The greatest prevalence of most MNDs occurs in less developed countries, including in sub-Saharan Africa (Muthayya et al., 2013; Joy et al., 2014; Kumssa et al., 2015a,b). However, estimating the prevalence of MNDs at national and sub-national scales remains a considerable challenge in terms of selecting appropriate biomarkers of nutritional status, measuring these in population-level surveys, and linking these with health outcomes. In turn, this constrains the development of policies to alleviate MNDs, including the application of innovations from the agriculture/nutrition research sectors.

The scope of this review is to provide an overview of dietary supplies of Zn and Fe in current global food systems. Dietary deficiencies of Zn and Fe have been estimated as the 40th and 16th leading risk factors, respectively, underlying global burden of disease (GBD, 2016). It has been estimated that Zn and Fe deficiency reduces the Gross Domestic Product (GDP) of developing countries by 2–5% (Stein, 2014). The potential to develop policies to address deficits of Zn and Fe in food systems are considered from an agriculture/nutrition perspective, including the potential to use micronutrient fertilization and crop breeding to benefit human health.

1.2. Functions of zinc and iron in humans

An adult human body contains ~2 g of Zn of which ~60% is found in skeletal muscle and 30% in bone mass (Saltzman et al., 1990). Zinc has many fundamental roles for all life forms (Broadley et al., 2007), and binds with >900 proteins in the human body (Oliver and Gregory, 2015). The World Health Organization and Food and Agriculture Organization (WHO & FAO, 2004) Reference Nutrient Intake (RNI) for Zn is 14 and 10 mg *capita*$^{-1}$ d^{-1} for adult males and females, respectively; the requirements for adolescents are greater. In children, Zn deficiency increases the incidence and severity of diarrhoea and increases the risk of stunting (Brown et al., 2009; Mayo-Wilson et al., 2014). There is mixed evidence to suggest an increase in mortality and morbidity due to lower respiratory tract infections and malaria (Bates et al., 1993; Salgueiro et al., 2002; Brown et al., 2009; Mayo-Wilson et al., 2014).

An adult human body contains ~4.0 g of Fe of which ~75% is in the oxygen-transporting proteins haemoglobin and myoglobin (Bothwell et al., 1979). The redox potential of Fe is critical in binding and releasing oxygen and for its functions in enzymes including energy, protein and nucleotide metabolism. The RNI for Fe is 13.7 mg *capita*$^{-1}$ d^{-1} for adult males (WHO & FAO, 2004). Dietary requirements are greater for women of reproductive age (up to 29.5 mg *capita*$^{-1}$ d^{-1} for adolescent females) due to increased blood losses, and during pregnancy. Recommended intakes of Fe are also greater in cereal-based diets that are low in animal products, due to the presence of inhibitors of Fe (and Zn, Ca, Mg etc.) absorption, such as phytate (Gibson et al., 2010; Kumssa et al., 2015a,b). The consequences of dietary Fe deficiency include Fe-deficiency anaemia (Lynch, 2007), which is defined as low haemoglobin together with one or more indicators of Fe deficiency, e.g. low body Fe stores (Cook et al., 2003). Anaemia results in decreased physical capacity (Hass and Brownlie, 2001), and increased risk of low-birth weight, perinatal and neonatal mortality (Rasmussen, 2001; Kozuki et al., 2012; Rahman et al., 2016). In children, Fe deficiency impairs cognitive development and the immune system leading to increased susceptibility to infectious diseases (Oliver and Gregory, 2015).

1.3. Prevalence of zinc and iron deficiencies

Various types of data are used to estimate the prevalence of Zn and Fe deficiencies, including proxies based on (1) national food supply; (2) dietary intake surveys; and (3) health data, and (4) biomarkers of status. Caution is needed when interpreting single sources of data and a combination of data sources and approaches is therefore generally considered to the most reliable method to assess MND prevalence (e.g. King et al., 2016). For example, food balance sheets (FBSs; FAO, 2016) represent net *per capita* food supply calculated from national production, trade, transport losses, storage, non-food uses, livestock feed, etc., but with no adjustment for household waste or inter- and intra-household variation in access to food (Joy et al., 2014; Kumssa et al. 2015a,b). Household or individual-level consumption surveys can also be affected by behavioural factors and systematic misreporting (Rennie et al., 2007; Archer et al., 2013). Uncertainties about food supply or consumption can also be compounded by a lack of good quality data on the micronutrient composition of foods, which can be affected greatly by soil type and cultivation conditions (Joy et al., 2015a).

Tissue biomarkers and proxy health data for estimating Zn deficiency can be difficult to interpret. For example, King et al. (2016) concluded that the prevalence of Zn deficiency in a population was best achieved using a combination of intake data, plasma/serum Zn concentration, and height-to-weight ratios (stunting). However, data are often not available at appropriate scales. Using FBSs for 2011 and United States Department of Agriculture (USDA) food composition data, the prevalence of inadequate dietary Zn supplies was estimated to be 17% globally (Kumssa et al., 2015b; Fig. 1). The data are consistent with earlier studies (Wuehler et al., 2005; Wessells and Brown, 2012), including a study in Africa which used more regional food composition information (Joy et al., 2014), indicating that Zn deficiency is widespread in low-income countries. Recent studies of tissue biomarkers have shown that the prevalence of Zn deficiency appears to be higher than that of Fe deficiency in both Ethiopia (Gashu et al. 2016) and Malawi (Siyame et al., 2013; Gibson et al., 2015).

Quantifying the prevalence of Fe deficiency at wide scales can be particularly problematic. Currently, the prevalence of anaemia is used as a proxy for Fe deficiency with an assumption that half of all anaemia cases result from Fe deficiency (Stoltzfus et al., 2004 Lynch, 2007). However, the prevalence of dietary Fe deficiency estimated from food supply was lower than expected from anaemia rates in continental Africa (Joy et al., 2014; Fig 2). Anaemia is also caused by other nutritional deficiencies (e.g. vitamin A and folic acid), impaired Fe absorption or increased Fe losses due to inflammatory and infectious diseases. The regulation of serum Fe is an important component of the immune system, starving pathogens of Fe (Ward et al., 2011; Guida et al., 2015); for example, anaemia offers children protection against *Plasmodium falciparum* malaria (Goheen et al., 2016). In a recent review, Petry et al. (2016) pooled data from 23 nationally-representative surveys of pre-school children and non-pregnant women, finding that the proportion of anaemia associated with Fe deficiency is typically <<50%, especially in countries with a high prevalence of anaemia, among rural populations and in countries with very high inflammation exposure. Progress is being made to define complementary markers of Fe status including serum ferritin, soluble transferrin receptor and hepcidin to quantify Fe stores and the adequacy of Fe supplies, although their application in developing countries has mainly been limited to small-scale studies (Lynch, 2012; Prentice et al., 2012).

2. Crop nutrition and Zn and Fe concentrations of edible plant parts

Zinc and Fe are both essential nutrients for plants, and in many low-income settings where consumption of animal-source foods is low, plant-based foods provide the majority of dietary Zn and Fe. The quantity of Zn and Fe contained in plant organs depends on several interacting factors including soil type, plant type and variety, and the growing environment and its management.

2.1 Soil type

Soil is the source of most Zn and Fe within plants, so soil type has a major role in determining the amounts contained in crops. Most soils used for agriculture contain 10–300 µg Zn g^{-1} soil with the concentration in soil solution ranging from 10^{-8}–10^{-6} M (White and Greenwood, 2013). Concentrations of Fe in most agricultural soil solutions also range from 10^{-8}–10^{-6} M but only 10^{-10} M in alkaline or calcareous soils (White and Greenwood, 2013). Table 1 summarises the major soil types and their association with both Zn and Fe deficiency and toxicity. Zinc deficiency in plants is often associated with alkaline and calcareous soils of high pH, and also with highly weathered soils, so occurs on a number of soil types. Iron deficiency in plants occurs on several soil types but is typically associated with low phytoavailability rather than low abundance *per se* (Fageria, 2009; White and Greenwood, 2013). The concentration of Fe in soil solution decreases as the redox potential and/or pH increases, with concentrations in calcareous and alkaline soils (such as the Aridisols and some Entisols and Inceptisols shown in Table 1) typically 100–1000 times lower than in soils with a pH of 6–7 (Fageria, 2009). It is estimated that up to one-third of the world's soils used for agriculture are calcareous with the plants grown on them susceptible to what is called 'lime-induced Fe chlorosis' (White and Greenwood, 2013; FAO, 2015). Toxicity of Fe occurs in soils with inherently high concentrations of Fe (such as some Oxisols) but more commonly on other soil types where flooding or waterlogging occurs resulting in the reduction of ferric Fe to ferrous Fe thereby increasing its bioavailability to plants. In contrast, Zn toxicity is rare but can occur on some acidic soils (especially in urban and peri-urban areas) enriched with sewage sludge or land contaminated by mining or smelting activities (White and Greenwood, 2013).

2.2 Plant type and variety

The concentration of mineral elements in plant tissues varies between plant taxa growing in the same environment (Watanabe et al., 2007; White et al., 2012). Whilst phylogenetic studies of flowering plants (angiosperms) have shown that there can be systematic general differences between plant families, closely related species and even sub-species can often have substantially different Zn and Fe concentrations in their tissues. For example, some plant species can hyperaccumulate Zn in their leaves at concentrations several orders of magnitude greater than those in closely-related species grown on in the same environment (Broadley et al., 2007).

Table 2 shows the range of Zn and Fe concentrations measured in the edible parts of several crop species grown under field conditions. Typically, the results were for a collection of different genotypes of the crop, but the environments were different for each crop collection so that the differences in concentration cannot be ascribed solely to plant species. Nevertheless, some generalizations can be made. The seeds of most cereals (maize, rice and wheat) have lower concentrations of Zn and Fe than seeds of legumes (Table 2; White and Broadley, 2005a; Graham et al., 2012). In addition to taxonomic differences that affect the ability of plants to accumulate mineral elements, the concentration in edible plant parts is also influenced by their mobility in the plant. Thus, Zn and Fe are not readily transported in the phloem so that phloem-fed tissues such as tubers, fruits and seeds are frequently poorer sources of Zn and Fe than the leaves; leafy vegetables are particularly rich sources of Zn and Fe (White and Broadley, 2009).

Several workers have studied the heritability of Zn and Fe concentrations in crops as a means to identifying the potential for breeding to alleviate deficiencies in human diets. For example, Blair et al. (2009) used a quantitative trait locus (QTL) approach to identify genomic regions important in Zn and Fe accumulation in common bean (*Phaseolus vulgaris*) as a prelude to developing marker assisted selection in breeding programmes. Similarly, Broadley et al. (2010) identified QTL associated with Zn concentration in shoots of *Brassica oleracea*, but these were generally weak and markedly influenced by growing conditions. Other approaches, such as association mapping, have demonstrated promise for enhancing mineral element concentrations in plants. For example, Velu et al. (2016) found that genomic selection had moderate to high levels of predictability sufficient to support the potential of breeding for enhanced Zn and Fe concentrations in bread wheat germplasm.

Some studies suggest that the concentrations of mineral elements in edible parts have decreased over the last 50 years or so (Davis et al., 2004; Davis, 2009; White and Broadley, 2005b). Such decreases are difficult to substantiate precisely because historical data are confounded by changes in genotype, crop management, environmental factors, analytical method, and yield. However, decreased concentrations of Zn and Fe in wheat, are coincident with the introduction of semi-dwarf cultivars in the UK and not with depletion of Zn and Fe in the soil (Fan et al., 2008).

2.3 Environment and crop management

It has been known for a long time that growing conditions have large effects on both crop yield and the quality of produce available for human consumption. Horticultural production often seeks to minimise these environmental effects to deliver products with defined composition and market acceptance. Chief among these environmental effects (beside soil, described in Section 2.1) are the weather (especially rain), the availability of nutrients, and the incidence of pests and diseases, all of which may also influence Zn and Fe composition of edible plant parts.

Generally, environmental factors that increase plant growth rates reduce the concentrations of mineral elements in plant organs – known as a ‘yield dilution’ effect (Davis et al., 2004; Davis, 2009; White and Broadley, 2009). However, inputs of nutrients to increase yield are not always associated with decreases in mineral element concentrations of edible plant parts. For example, Monasterio and Graham (2000) reported that grain concentrations of Zn and Fe in wheat grown on a nitrogen (N)-deficient soil were increased by 8–10 $\mu g\ g^{-1}$ when N fertilizer was applied. They concluded that although there was a trend for new genotypes of wheat to have lower Zn and Fe concentrations in their grain, this was more than compensated for by the positive effects of N application. White et al. (2009) summarised the literature for potato tubers and highlighted that additions of different fertilizers could affect mineral composition in different ways. Addition of N fertilizers decreased tuber Fe and phosphorus (P) concentrations whereas application of potassium (K) fertilizers often increased tuber Mg, but reduced P and Ca concentrations. Furthermore, when different potato genotypes were grown on the same soil type there was no significant relation between tuber Zn and Fe concentrations and tuber yield.

The effects of organic manures and organic systems of production on Zn and Fe concentrations in edible organs appears to be small. On an Aridisol, Srivastava and Sethi (1981) found that applications of farmyard manure over a period of three years increased the amount of soil Zn that was extractable, with a 0.1% increase of soil organic carbon associated with a 0.2 µg g^{-1} increase of DTPA extractable Zn. However, Warman and Havard (1998) grew potato and sweet corn crops either conventionally or with the same amounts of N and P in composts but found no significant effects on Zn of Fe concentrations in tubers or grain. Ryan et al. (2004) found that on soils with pH about 6, organic management (principally via applications of rock phosphate) reduced wheat grain yields by 17–84% due to P limitations and weeds, but grain Zn concentrations were increased by 25–56% with Fe concentrations not significantly affected. These results demonstrate that there is not a simple relation between plant size (yield) and mineral element concentration, but rather that there are complex interactions between the phytoavailability of different elements and their distribution within plants.

One interaction that is particularly important for Zn nutrition of plants is that with P, because applications of P fertilizers can decrease the bioavailability of Zn in soil (Loneragan et al., 1979). Ryan et al. (2008) found a 33–39% reduction in Zn concentration in wheat grain when only 20 kg P ha^{-1} was applied to a low-P soil; this was a consequence of a dilution of Zn due to increased grain yield (by an average of 78%); Zn uptake *per se* was not reduced. However, there are additional physiological interactions within the plant (see Broadley et al. 2012 for details) that result in Zn deficiency symptoms becoming more severe even though Zn concentration in tissues may not be decreased (Cakmak and Marschner, 1987). Because of the narrow range of Zn concentrations in soil solution, optimizing both P and Zn nutrition remains challenging. Zhang et al. (2015) studied this interaction in a high-yielding winter wheat system on the North China Plain over two growing seasons and found that P application significantly increased grain yield, shoot biomass and P concentration in shoots but decreased Zn concentration. Zhang et al. (2015) concluded that optimal P management in intensive agricultural systems is needed to ensure both high wheat yields and high concentrations of Zn in grain for human nutrition.

The concentration of Fe is typically about three orders of magnitude greater in soil than in plant tissues. Thus, the presence of even small amounts of contaminated soil may greatly affect the concentration of Fe when plant tissues are analysed, and indeed consumed. The contribution of contaminant soil to dietary Fe intakes has been demonstrated in Ethiopia where the staple grain *teff* (*Eragrostis tef*) is threshed by the hooves of oxen (Harvey et al., 2000), and extraneous Fe may be an important determinant of Fe status in Malawi (Gibson et al., 2015). Soil was shown to contribute ~77% and 34% of Fe in leaf and grain samples, respectively, prior to cooking (Joy et al., 2015a; 2016b).

3. Factors affecting Zn and Fe bioavailability

A primary cause of Zn and Fe deficiencies is insufficient dietary supply of the element. However, it is also possible that the quantity of Zn and Fe consumed is sufficient to meet needs, but that absorption is impaired due to physiological reasons or the presence of large quantities of anti-nutrients in the diet.

In humans, various mechanisms support Zn and Fe homeostasis at systemic levels to support essential functions and protect against toxicity despite wide ranges of intakes. Regulation of serum Fe is also an important function of immune response to pathogens. Homeostasis of Zn is maintained through regulating gastrointestinal absorption and endogenous intestinal excretion (August et al., 1989; Ziegler et al., 1989; Lönnerdal, 2000; King et al., 2000). Other homeostatic mechanisms may occur with very low Zn intakes or prolonged, marginally inadequate intakes, including reduced urinary excretion and changes in plasma Zn turnover (King et al., 2000). Homeostasis of Fe is maintained through regulation of gastrointestinal absorption, Fe recycling and release from body Fe stores (Collins et al., 2008).

The bioavailability of Zn and Fe may be affected by other components of the diet. Phytate forms insoluble complexes with Zn and Fe, inhibiting their absorption in the human intestine. Phytate is not easily digestible by monogastric animals, such as humans, due to a lack of endogenous phytase enzymes (Hurrell and Egli, 2010). A phytic acid:Zn molar ratio >15 is typically used to define diets with inadequate bioavailable Zn (Gibson et al., 2010). The Fe in plant tissues is found in non-haem forms and its bioavailability is inhibited by tannins, phytate, polyphenols and other dietary components (McMillian, 2002; Hurrell and Egli, 2010). Conversely, ascorbic acid may increase the bioavailability of Fe by reducing ferric to ferrous forms and by acting as a chelate (Conrad and Schade, 1968; Siegenberg et al., 1991). In meat, ~20–60% of Fe is found in haemoproteins including haemoglobin and myoglobin (Cross et al., 2012) and this form of Fe is significantly more bioavailable.

4. Strategies to increase Zn and Fe concentrations in edible plant parts and in human diets

Policy makers can call upon a range of strategies to address human dietary Zn and Fe deficiencies. There are four main approaches to increase intakes of bioavailable micronutrients: (1) direct supplementation, (2) food fortification at home or processing stage, (3) dietary diversification, and (4) crop biofortification, including breeding and fertilizer-based approaches. Alternative approaches may look to address micronutrient losses or malabsorption, e.g. due to infection or inflammation, but are considered outside the scope of this review of Zn and Fe in food systems. The best strategy will, of course, depend upon the context of the deficiency. For example, a high prevalence of a deficiency in a small population group might be best addressed with a targeted supplementation scheme, whereas wide-scale deficiencies might warrant a national food fortification or crop biofortification scheme. The merits of different approaches can be assessed on the criteria of ‘effectiveness’ and ‘cost-effectiveness’. The Disability Adjusted Life Year (DALY) framework provides a mechanismto test effectiveness measured as the reduction in DALYs lost due to deficiency and cost-effectiveness measured as cost-*per*-DALY saved (Stein, 2014). The relative cost-effectiveness of interventions, specifically to address Zn deficiency, are summarised in Table 3.

4.1 Direct supplementation

Diets can be supplemented with nutrients including Zn and Fe, often in the form of tablets. This approach may be suitable for specific target groups, e.g. Fe supplements for pregnant women. However, supply chain issues and poor compliance often undermine the success of supplementation schemes in addressing widespread, highly prevalent deficiencies (WHO and FAO, 2006). Supplements are not discussed further as they are considered outside the scope of this review of Zn and Fe in food systems.

4.2 Food fortification

Food fortification can occur during meal preparation, such as the addition of Zn and Fe 'sprinkles' to infants' complementary foods or dishes to be consumed by other at-risk populations, e.g. pregnant women, young children, individuals suffering HIV/AIDS etc., in home, school or community-based settings (Zlotkin et al., 2003). Such approaches may be favoured because they typically require minor changes in behaviour or diets. However, certain groups may be excluded. For example, disabled children have been shown to have less access to community-based programmes (Kuper et al., 2015).

Food fortification can also occur at processing stages and may be mandated by government or undertaken by individual processers/manufacturers to add value to their products. Staple foods such as cereal flours, breakfast cereals, cooking oil and salt are typically chosen as food vehicles. Although the conceptual potential of food fortification for addressing Fe and Zn deficiencies is clear, especially where the consumption of processed food is high, such approaches are likely to be less successful in settings where the majority of households depend on subsistence production, including in much of sub-Saharan Africa and South Asia. Typically, the consumption of processed foods is greater in wealthier and urban households while there is greater prevalence of MNDs in poorer and rural households, thus limiting the effectiveness and equitability of schemes (Fiedler et al., 2013). Mandatory schemes also require sufficient government capacity to monitor compliance and to ensure that fortificant levels are sufficient and safe. However, there is also still a general lack of evidence of the effectiveness of large fortification programmes. A large systematic review of the effectiveness of Fe fortification of flour found various case studies in Asia and South America, with limited evidence of a reduction in anaemia prevalence although fortification did consistently reduce the prevalence of low ferritin in women (Pachón et al., 2015).

4.3 Dietary diversification

In many settings, cereals and other starchy staples typically contribute >50% of dietary energy supply with a low (or seasonal) consumption of animal products, fruits and vegetables, particularly among poorer households (Joy et al., 2015b). For example, in Ethiopian food systems, the supply of energy, carbohydrates, protein, Zn, and Fe from cereals was 68, 73, 65, 62 and 74%, respectively (data for 2009; Joy et al., 2014). Dietary diversification can potentially improve intakes of multiple micronutrients. However, greater consumption of fish and other nutrient-dense food products in wealthier households suggests that resource constraints, including household purchasing power, limit dietary diversity and successful interventions that reach the poorest households are likely to require intensive financial support and nutrition education (Tontisirin, 2002).

4.4 Biofortification

In its broadest definition, biofortification is considered to be the production of crops with greater bioavailable concentrations of nutrients in their edible portions (White and Broadley, 2009). This can be achieved by (i) using breeding to develop crops with increased concentrations of the target nutrient, or decreased concentration of molecules that inhibit absorption such as phytate, or (ii) using fertilizers.

4.4.1 Biofortification through crop breeding

Efficacy of breeding programmes require that variation in the Zn and Fe concentration in the edible portions of crops are sufficiently heritable and that increased concentrations do not correlate with decreased yields (Section 2.2). Ultimately, it is also essential that varieties are readily taken up by farmers. The most successful example of breeding crops for increased Zn and Fe concentration, and subsequent take-up by farmers has been through the HarvestPlus programme. Crops released to date include high-Fe bean (*Phaseolus vulgaris*) in Rwanda, high-Fe pearl millet (*Pennisetum glaucum*) in India, and high-Zn wheat in India and Pakistan (http://www.harvestplus.org/ [accessed November 2016]). In 2015, HarvestPlus released 70 t of high-Zn wheat for seed bulking in Pakistan with a target of 2000 t of seed for the 2016/17 cropping season. In India, farmers received 350 t of high-Zn wheat through partner seed companies.

It is likely that crop breeding will be a highly cost-effective solution to addressing Zn and Fe deficiencies in some food systems. However, the efficacy of high-Zn and Fe crops to alleviate dietary Zn and Fe deficiencies can be limited by high concentrations of phytate and polyphenols which co-occur in the edible tissues of crops (Donangelo et al., 2003; Petry et al., 2012). For example, up to 80% of the P content of seeds occurs as mixed salts of phytic acid (myo-inositol hexakisphosphate, IP6; Raboy, 2009), collectively termed phytate. In most countries in sub-Saharan Africa, dietary phytate supplies are likely to exceed 2000 mg *capita*$^{-1}$ d^{-1} and phytate:Zn molar ratios are likely to exceed 15, indicating widespread risk of Zn deficiency (Kumssa et al. 2015a,b; Figure 3). This is likely to remain a major constraint to realising the full potential of crop Zn and Fe biofortification. Crop breeding can also be used to reduce the phytate content of cereals and legumes and thereby complement other biofortification strategies (White and Broadley, 2009, Bouis and Welch, 2010; Joy et al., 2014).

4.4.2 Agronomic Biofortification

Agronomic biofortification involves the application of micronutrient-enriched fertilizers to increase their bioavailable concentrations in the edible portion of crops (Cakmak, 2008; White and Broadley, 2009). Micronutrients can be applied in combination with commonly-used granular fertilizers applied to soils, or as foliar sprays. There are often already considerable reserves of Zn and Fe in soils, albeit of limited phytoavailability. Soil-applied fertilizers are often fixed rapidly within the interlayer spaces of aluminosilicate clays and/or bind to negatively-charged manganese oxides in low pH soils, or fixed rapidly to Ca carbonates in high-pH soils. For soil-applied Zn, it has been shown that applications of organic nutrients such as cattle manure and woodland litter, in combination with NPK and Zn fertilizers, provided additional increase in maize grain Zn concentration beyond that expected from the additional Zn inputs from these sources, presumably through improvements to soil structure (Manzeke et al., 2012; 2014). To minimise the effects of soil fixation, Fe-chelates have been used as soil Fe fertilizers (Shuman, 1998; Rengel et al., 1999). Typically, lower amounts of Zn and Fe fertilizers are needed if foliar forms are used, albeit at a higher cost of application. To reduce these costs, it may be possible to combine foliar applications of Zn and Fe fertilizers with pesticide applications for some crops (Ram et al., 2016; Wang et al., 2016).

Three *ex ante* macro-economic analyses of Zn fertilizer use have recently been published, in sub-Saharan Africa (Joy et al., 2015c), Pakistan (Joy et al., 2016a) and China (Wang et al., 2016). These studies all show that Zn fertilizers are highly likely to be a cost-effective way to increase grain Zn concentration. In Pakistan, increased Zn fertilizer-use scenarios were explored for the major wheat production areas of Punjab and Sindh Provinces. An estimated

245,000 DALYs y^{-1} are lost in Punjab and Sindh due to Zn deficiency. The wheat area currently receiving Zn fertilizers, and actual grain yield responses to Zn of 8 and 14 % in Punjab and Sindh, respectively, were obtained from a survey of >2500 farmers. Increased grain Zn concentrations with foliar and granular forms of Zn fertilization, estimated from previous literature reviews were converted to improved Zn intake in humans and a reduction in DALYs lost. Application of Zn fertilizers to the full area under wheat production in Punjab and Sindh, at current soil:foliar usage ratios (70:30), was projected to halve the prevalence of Zn deficiency, assuming no other changes to food consumption. If each DALY lost to Zn deficiency was monetised at a single multiple of Gross National Income *per capita* on purchasing power parity (GNI_{PPP}), the additive Benefit-Cost Ratio (BCR) is similar to those for yield alone (13 and 18 for Punjab and Sindh, respectively). Monetised health benefits dwarf monetised yield benefits if a 3-fold multiple of GNI_{PPP} is used, in line with WHO approaches (Stein, 2014). In China, it has been estimated that the cost *per* DALY saved could be as little as US$ 41, using foliar-applied Zn on wheat combined with pesticides (Wang et al., 2016). It therefore seems highly likely that there are both market- and subsidy-based incentives, for yield and health returns, respectively, to increase Zn fertilizer-use in many countries.

5. Recent advances in quantifying the movement of Zn and Fe in the food chains

There are many techniques to measure Zn and Fe directly in soil, crop, food and human matrices which can involve both 'wet' and 'dry' chemistry methods (reviewed by van Maarschalkerweerd and Husted, 2015). Wet chemistry methods involve the total or partial dissolution of the matrix under investigation followed by analysis using a variety of spectrometric methods, the most accurate being inductively coupled plasma-mass spectrometry (ICP-MS). For total elemental analysis, dissolution of the matrix under investigation requires a strong oxidising agent, e.g. *aqua regia* or hydrofluoric acid. To quantify plant-available Zn and Fe in soils, weaker extractants are used, depending on soil type. To quantify bioavailable fractions in humans, food matrices can be digested *in vitro* with enzymes prior to spectrometric quantification. Dry methods include near and mid-infrared (NIR and MIR) spectroscopy, chlorophyll fluorescence, and X-ray fluorescence (van Maarschalkerweerd and Husted, 2015), and these are becoming attractive options for multi-scale soil mapping (e.g. Hengl et al., 2015).

Radioactive isotopes of Zn (^{65}Zn) and Fe (^{55}Fe) have long been used as tracers to study the movement of these elements in the food chain (e.g. Hendricks and Dean, 1952). In recent decades, a range of stable isotopes of Zn (e.g. ^{64}Zn, ^{66}Zn, ^{70}Zn) and Fe (^{54}Fe, ^{57}Fe, ^{58}Fe) have become the preferred approach. Thus, it is possible to add stable-isotope enriched forms of Zn and Fe to different parts of the food chain (e.g. fertilizers, crops, foods, people), and to then track the movement of this 'label' based on the altered ratios compared to natural isotopic abundances. It is even now possible to study subtle differences in the fractionation of stable isotopes of Zn and Fe, across physical and biological boundaries, in their naturally-occurring concentration ranges (Caldelas and Weiss 2016). These approaches were pioneered recently by studying Zn in soil/plant systems using ultra-sensitive multicollector ICP-MS (MC-ICP-MS) (Weiss et al., 2005; Arnold et al., 2010; Deng et al., 2014). These techniques have shed new light on mechanisms of Zn uptake and translocation in plants. For example, Weiss et al. (2005) showed that the roots of rice, lettuce, and tomato were enriched in ^{66}Zn ($\Delta^{66}Zn_{root\text{-}solution}$=0.08–0.16‰). This was attributed to (1) preferential adsorption/binding of ^{66}Zn onto root cell walls and (2) uptake of isotopically lighter Zn^{2+} into root cells and translocation to shoots. Arnold et al. (2010) showed subsequently that in soils with low Zn available, ^{66}Zn was enriched in the shoots of a rice variety tolerant to Zn deficiency (RIL46) compared with the soils, and also the shoots of intolerant plants. They attributed this to the uptake of Zn in the form of complexes with deoxymugineic acid (DMA). In a survey involving ten species grown in agricultural soil, the stems, leaves, and grains of strategy I (non-graminaceous species) plants accumulated ^{54}Fe compared to the soil while those of strategy II plants (graminaceous) were isotopically heavier in ^{56}Fe (Guelke-Stelling and von Blanckenburg, 2007).

6. Concluding remarks

This review highlights widespread deficiencies of both Zn and Fe contributing to widespread malnutrition and under-achievement of human potential. The wide-scale surveillance of Zn and Fe deficiency in humans is likely to remain a hugely challenging but essential component of strategies to alleviate ‘hidden hunger’ through policy interventions. Several interventions are possible to reduce the incidence of such deficiencies including increased dietary diversity, food supplementation and biofortification of crops through breeding and more balanced fertilizer practices. Further innovative approaches with stable isotopes of Zn and Fe have considerable potential applications in wider food systems studies to quantify flows within the system and to increase understanding of crucial processes and mechanisms contributing to their bioavailability.

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Table 1 The prevalence of Fe and Zn deficiency and toxicity in USDA soil orders used for agriculture (data from USDA (2006); Fageria et al. (2006))

Soil order	Distinguishing features	Zn	Fe
Alfisols	Moderately weathered soils that have a horizon in which clay-sized particles have accumulated. Common under boreal forests and in the humid semi-tropics. Occupy 9.6% of global land area	Deficiency	Deficiency
Andisols	Formed from volcanic ejections; high in poorly crystalline Fe and Al minerals. Occupy 0.7% of global land area	-	-
Aridisols	Dry soils found commonly in arid regions. Can have a variety of horizons but pale colours are common. Occupy 12.7% of global land area	-	Deficiency
Entisols	These soils have the least development of soil horizons. Pale colours are common. Occupy 16.3% of global land area	Deficiency	Deficiency; toxicity in some river deposits
Histosols	Soils in which either half of the upper 80 cm is organic material or if organic soil material of any thickness rests on rock or fragmented material infilled with organic materials. Common in wetlands. Occupy 1.2% of global land area	-	-
Inceptisols	Similar to an Entisol but have a clear distinction between upper and sub-surface horizons. Common on eroded or young deposits. Occupy 9.9% of global land area	Deficiency	Deficiency; some toxicity in wet areas
Mollisols	Soils with a surface horizon of mineral matter that is finely structured and dark in colour. Common in grasslands. Occupy 6.9% of global land area	Deficiency	Deficiency; some toxicity in wet areas
Oxisols	Very weathered soils with low nutrient availability dominated by Al and Fe oxides; typically red. Common in old landscapes of the	-	Toxicity

	tropics. Occupy 7.6% of global land area		
Spodosols	Typically have a sub-surface horizon that is continuously cemented by some combination of organic matter, Fe or Al. Often with both light and dark horizons, and acidic. Occupy 2.6% of global land area	Deficiency	-
Ultisols	Must have a sub-surface horizon in which clay has accumulated; typically red. Common in subtropical regions. Occupy 8.5% of global land area	Deficiency	Deficiency; some toxicity
Vertisols	Soils with >30% clay to a depth of 50 cm or more. Typically crack in the dry season, self-mulch at the surface and mix soil materials to depth. Often black but can be red. Occupy 2.4% of global land area	-	Deficiency

Table 2 Typical concentrations of Fe and Zn in the dry tissue of edible plant parts

Crop		Fe ($\mu g\ g^{-1}$)	Zn ($\mu g\ g^{-1}$)	Source
Cereals				
Barley	*Hordeum vulgare*	22.6-36.7	20.0-49.7	El-Haramein and Grando (2008)
Maize	*Zea mays*	16.4-22.9 (mean 19.6)	14.7-24.0 (mean 19.8)	Welch and Graham (2004)
Rice	*Oryza sativa*	7.5-24.4	13.5-58.4	Welch and Graham (2004)
Sorghum	*Sorghum bicolor*	11.0-95.4	11.2-75.8	Badigannavar et al. (2016)
Wheat	*Triticum aestivum*	28.8-56.5 (mean 37.2)	25.2 – 53.3 (mean 35.0)	Welch and Graham (2004)
Legumes				
Chickpea	*Cicer arietinum*	24-41	35-60	Zia-ul-Haq et al (2007)
Common bean	*Phaseolus vulgaris*	34-89 (mean 55)	21-54 (mean 35)	Welch and Graham (2004)
Common bean	*Phaseolus vulgaris*	40.0-84.6	17.7-42.4	Blair et al (2009)
Pea	*Pisum sativum*	23-105	16-107	Grusak and Cakmak (2005)
Soybean	*Glycine max*	38.4-90.6 (mean 70.4)	31.5-39.3 (mean 34.1)	Wiersma and Moraghan (2013)
Soybean	*Glycine max*	58-163 (mean 78)	31-48 (mean 40)	Oliveira et al. (2016)
Roots and tubers				
Cassava	*Manihot esculenta*	6-230	3-38	Chávez et al. (2005)
Potato	*Solanum tuberosum*	9-37	8-20	Burgos et al. (2007)
Potato	*Solanum tuberosum*	32-374	7-17	White et al. (2009)
Vegetables				

Spinach	*Spinacia oleracea*	50-139	31-387	Grusak and Cakmak (2005)

Table 3. Estimated cost per DALY saved for a range of food system approaches to alleviate Zn and Fe defieciencies

Intervention	Cost per DALY saved (US $)	Notes	Source
Granular fertilizer	773-6457	sub-Saharan Africa	Joy et al., 2015c
Foliar fertilizer	81-575	sub-Saharan Africa	Joy et al., 2015c
Soil + foliar fertilizer	256-549	Pakistan (Punjab and Sindh Provinces)	Joy et al., 2016a
Foliar (with pesticide)	41-594	China	Wang et al. 2016
Crop breeding	0.7-7.3	India	Stein et al., 2006
Supplements	65-2758	Prophylactic, 1-4 years	Fink & Heitner, 2014
Flour fortification	401	Zambia, vitamin A, Fe, Zn	Fielder et al., 2013

Legends to Figures

Fig. 1. Global supply data and deficiency risks for Zn at a national scale, redrawn from Kumssa et al 2015b. Data are from 2011, except for Democratic Republic of Congo (DRC) which uses data from 2009; Sudan data used for South Sudan.

Fig. 2. Supply data and deficiency risks for Fe in Africa, redrawn from Joy et al. (2014). Data are from 2009.

Fig. 3. Global estimates of phytate : zinc molar ratios in national level food supplies, redrawn from Kumssa et al (2015b). Data are from 2011, except for DRC which is from 2009; Sudan data used for South Sudan.