Review

Not peer-reviewed version

Effectiveness of Agronomic Biofortification Strategy in Fighting against Hidden Hunger

Demeke Teklu , Dawd Gashu * , Edward J.M. Joy , Tilahun Amede , Martin R Broadley

Posted Date: 13 July 2023

doi: 10.20944/preprints202307.0907.v1

Keywords: agronomic biofortification; dietary intake; effectiveness; fertilizers; micronutrient deficiencies doi:10.20944/preprints202307.0907.v1

Review

Effectiveness of Agronomic Biofortification Strategy in Fighting against Hidden Hunger

Demeke Teklu [1], Dawd Gashu [1,*], Edward J. M. Joy [2,3], Tilahun Amede [4] and Martin R. Broadley [3,5]

1 Center for Food Science and Nutrition, Addis Ababa University, Addis Ababa, Ethiopia
2 Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK
3 Rothamsted Research, West Common, Harpenden, Hertfordshire, UK
4 Alliance for a Green Revolution in Africa (AGRA); Sustainably Growing Africa's Food Systems, Nairobi, Kenya
5 School of Biosciences, University of Nottingham, Sutton Bonington Campus, Loughborough, Leicestershire, UK
* Correspondence: dawd.gashu@aau.edu.et

Abstract: Micronutrient deficiencies (MNDs), also known as hidden hunger, affects more than a quarter of the global population. Agronomic biofortification helps to increase concentration of a target mineral in food crops and improve human mineral dietary intake. It is a means of providing nutrient dense foods to a larger population especially among rural resource poor settings, providing that they have access to mineral fertilizers. However, the feasibility of agronomic biofortification in combating hidden hunger depends on several factors besides fertilizer access, including crop type, genotype, climate, soils, and soil mineral interactions. Consideration of its effectiveness to increasing human mineral intakes to daily requirements and improvement to human health and the cost effectiveness the program is also important. In this paper we reviewed available literature regarding the potential effectiveness and challenges of agronomic biofortification to improve crop micronutrient concentrations and reduce hidden hunger.

Keywords: agronomic biofortification; dietary intake; effectiveness; fertilizers; micronutrient deficiencies

Introduction

Micronutrient deficiencies (MNDs), also known as 'hidden hunger', occurs when dietary intakes of vitamins and mineral micronutrients are not adequate for optimal human health. MNDs are a public health concern worldwide and have been the focus of intensive research for many years. It is estimated that more than a quarter of the global population are affected by the deficiency of one or more micronutrients [1]. MNDs are a risk factor for many diseases, contributing to the existing high rates of morbidity and mortality. For example, MNDs can lead to reduced resistance to infections which can cause severe illnesses and developmental challenges, including anaemia, mental retardation, blindness, and spinal and brain birth defects. The most prevalent forms of MNDs are iron (Fe), Iodine (I), zinc (Zn) and vitamin A [2,3]. In terms of the loss of healthy life years, deficiency of these micronutrients are responsible to 1.5-12% of the total disability-adjusted life years (DALYs) lost in sub Saharan Africa (SSA) [4]. It has been estimated that undernutrition and MNDs combined costs the world up to 3.5 trillion USD every year [5]. Research also shows that MNDs among women of reproductive age leads to undesirable birth outcomes to new-borns, together with a higher risk of physical and cognitive impairment, leading to economic stagnation and intergenerational poverty [6].

Understanding the aetiology of MNDs is vital in the process of designing and implementing strategies for the prevention of diet-related diseases [7]. MNDs can be addressed through the implementation of programs. Strategies can include dietary diversification, food fortification and supplementation, and genetic and agronomic biofortification of food crops. Besides improving micronutrient intake, dietary diversification has the potential to improve the intake of many food constituents at the same time. It is typically considered to be most sustainable and preferred strategy as compared to the others. However, availability and affordability of diversified foods are often the barriers in resource poor societies. Changes in dietary patterns through series of nutrition education and behavioural change communication also makes the strategy tough to achieve [2].

Supplementation of high dose vitamins and minerals is a strategy which can quickly improve the micronutrient status of individuals or targeted population [2]. However, supplementation depends on the availability of supplements to the individual at the correct level. In addition, it is not necessarily sustainable because it does not address the root cause of the particular MND, or multiple MNDs. Nutrients from supplements can also show different physiological responses and absorption rate than nutrients in food [2]. The procurement of micronutrients in a relatively expensive pre-packaged form is also a challenge in resource poor communities [2].

Food fortification can have a wider impact and is potentially more sustainable than supplementation. However, fortification is dependent on centrally processed food vehicles and requires the engagement of food processing industries. Furthermore, some communities can be difficult to reach through the implementation of food fortification, especially those which consume locally produced food sources. Sustainability of the mineral supply to food industries, bioavailability of fortified minerals, and possible sensory changes as a result of fortification could be additional challenges to this strategy [2]. Overall, food fortification, supplementation and diet diversification strategies may work well only in urban settings [8,9].

Biofortification is the process of increasing the content and/or bioavailability of essential nutrients in the edible portions of crops during plant growth through genetic and agronomic pathways [10]. Genetic biofortification involves either genetic engineering or classical breeding. Agronomic biofortification is achieved through micronutrient fertilizer application to the soil known as basal application or application directly to the leaves of the crop known as foliar application [11,12]. The focus of this review is agronomic biofortification.

Agronomic biofortification

Agronomic biofortification is the strategy to increase micronutrient content in the edible part of food crops through soil and/or foliar application of mineral fertilizers [11,12]. Agronomic biofortification can enrich crops with multiple elements but most common ones are Fe, Se, Zn, and I. It may be a suitable approach to reach resource poor rural populations, providing they have access to chemical fertilisers. Soil to plant transfer and accumulation of minerals in the edible portion of food crops determine the success of biofortification. In addition, bioavailability of minerals from biofortified crops into the body influences the effectiveness of biofortification programs.

Evidence from agronomic biofortification

Agronomic biofortification has mainly done on staple cereal crops like rice, wheat, and maize, because they dominate diets worldwide and especially among groups vulnerable for MND. Dimpka & Bindraban [13] recommend that micronutrient fertilization should improve yields as well as nutrient content of crops. This is because fertilization programmes in developing countries typically focus on NPK and/or S fertilizers, yet crop yields can still be limited by multiple soil micronutrient deficiencies [14]. Basal application of multiple elements in small amount to the soil has therefore been recommended as a sustainable strategy to increase both yields and nutrient quality of crops [14–16].

Most research on agronomic biofortification has focused on Se and Zn, and these micronutrients are the focus on this review. Selenium is an essential trace element with many roles in human health however has no known biological roles in plant. Blending or granulating Se with macronutrient fertilizers can be highly effective [12]. For example, crops in Finland showed a 15-fold increase in their Se concentration due to application of Se with NPK fertilizers [17]. Similarly, in a recent study from Malawi, an 88-97% increase in the Se concentration of maize grain was observed due to the application of 20 g ha^{-1} Se fertilizer [18]. Grain Se increase about 10 folds as a result of 25 g ha^{-1} Se fertilizer application in Brazil [19]. de Lima Lessa et al., [20] and Chilimba et al., [18] showed an approximately linear increment of grain Se concentration with increased Se fertilizer application in their study conducted in Brazil and Malawi, respectively. Other studies from Kenya and Australia also report a linear increase in grains Se concentration with increase in Se fertilizer application dose [21,22]. There was no evidence that Se fertilizer application had an effect on crop yield in these studies.

In contrast to Se, Zn is an essential plant nutrient and is a yield-limiting factor in many production systems. Cakmak [12] showed that Zn fertilization enhances yield as well as crop Zn concentration. A recent study from Malawi indicates grain yield and Zn concentration increased by 11% and 15%, respectively, as a result of 30 kg ha^{-1} elemental Zn application [23]. A study from India also shows 14.2% yield as well as 51.6% grain Zn increment as a result of application of Zn fertilization [24]. Similarly, Phattarakul et al. [25] reported an increase of 10% crop yield and 66% grain Zn concentration in their experiments conducted in China and India. Another experiment from India indicates 23.5% increase in grain yield as well as linear increase in grain Zn concentration by applying Zn fertilization [26]. Increase in yield up to 33% and grain Zn concentration by 2-fold was observed as a result of application of Zn fertiliser [27]. Narwal et al. [28] also found 5% yield and 5-fold grain Zn concentration enhancement by applying Zn fertiliser. Joy et al. [29] systematically reviewed studies and reported an incremental effect of Zn fertilizer application on Zn concentrations in maize (20%), rice (7%) and wheat (19%) from 10 African countries. That same review indicated that foliar Zn application even resulted more grain Zn concentration in maize (30%), rice (25%), and wheat (63%).

Overwhelming evidence from many countries has shown application of Zn fertilizer on Zn deficient soils improves yield and/or grain Zn concentration [11,30–47]. However, one study in Pakistan reported little or no significant effect of Zn fertilizer application on rice yield or grain Zn concentration [25]. This could be due to the presence of high DTPA extractable Zn (2.2 to 6.5 mg kg^{-1}) in the soil, while, DTPA extractable Zn in soil considered to be critical for Zn deficiency for rice is 0.5– 0.8 mg Zn kg^{-1} [48]. Zia et al. [49] also reported no significant effect on wheat grain Zn concentration as a result of soil Zn application, again which may be linked to soil properties.

There are fewer studies on the effect of Fe agronomic biofortification compared to Se and Zn. For example, a study from India reported a 13 % yield and 2-fold wheat grain Fe concentration increase due to Fe fertilization [28]. In contrast, Zhang et al., [46] and Pahlavan-Rad & Pessarakli, [50] from China and Iran observed 36% and 21% wheat grain Fe concentration increase, respectively; but yield remained unaffected. However, studies from Turkey and Canada on Fe biofortification of barley and wheat, respectively, shows neither yield nor grain Fe concentration improvement [30,51]. This might be due to two reasons. First, graminaceous species release phytosiderophores (Fe-mobilizing compounds) to solubilize and absorb Fe from soils with low Fe concentration, thus, they can maintain adequate plant growth by satisfy Fe demand without requirement for Fe fertilization [52–54]. The other possibility is that when applied to calcareous soils, Fe is rapidly converted into unavailable forms and the poor mobility of Fe in phloem makes Fe fertilization unsuccessful [11,46]. It seems crop response to Fe fertilization is more dependent on the synergetic effect of nitrogen fertilizer [30,55] and details are discussed in the "Application method" section below.

Effectiveness on human nutrition and health

It is suggested that agronomic biofortification potentially improves the daily intake of minerals and helps to alleviate MNDs [18,56]. However, the effectiveness of agronomic biofortification on improvement of human micronutrient status and health is yet less well studied. The only large-scale effectiveness study that links agronomic biofortification to the improvement of human Se status and health is reported from Finland. The average dietary intake of Se was 0.04 mg Se/day/10 MJ when Finland starts agronomic biofortification of Se in 1985. After six years of extensive application, average dietary intake of Se was enhanced to 0.12 mg Se/day. After four years the mean human plasma Se concentration increased from 0.89 μmol/L to 1.50 μmol/L. The authors concluded that the nationwide agronomic biofortification of Se was found to be effective and safe in increasing the Se intake of the whole population [17]. A randomized control feeding trial study in Malawi to test the effectiveness of consumption of Se biofortified maize shows a significant increase in serum Se concentration over two months intervention period from 57.6 (17.0) μg L^{-1} (n=88) to 107.9 (16.4) μg L^{-1} (n=88) among WRA and from 46.4 (14.8) μg L^{-1} (n=86) to 97.1 (16.0) μg L^{-1} (n=88) among SAC without a significant increase among their counter parts who received non-biofortified maize [57].

Lowe et al. [59] also reported an additional daily Zn intake of between 3 and 6 mg for refined and whole grain flour, respectively, as a result of an average flour consumption of 224 g d^{-1} of Zn biofortified wheat flour. After 4 weeks of consumption a significant increase in plasma Zn concentration 41.5 μg L^{-1} was observed. Study investigate the impact of zinc-biofortified wheat flour consumption on zinc status of Pakistani adolescent girls (n = 517) and indicated a moderate increase in intakes of zinc (1.5 mg/day) and iron (1.2 mg/day) but didn't have significant effect on plasma Zn concentration [59]. Study on the efficacy of Fe-biofortified pearl millet in improving attention and memory in Indian adolescents (n = 140) indicates 30% haemoglobin increase due to four months consumption of Fe-biofortified pearl millet (Fe = 86 ppm) as compared to non-biofortified one (Fe = 21–52 ppm) [60].

Ex ante analysis of the potential of Zn-fertilisers to alleviate human dietary Zn deficiency focusing on ten African countries where dietary Zn supply is low shows considerable reduction of DALYs lost due to Zn deficiency from 0.5-18.6% in Burkina Faso, 8.8-53.8% in Ethiopia, 1.2-22.8% in Ghana, 2.9-28.9% in Kenya, 9.5-29.4% in Malawi, up to 22.2% in Mali, 2.2-24.4% in Nigeria, 2.1-32.7% in Senegal, 1.8-25.8% in Tanzania, and 6.6-27.7% in Zambia. The cost per DALY saved ranges from US$ 624 to 5,893 and US$ 46 to 347 due to the granular and foliar fertiliser applications, respectively. The scenario of foliar Zn application is predicted to be cost-effective in all the nations according to WHO standard [29]. Joy et al. [61] also reported that the application of Zn fertilisers to wheat in Punjab and Sindh areas of Pakistan, could increase dietary Zn supply from ~12.6 to 14.6 mg $capita^{-1}$ d^{-1} with the cost per DALY saved of US$ 461–619. Another Ex ante analysis aiming to quantify the potential cost-effectiveness of agronomic biofortification of staple crops with Zn for alleviating Zn deficiency in Ethiopia indicates that biofortification with granular Zn could reduce the burden of Zn deficiency by 29 and 38% and cost US$502 and US$505 to avert each DALY lost under pessimistic and optimistic scenarios, respectively. Foliar Zn application was predicted to cost US$226 and US$ 496 to avert each DALY lost under pessimistic and optimistic scenarios, respectively [62].

Another study that explores the potential of agronomic biofortification of rice with Zn and Fe to alleviate human dietary Zn and Fe deficiency was conducted in four regions of China (North East/NE, Central China/CC, South East/SE, and South West/SW). The result shows considerable (0.92%-28%) reduction of DALYs lost due to Fe deficiency. Similarly, reductions of DALYs lost due to Zn deficiency was in the range of 3%-55%. The cost per DALY saved ranged from US$ 376 to 4,989, US$ 194 to 2,730, and US$ 37.6 to 530 for the single, dual, and triple foliar Fe and Zn application respectively. The combined foliar Fe and Zn spray at CC, SE, and SW found to be cost-effective according to The World Bank standard [63].

Potential challenges to agronomic biofotification

Mineral fertilizer manufacturing

One of the major challenges of agronomic biofortification as a strategy is the manufacturing of fertilizers containing a suitable quantity of mineral micronutrients, especially in many developing countries where most fertilizer is imported. Strategies aiming to reduce MNDs are likely to be more effective where the intervention is case sensitive in local situation [21,64]. To produce a fertilizer blend for a specific location is likely to require the close involvement of public and private fertilizer production and distribution sectors.

Mineral fertilizer application method

Mineral fertilizers can in theory be applied directly on the leaves of crops (foliar application), typically before the flowering stage in cereals, or directly into the soil. The two approaches have their costs and benefits on logistics, economic feasibility, and final grain mineral concentration.

In the short-term, foliar Zn applications are more effective than soil application at increasing grain Zn concentration in wheat [29,49]. For example, foliar Zn application to rice and wheat represents an effective agronomic practice to enhance grain Zn concentration up to 66%, while soil application has no effect [25,32]. Soil applications of Zn are less effective than foliar applications to increase grain Zn concentration. Joy et al. [29] indicated that soil Zn application led to an increase in median Zn concentration in maize, rice and wheat grains of 23%, 7% and 19 %, respectively while foliar application led to increases of 30%, 25% and 63 %, respectively. The authors suggested that Zn fixation in soil makes foliar applications more cost effective than soil applications however the deployment might be more complicated. Botoman et al., [23] reported that many studies on soil Zn applications are underpowered to detect small increases in crop Zn concentration; they reported a 15% increase in maize Zn concentration as a result of 30 kg ha^{-1} elemental Zn application. Study from Zimbabwe aiming at quantifying potential health benefits of alleviating dietary Zn deficiency with soil-applied Zn fertilizer and improved soil fertility management (ISFM) to increase maize grain Zn concentration reported that soil Zn fertilizers is estimated to increase dietary Zn supply from 9.3 to 11.9 mg Zn $capita^{-1}$ day^{-1}, reduce dietary Zn deficiency prevalence from 68% to 31% and saved 6576 DALYs lost per year. On the other hand, soil Zn fertilizer together with ISFM is estimated to increase dietary Zn supply from 9.3 to 12.5 mg Zn $capita^{-1}day^{-1}$, reduce dietary Zn deficiency prevalence from 68 to 25% and saved 7606 DALYs lost per year [65]. Therefore, this report indicates strong effects of other ISFM on effectiveness of soil applied Zn.

One benefit of soil application of Zn fertilizer is its potential residual effects in subsequent cropping seasons. For example, Narwal et al. [28] reported that soil application of Zn to wheat has a significant effect for multiple years and could be more effective and economical for wheat in the long run as compared to foliar application. Another study reported that soil application of 28 kg ha^{-1} $ZnSO_4$ fertilizer was an effective strategy to correcting soil Zn deficiencies for about 7 years [66]. Similarly, Frye et al. [67] reported residual effect ranging from 4 to 5 years as a result of soil application of 34 kg ha^{-1} $ZnSO_4$ fertilizer. Similar researchers reported that soil application of $ZnSO_4$ ranging from 18 to 28 kg h^{-1} is adequate to correct Zn deficiency in plants for four to seven years [68–70]. Therefore, the argument is, if the application of Zn fertilization is planned for more than one season, basal application could be more cost-effective method due to its residual effect whereas foliar application may provide highest grain Zn concentration for a single production season.

Some studies indicate that the combined application of soil and foliar Zn and Fe are more effective than a single soil or foliar application. Results indicates an increase from 25 to 100% grain mineral content due to combined soil and foliar fertilization application [25,27,32,36,44,71]. However, it is very crucial to consider the soil type effect since the combined foliar and basal application method of Zn on wheat is reported to highly depend on the soil type [49].

Ngigi et al. [21] suggested that foliar application of Se was more effective than soil application for maize and beans. However, is important to consider that Se can act both as an antioxidant and a pro-oxidant and in its concentrated form Se is toxic [72], therefore, blended or granular Se applied to soils is the only safe approach for farmers. Ros et al. [73] argue that soil application of Se could result in similar responses to foliar applied Se fertilizer and the effects of soil applied Se lasted longer than foliar applied Se since residual effects were observed of up to 4 years. Chilimba et al. [18] also reported no significant difference between basal and foliar application of Se. They reported for each gram of Se ha^{-1} applied, Se concentration in maize grain increased by 11–29 μg Se kg^{-1} and by 11–33 μg Se kg^{-1} for foliar and basal application, respectively. The only comprehensive nationwide experience which has deployed Se fertilization with basal application, in Finland, reported 15-fold increase in crop Se content [17].

Soil application of Fe usually has no or only limited residual effects as Fe^{2+} is rapidly converted to Fe^{3+} in soils, therefore, foliar application has been considered as the most effective method especially for plants that develop grain months after germination [25,28,46,50]. However, other studies found that neither soil nor foliar application of Fe fertilization remained ineffective methods to enhance wheat, barley and oat Fe concentration [30,51]. In contrast, regular foliar Fe application could result in a potential environment hazard [74]. Manzeke-Kangara et al. [55] and Aciksoz et al.

[30] argued that the efficiency of soil Fe application is more dependent on other factors especially integration of N fertilization and ISFM than the Fe fertilizer application method (foliar or basal).

Studies suggested the potential of a multi-mineral agronomic biofortification strategy to address multiple mineral deficiencies, based on a site-specific biofortification strategy. Mao et al. [64] reported that combined Se, Zn and I fertilizers were as effective as singly-applied fertilizers, when applied to maize, soybean, potato, and cabbage. This suggests multi-mineral agronomic biofortification has the potential to address multiple MNDs simultaneously. However, knowledge about the elemental antagonistic and synergetic interaction effect is very critical. Pahlavan-Rad & Pessarakli, [50] reported 8% and 13% increase of wheat grain Fe and Zn concentration, respectively, as a result of Fe and Zn interaction in their study on combined application of Fe and Zn fertilization. Even though the mechanism of Zn and Fe interaction is not well understood [75], it has been reported that Zn treatment resulted in Fe accumulation in soybean roots and increased root to fruit Fe translocation in tomato plants [76].

Interactions between phosphorus (P) and Zn, and between P and Fe, in soils and plants have long been recognized and well documented. Studies have reported that high soil P levels can negatively affect Zn and Fe uptake by crops by inhibits mycorrhizal colonization of roots and resulting in impaired nutrient uptake [77,78]. Multiple studies reported that the P deficiency in soil results in higher accumulation of Zn whereas Zn deficiency in soil leads to higher accumulation of P in plant [79–81]. Similarly, Fe deficiency stimulates the absorption of P in both roots and shoots [82–85]. Erdal, [86] reported that the soil Zn application enhances wheat grain Zn and at the same time significantly reduces grain P concentration. Another study also reported the association between Zn fertilization and reduction in phytic acid in rice grain ranging from 14.8 to 30.4% [27]. These findings suggest that the agronomic biofortification with Fe and Zn might also be a useful strategy to reduce the antinutritional factors like phytate besides increasing the grain mineral concentration.

The study which employ factorial design involving the application of N up to 60 kg ha^{-1} and Zn up to 10 kg ha^{-1} on pearl millet indicated that the highest grain Zn concentration was observed at the application of 20 kg N ha^{-1} and 5 kg Zn ha^{-1} [87]. Similarly, Zn uptake rate was enhanced 4 folds due to the increased N application [91]. Similarly, multiple studies indicated that N significantly enhances the grain Zn [30,65,88] and Fe [24,30,55,89] concentrations. Nitrogen can increase the activity of transporter proteins and nitrogenous compounds like nicotianamine which helps to maintain Zn root uptake and shoot translocation [89,90] and by increasing activity and abundance of Fe transporter proteins such as yellow stripe 1 (YS1) in root cell membranes [91,92], which positively affects root uptake and shoot transport of Fe. Similarly, Se concentration of rice grains increased 54.6% as a result of combined Se and N application as compared to only Se application as a fertilizer [19]. These findings suggest the application of Zn, Fe and Se as a fertilizer is more effective when they are applied along with N fertilization and ISFM.

Mineral fertilizer application timing

Timing of the mineral application is always critical to its effectiveness in improving grain mineral concentration and/or yield. Foliar Zn applications resulted in a marginal effect on rice grain Zn when applied at stem elongation plus booting stage, but much greater increases of grain Zn concentration were achieved when foliar Zn application was performed when the crop had reached milk stage [25]. Fang et al. [93] suggested the foliar Zn application at heading stage as a best practice to improved Zn concentration of white rice. Sharma et al. [94] and Zeidan et al. [95] argued that application of Zn fertilization on wheat at grain-filling stage is an ideal method to increase grain Zn concentrations. Application of Zn fertilizer at flowering and pod formation stages of chickpea reported to result in the maximum grain Zn concentration [24].

Application of Se fertilizer during the vegetative stage of crops have been observed to enable and stimulate the quick uptake of Se by the crop [72], although the optimal timing will likely be context specific. Wheat grain Se concentration increased more when Se fertilizer was applied at the booting stage as compared to the earlier jointing stage [96]. Deng et al. [97] also reported that Se fertilizer treatment on rice resulted in 2-fold higher grain Se concentration at full heading application

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 July 2023 doi:10.20944/preprints202307.0907.v1

than at late tillering application. Application of Se fertilizer at flowering increased grain Se concentrations more than when Se was applied earlier stages in winter wheat [98]. Galinha et al. [99] reported that Se fertilizer application at booting stage is more effective in enhancing wheat grain Se concentration as compared to grain filling stage.

Maximum Fe concentration was achieved from foliar application during maximum tillering stage [100]. The combination of soil Zn application at sowing and foliar application of Zn along with urea at flowering and pod formation stages can be the best strategy to enhance Zn and Fe content in chickpea grain [24]. Study shows grain-filling stage of wheat might be the best crop development stage to apply Fe fertilization to attain maximum grain Zn concentrations [95]. This finding suggests that it is very critical to understand crops as well as genotypes timing of mineral mobilization, remobilization and translocation with in the plant to achieve the best result with respect to grain mineral concentration.

Cost of mineral fertilizer

Farmers might be willing to pay for the extra cost incurred due to biofortification for minerals that can increase yields effect like Zn. However, covering the cost for minerals that do not increase yield, such as Se, is a challenge for fertilizer policy discussions. Given Se deficiency leads to health complications, it may be appropriate for public health policies to consider whether agronomic biofortification is cost effective. Further, Joy et al. [61] argue that the application of 7.3 kilo ton $ZnSO_4H_2O$ on wheat per year increase yield by ~7.5%, dietary Zn by 15.9% capita^{-1}day^{-1} and reduce the prevalence of Zn deficiency by ~50%. Therefore, consideration of cost effectiveness for minerals like Zn and Fe should not be seen only from the perspective of impact on crop yield, but should also include cost per DALYs saved. Manzeke-Kangara et al., [65] argue that the cost of Zn fertilization in Zimbabwe for maize was not likely to be as useful as investing in nitrogen, due to the yield gaps.

Conclusion

A large number of studies have investigated the impact of agronomic biofortification with Se, Fe and Zn on grain mineral concentration, primarily on staple cereal crops. Most studies suggest the agronomic biofortification is likely to be a feasible strategy to enhance the grain mineral concentration, especially among rural resource poor settings, providing that they have access to mineral fertilization. It is also clear that agronomic biofortification is dependent on many factors like timing and method of mineral application, mineral-mineral and mineral-soil interactions, and adoption of ISFM and other practices. It is therefore important to have the right information on these factors prior to the intervention, in order to make agronomic biofortification successful. Very few studies have tried to investigate the effectiveness of agronomic biofortification on the improvement of human dietary intake as well as health and further studies are required. Reports on effectiveness of agronomic biofortification on indigenous crops like finger millet, teff and amaranth in tropical smallholding farming systems is lacking. However, those crops are highly adaptive to local climate and efficiently withstand biotic and abiotic stresses which is crucial in the effectiveness of agronomic biofortification. In general terms it is possible to conclude that agronomic biofortification can be a supplementary strategy to combat MND among resource poor rural settings where people are dependent on their own produces as a food source, and in which other interventions like supplementation and food fortification may not be suitable.

Author Contributions: Conceptualization—DT, DG, EJMJ, TA, MRB; Original draft preparation—DT; writing—review and editing— DT, DG, EJMJ, TA, MRB. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Bill & Melinda Gates Foundation [INV-009129]. Under the grant conditions of the Foundation, a Creative Commons Attribution 4.0 Generic License has already been assigned to the Author Accepted Manuscript version that might arise from this submission. The funders had no role in the design, execution, analyses or interpretation of the data.

Conflict of Interest: The authors declare no conflict of interest

References

1. World Health Organization (2023). Mineral Nutrition Information System. Available online: https://www.who.int/teams/nutrition-and-food-safety/databases/vitamin-and-mineral-nutrition-information-system (accessed on 21/02/2023).
2. Allen, L.; De Benoist, B.; Dary, O.; Hurrell, R. Guidelines on food fortification with micronutrients. FAO, Rome, Italy, 2006; pp. 11-19.
3. World Health Organization (2021). Micronutrients. Available online: https://www.who.int/health-topics/micronutrients (accessed on 17/11/2022).
4. Muthayya, S.; Rah, J. H.; Sugimoto, J. D.; Roos, F. F.; Kraemer, K.; Black, R. E.. The global hidden hunger indices and maps: an advocacy tool for action. *PloS one* 2013, 8, e67860.
5. Hoddinott, J. The economics of reducing malnutrition in sub-Saharan Africa. *Global Panel on Agriculture and Food Systems for Nutrition Working Paper*, 2016, 21.
6. Gonmei, Z., & Toteja, G. S. Micronutrient status of Indian population. *Indian J Med Res*, 2018, 148, 511-521.
7. Bouis, H.; Boy-Gallego, E.; Meenakshi, J. V. Micronutrient malnutrition: causes, prevalence, consequences, and interventions. *Fertilizing crops to improve human health: a scientific review* 2012, 1, 29-64.
8. Bouis, H. E.; Welch, R. M. Biofortification - a sustainable agricultural strategy for reducing micronutrient malnutrition in the global south. *Crop Sci.* 2010, 50, 20-32.
9. Kuper, H.; Nyapera, V.; Evans, J.; Munyendo, D.; Zuurmond, M.; Frison, S.; Mwenda, V.; Otieno, D.; Kisia, J. Malnutrition and childhood disability in Turkana, Kenya: results from a case-control study. *PLoS One* 2015, 10, e0144926.
10. White, P. J., & Broadley, M. R. (2009). Biofortification of crops with seven mineral elements often lacking in human diets–iron, zinc, copper, calcium, magnesium, selenium and iodine. *New Phytol.* 182, 49-84.
11. Cakmak, I. Enrichment of cereal grains with zinc: agronomic or genetic biofortification?. *Plant Soil* 2008, 302, 1-17.
12. Cakmak, I. Agronomic biofortification (Volume 16). International Food Policy Research Institute, Washington, DC, USA, 2014; pp 56-97.
13. Dimkpa, C. O.; Bindraban, P. S. Fortification of micronutrients for efficient agronomic production: a review. *Agron Sustain Dev.* 2016, 36, 1-27.
14. Vanlauwe, B.; Descheemaeker, K.; Giller, K.E.; Huising, J.; Merckx, R.; Nziguheba, G.; Wendt, J.; Zingore, S. Integrated soil fertility management in sub-Saharan Africa: unravelling local adaptation. *Soil* 2015, 1, 491-508.
15. Voortman, R.L.; Bindraban, P.S. Beyond N and P: Towards a land resource ecology perspective and impactful fertilizer interventions in Sub-Sahara Africa (VFRC Reports; 2015/1). Virtual Fertilizer Development Centre, Washington, DC, USA, 2015; pp 49-67.
16. Manzeke, G. M.; Mapfumo, P.; Mtambanengwe, F.; Chikowo, R.; Tendayi, T.; Cakmak, I. Soil fertility management effects on maize productivity and grain zinc content in smallholder farming systems of Zimbabwe. *Plant Soil* 2012, 361, 57-69.
17. Alfthan, G.; Eurola, M.; Ekholm, P.; Venäläinen, E.R.; Root, T.; Korkalainen, K.; Hartikainen, H.; Salminen, P.; Hietaniemi, V.; Aspila, P.; Aro, A. Effects of nationwide addition of selenium to fertilizers on foods, and animal and human health in Finland: From deficiency to optimal selenium status of the population. *J Trace Elem Med Biol* 2015, 31, 142-147.
18. Chilimba, A. D.; Young, S. D.; Black, C. R.; Meacham, M. C.; Lammel, J.; Broadley, M. R. Agronomic biofortification of maize with selenium (Se) in Malawi. *Field Crops Res.* 2012, 125, 118-128.
19. Reis, H.P.; de Queiroz Barcelos, J.P.; Junior, E.F.; Santos, E.F.; Silva, V.M.; Moraes, M.F.; Putti, F.F.; dos Reis, A.R. Agronomic biofortification of upland rice with selenium and nitrogen and its relation to grain quality. *J. Cereal Sci.* 2018 79, 508-515.
20. de Lima Lessa, J.H.; Araujo, A.M.; Ferreira, L.A.; da Silva Júnior, E.C.; de Oliveira, C.; Corguinha, A.P.; Martins, F.A.; de Carvalho, H.W.; Guilherme, L.R.; Lopes, G. Agronomic biofortification of rice (Oryza sativa L.) with selenium and its effect on element distributions in biofortified grains. *Plant Soil* 2019, 444, 331-342.
21. Ngigi, P.B.; Lachat, C., Masinde, P.W.; Du Laing, G. Agronomic biofortification of maize and beans in Kenya through selenium fertilization. *Environ. Geochem. Health* 2019, 41, 2577-2591.

22. Lyons, G.H., Judson, G.J.; Ortiz-Monasterio, I.; Genc, Y.; Stangoulis, J.C.; Graham, R.D. Selenium in Australia: selenium status and biofortification of wheat for better health. *J Trace Elem Med Biol* 2005, 19, 75-82.
23. Botoman, L.; Chimungu, J.G.; Bailey, E.H.; Munthali, M.W.; Ander, E.L.; Mossa, A.W.; Young, S.D.; Broadley, M.R.; Lark, R.M.; Nalivata, P.C. Agronomic biofortification increases grain zinc concentration of maize grown under contrasting soil types in Malawi. *Plant Direct* 2022, 6, e458.
24. Pal, V.; Singh, G.; Dhaliwal, S.S. Agronomic biofortification of chickpea with zinc and iron through application of zinc and urea. *Commun Soil Sci Plant Anal* 2019, 50, 1864-1877.
25. Phattarakul, N.; Rerkasem, B.; Li L.J.; Wu, L.H.; Zou, C.Q.; Ram, H.; Sohu, V.S.; Kang, B.S.; Surek, H.; Kalayci, M.; Yazici, A. Biofortification of rice grain with zinc through zinc fertilization in different countries. *Plant Soil* 2012, 361, 131-41.
26. Hussain, S.T.; Bhat, M.A.; Hussain, A.; Dar, S.A.; Dar, S.H.; Ganai, M.A.; Telli, N.A. Zinc fertilization for improving grain yield, zinc concentration and uptake in different rice genotypes. *J. pharmacogn. phytochem*. 2018, 7, 287-291.
27. Saha, S.; Chakraborty, M.; Padhan, D.; Saha, B.; Murmu, S.; Batabyal, K.; Seth, A.; Hazra, G.C.; Mandal, B.; Bell, R.W. Agronomic biofortification of zinc in rice: Influence of cultivars and zinc application methods on grain yield and zinc bioavailability. *Field Crops Res*. 2017, 210, 52-60.
28. Narwal, R.P.; Malik, R.S.; Dahiya, R.R. Addressing variations in status of a few nutritionally important micronutrients in wheat crop. In Proceedings of the 19th World Congress of Soil Science, Soil Solutions for a Changing World 2010, 3, pp. 1-6.
29. Joy, E.J.; Stein, A.J.; Young, S.D.; Ander, E.L.; Watts, M.J.; Broadley, M.R. (2015). Zinc-enriched fertilisers as a potential public health intervention in Africa. *Plant Soil* 2015, 389, 1-24.
30. Aciksoz, S.B.; Yazici, A.; Ozturk, L.; Cakmak, I. Biofortification of wheat with iron through soil and foliar application of nitrogen and iron fertilizers. *Plant Soil* 2011, 349, 215-225.
31. Cakmak, I. Enrichment of fertilizers with zinc: An excellent investment for humanity and crop production in India. *J Trace Elem Med Biol* 2009, 23, 281-289.
32. Cakmak, I.; Kalayci, M.; Kaya, Y.; Torun, A.A.; Aydin, N.; Wang, Y.; Arisoy, Z.; Erdem, H.A.; Yazici, A.; Gokmen, O.; Ozturk, L. Biofortification and localization of zinc in wheat grain. *J. Agric. Food Chem.* 2010, 58, 9092-9102.
33. Cakmak, I. HarvestPlus zinc fertilizer project: HarvestZinc. *Better Crops* 2012, 96, 17-19.
34. Haileselassie, B.; Stomph, T.J.; Hoffland, E. Teff (Eragrostis tef) production constraints on Vertisols in Ethiopia: farmers' perceptions and evaluation of low soil zinc as yield-limiting factor. *Soil Sci. Plant Nutr.* 2011, 57, 587-596.
35. Jat, S.L.; Shivay, Y.S.; Parihar, C.M. Dual purpose summer legumes and zinc fertilization for improving productivity and zinc utilization in aromatic hybrid rice (Oryza sativa). *Indian J Agron* 2011 56, 328-333.
36. Kumar, N.; Salakinkop, S.R. Agronomic biofortification of maize with zinc and iron micronutrients. *Mod. Concepts Dev. Agron.* 2018, 1, 1-4.
37. Mishra, J.S.; Hariprasanna, K.; Rao, S.S.; Patil, J.V. Biofortification of post-rainy sorghum (Sorghum bicolor) with zinc and iron through fertilization strategy. *Indian J. Agric. Sci.* 2015, 85, 721-724.
38. Pooniya, V.; Shivay, Y.S. Summer green-manuring crops and zinc fertilization on productivity and economics of basmati rice (Oryza sativa L.). *Arch. Agron. Soil Sci.* 2012, 58, 593-616.
39. Prasad, S.K.; Singh, M.K.; Singh, R.E.N.U. Effect of nitrogen and zinc fertilizer on pearl millet (Pennisetum glaucum) under agri-horti system of eastern Uttar Pradesh. *Significance* 2014, 400, 1-5.
40. Saleem, I.; Javid, S.; Bibi, F.; Ehsan, S.; Niaz, A.; Ahmad, Z.A. Biofortification of maize grain with zinc and iron by using fertilizing approach. *J. Agric. Ecol* 2016, 7, 1-6.
41. Shivay, Y.S.; Kumar, D.; Prasad, R. Effect of zinc-enriched urea on productivity, zinc uptake and efficiency of an aromatic rice–wheat cropping system. *Nutr. Cycling Agroecosyst.* 2008, 81, 229-243.
42. Shivay, Y.S.; Prasad, R.; Rahal, A. Relative efficiency of zinc oxide and zinc sulphate-enriched urea for spring wheat. *Nutr. Cycling Agroecosyst.* 2008, 82, 259-264.
43. Singh, M.V. Micronutrient Deficiencies in Crops and Soils in India. In *Micronutrient deficiencies in global crop production*; Alloway, B.J., Eds.; Springer, Dordrecht, Switzerland, 2008; pp. 93-125.
44. Yilmaz, A.; Ekiz, H.; Torun, B.; Gultekin, I.; Karanlik, S.; Bagci, S.A.; Cakmak, I. Effect of different zinc application methods on grain yield and zinc concentration in wheat cultivars grown on zinc-deficient calcareous soils. *J. Plant Nutr.* 1997, 20, 461-471.

45. Zhang, J.; Wu, L.H.; Wang, M.Y. Iron and zinc biofortification in polished rice and accumulation in rice plant (Oryza sativa L.) as affected by nitrogen fertilization. *Acta Agric. Scand. - B Soil Plant Sci.* 2008, 58, 267-272.
46. Zhang, Y.; Shi, R.; Rezaul, K.M.; Zhang, F.; Zou, C. Iron and zinc concentrations in grain and flour of winter wheat as affected by foliar application. *J. Agric. Food Chem.* 2010, 58, 12268-12274.
47. Zou, C.Q.; Zhang, Y.Q.; Rashid, A.; Ram, H.; Savasli, E.; Arisoy, R.Z.; Ortiz-Monasterio, I.; Simunji, S.; Wang, Z.H.; Sohu, V.; Hassan, M.U. Biofortification of wheat with zinc through zinc fertilization in seven countries. *Plant Soil* 2012, 361, 119-130.
48. Sims, J.T.; Johnson, G.V. Micronutrient soil tests. *Micronutrients in Agriculture* 1991 4, 427-476.
49. Zia, M.H.; Ahmed, I.; Bailey, E.H.; Lark, R.M.; Young, S.D.; Lowe, N.M.; Joy, E.J.; Wilson, L.; Zaman, M.; Broadley, M.R. Site-specific factors influence the field performance of a Zn-biofortified wheat variety. *Front. Sustain. Food Syst.* 2020, 4, 135.
50. Pahlavan-Rad, M.R.; Pessarakli, M. Response of wheat plants to zinc, iron, and manganese applications and uptake and concentration of zinc, iron, and manganese in wheat grains. *Commun Soil Sci Plant Anal* 2009, 40, 1322-1332.
51. Gupta, U. C. Iron status of crops in Prince Edward Island and effect of soil pH on plant iron concentration. *Can. J. Soil Sci.* 1991, 71, 197-202.
52. Marschner, H.; Römheld, V.; Kissel, M. Different strategies in higher plants in mobilization and uptake of iron. *J. Plant Nutr.* 1986, 9, 695-713.
53. Römheld, V. The role of phytosiderophores in acquisition of iron and other micronutrients in graminaceous species: An ecological approach. *Plant Soil* 1991, 130, 127-134.
54. Takagi, S.I.; Kamei, S.; Yu, M.H. Efficiency of iron extraction from soil by mugineic acid family phytosiderophores. *J. Plant Nutr.* 1988, 11, 643-651.
55. Manzeke-Kangara, M.G.; Mtambanengwe, F.; Watts, M.J.; Broadley, M.R.; Lark, R.M.; Mapfumo, P. Can nitrogen fertilizer management improve grain iron concentration of agro-biofortified crops in Zimbabwe?. *Agronomy* 2021, 11, 124.
56. Broadley, M.R.; White, P.J.; Bryson, R.J.; Meacham, M.C.; Bowen, H.C.; Johnson, S.E.; Hawkesford, M.J.; McGrath, S.P.; Zhao, F.J.; Breward, N.; Harriman, M. Biofortification of UK food crops with selenium. *Proc Nutr Soc* 2006, 65, 169-181.
57. Joy, E.J.; Kalimbira, A.A.; Sturgess, J.; Banda, L.; Chiutsi-Phiri, G.; Manase, H.; Gondwe, J.; Ferguson, E.L.; Kalumikiza, Z.; Bailey, E.H.; Young, S.D. Biofortified maize improves selenium status of women and children in a rural community in Malawi: results of the addressing hidden hunger with agronomy randomized controlled trial. *Front. Nutr* 2022, 8, 1189.
58. Lowe, N.M.; Zaman, M.; Khan, M.J.; Brazier, A.K.; Shahzad, B.; Ullah, U.; Khobana, G.; Ohly, H.; Broadley, M.R.; Zia, M.H.; McArdle, H.J. Biofortified wheat increases dietary zinc intake: A randomised controlled efficacy study of zincol-2016 in rural Pakistan. *Front. Nutr* 2022, 8, 1238.
59. Gupta, S.; Zaman, M.; Fatima, S.; Shahzad, B.; Brazier, A.K.; Moran, V.H.; Broadley, M.R.; Zia, M.H.; Bailey, E.H.; Wilson, L.; Khan, I.M. The impact of consuming zinc-biofortified wheat flour on haematological indices of zinc and iron status in adolescent girls in rural pakistan: A cluster-randomised, double-blind, controlled effectiveness trial. *Nutrients* 2022 14, 1657.
60. Scott, S.P.; Murray-Kolb, L.E.; Wenger, M.J.; Udipi, S.A.; Ghugre, P.S.; Boy, E.; Haas, J.D. Cognitive performance in Indian school-going adolescents is positively affected by consumption of iron-biofortified pearl millet: a 6-month randomized controlled efficacy trial. *J Nutr* 2018, 148, 1462-1471.
61. Joy, E.J.; Ahmad, W.; Zia, M.H.; Kumssa, D.B.; Young, S.D.; Ander, E.L.; Watts, M.J.; Stein, A.J.; Broadley, M.R. Valuing increased zinc (Zn) fertiliser-use in Pakistan. *Plant Soil* 2017, 411, 139-150.
62. Abdu, A.O.; De Groote, H.; Joy, E.J.M.; Kumssa, D.B.; Broadley, M.R.; Gashu, D. (2022). Zinc agronomic biofortification of staple crops may be a cost-effective strategy to alleviate zinc deficiency in Ethiopia. *Front. Nutr*, 2022, 9, 1037161.
63. Zhang, C.M.; Zhao, W.Y.; Gao, A.X.; Su, T.T.; Wang, Y.K.; Zhang, Y.Q.; Zhou, X.B.; He, X.H. How could agronomic biofortification of rice be an alternative strategy with higher cost-effectiveness for human iron and zinc deficiency in China?. *Food Nutr Bull* 2018, 39, 246-259.
64. Mao, H.; Wang, J.; Wang, Z.; Zan, Y.; Lyons, G.; Zou, C. Using agronomic biofortification to boost zinc, selenium, and iodine concentrations of food crops grown on the loess plateau in China. *J. Soil Sci. Plant Nutr* 2014, 14, 459-470.

65. Manzeke-Kangara, M.G.; Joy, E.J.; Mtambanengwe, F.; Chopera, P.; Watts, M.J.; Broadley, M.R.; Mapfumo, P. Good soil management can reduce dietary zinc deficiency in Zimbabwe. *CABI Agric Biosci* 2021, 2, 1-5.
66. Robertson, L.S.; Lucas, R.E. Essential micronutrients: zinc [for both plants and animals, fertilizers]. Extension Bulletin-Michigan State University, Cooperative Extension Service: USA, 1976; pp 4-8.
67. Frye, W.W.; Miller, H.F.; Murdock, L.W.; Peaslee, D.E. Zinc Fertilization of Corn in Kentucky. Available online: https://uknowledge.uky.edu/pss_notes/110 (accessed on 22/7/2022).
68. Martens, D.C.; Westermann, D.T. Fertilizer applications for correcting micronutrient deficiencies. *Micronutrients in Agriculture* 1991, 4, 549-592.
69. Singh, M.V.; Abrol, I.P. Direct and residual effect of fertilizer zinc application on the yield and chemical composition of rice-wheat crops in an alkali soil. *Fertilizer Research*, 1985, 8, 179-191.
70. Takkar, P.N.; Walker, C.D. The distribution and correction of zinc deficiency. In *Zinc in Soils and Plants: Proceedings of the International Symposium on 'Zinc in Soils and Plants'*; Robson, A.D. Eds; Springer, Netherlands, 1993; pp. 151-165.
71. Meena, N.; Fathima, P. S. Nutrient uptake of rice as influenced by agronomic biofortification of Zn and Fe under methods of rice cultivation. *Int. J. Pure App. Biosci*, 2017, 5, 456-459.
72. Chauhan, R.; Awasthi, S.; Srivastava, S.; Dwivedi, S.; Pilon-Smits, E.A.; Dhankher, O. P.; Tripathi, R.D. (2019). Understanding selenium metabolism in plants and its role as a beneficial element. *Crit. Rev. Environ. Sci. Technol.* 2019, 49, 1937-1958.
73. Ros, G.H.; Van Rotterdam, A.M.D.; Bussink, D.W.; Bindraban, P.S. Selenium fertilization strategies for bio-fortification of food: an agro-ecosystem approach. *Plant Soil* 2016, 404, 99-112
74. Sperotto, R.A.; Ricachenevsky, F.K.; de Abreu Waldow, V.; Fett, J. P. Iron biofortification in rice: it's a long way to the top. *Plant Sci.* 2012, 190, 24-39.
75. Xie, X.; Hu, W.; Fan, X.; Chen, H.; Tang, M. Interactions between phosphorus, zinc, and iron homeostasis in nonmycorrhizal and mycorrhizal plants. *Front. Plant Sci.* 2019, *10*, 1172.
76. Ibiang, Y.B.; Innami, H.; Sakamoto, K. Effect of excess zinc and arbuscular mycorrhizal fungus on bioproduction and trace element nutrition of tomato (*Solanum lycopersicum* L. cv. Micro-Tom). *Soil Sci. Plant Nutr.* 2018, 3, 342–351.
77. Lynch, J.; Marschner, P.; Rengel, Z. 2012). Effect of internal and external factors on root growth and development. In *Marschner's Mineral Nutrition of Higher Plants*, 3rd ed. Academic Press, Amsterdam, Netherlands, 2012; pp. 331-346.
78. Watts-Williams, S.J.; Patti, A.; Cavagnaro, T.R. Arbuscular mycorrhizas are beneficial under both deficient and toxic soil zinc conditions. *Plant Soil* 2013, 371, 299–312.
79. Bouain, N.; Kisko, M.; Rouached, A.; Dauzat, M.; Lacombe, B.; Belgaroui, N.; Ghnaya, T.; Davidian, J.C.; Berthomieu, P.; Abdelly, C.; Rouached, H. Phosphate/zinc interaction analysis in two lettuce varieties reveals contrasting effects on biomass, photosynthesis, and dynamics of Pi transport. *Biomed Res. Int*. 2014, 2014, 548254.
80. Khan, G.A.; Bouraine, S.; Wege, S.; Li, Y.; de Carbonnel, M.; Berthomieu, P.; Poirier, Y.; Rouached, H. Coordination between zinc and phosphate homeostasis involves the transcription factor PHR1, the phosphate exporter PHO1, and its homologue PHO1; H3 in Arabidopsis. *J. Exp. Bot* 2014, 65, 871-84.
81. Ova, E.A.; Kutman, U.B.; Ozturk, L.; Cakmak, I. High phosphorus supply reduced zinc concentration of wheat in native soil but not in autoclaved soil or nutrient solution. *Plant Soil* 2015, 393, 147-162.
82. Briat, J.F.; Rouached, H.; Tissot, N.; Gaymard, F.; Dubos, C. Integration of P, S, Fe, and Zn nutrition signals in Arabidopsis thaliana: potential involvement of PHOSPHATE STARVATION RESPONSE 1 (PHR1). *Front. Plant Sci.* 2015, 6, 290.
83. Nafady, N.A.; Elgharably, A. Mycorrhizal symbiosis and phosphorus fertilization effects on Zea mays growth and heavy metals uptake. *Int. J. Phytoremediation* 2018, 20, 869-875.
84. Ward, J.T.; Lahner, B.; Yakubova, E.; Salt, D.E.; Raghothama, K.G. The effect of iron on the primary root elongation of Arabidopsis during phosphate deficiency. *Plant Physiol.* 2008, 147, 1181-1191.
85. Zheng, L.; Huang, F.; Narsai, R.; Wu, J.; Giraud, E.; He, F.; Cheng, L.; Wang, F.; Wu, P.; Whelan, J.; Shou, H. Physiological and transcriptome analysis of iron and phosphorus interaction in rice seedlings. *Plant Physiol.* 2009, 151, 262-274.
86. Erdal, I. Effects of various zinc application methods on grain zinc and phytic acid concentration of different cereal species and wheat cultivars grown in Central Anatolia. Doctoral dissertation, Graduate School of Natural and Applied Sciences: Ankara University, Ankara, Turkey, 1998.

87. Prasad, S.K.; Singh, R.; Singh, M.K.; Rakshit, A. Zinc biofortification and agronomic indices of pearl millet under semi-arid region. *Int. J. Agric. Environ. Biotechnol.* 2015, 8, 171-175.
88. Monsant, A.C.; Wang, Y.; Tang, C. Nitrate nutrition enhances zinc hyperaccumulation in Noccaea caerulescens (Prayon). *Plant Soil* 2010, 336, 391-404.
89. Kutman, U.B.; Yildiz, B.; Ozturk, L.; Cakmak, I. Biofortification of durum wheat with zinc through soil and foliar applications of nitrogen. *Cereal Chem.* 2010, 87, 1-9.
90. Erenoglu, E.B.; Kutman, U.B.; Ceylan, Y.; Yildiz, B.; Cakmak, I. Improved nitrogen nutrition enhances root uptake, root-to-shoot translocation and remobilization of zinc (65Zn) in wheat. *New Phytol.* 2011, 189, 438-448.
91. Murata, Y.; Harada, E.; Sugase, K.; Namba, K.; Horikawa, M.; Ma, J.F.; Yamaji, N.; Ueno, D.; Nomoto, K.; Iwashita, T.; Kusumoto, S. Specific transporter for iron (III): Phytosiderophore complex involved in iron uptake by barley roots. *Pure Appl. Chem.* 2008, 80, 2689-2697.
92. Curie, C.; Cassin, G.; Couch, D.; Divol, F.; Higuchi, K.; Le Jean, M.; Misson. J.; Schikora, A.; Czernic, P.; Mari, S. Metal movement within the plant: contribution of nicotianamine and yellow stripe 1-like transporters. *Ann. Bot.* 2009, 103, 1-11.
93. Fang, Y.; Wang, L.; Xin, Z.; Zhao, L.; An, X.; Hu, Q. Effect of foliar application of zinc, selenium, and iron fertilizers on nutrients concentration and yield of rice grain in China. *J. Agric. Food Chem.* 2008, 56, 2079-2084.
94. Sharma, P.; Sheikh, I.; Singh, D.; Kumar, S.; Verma, S.K.; Kumar, R.; Vyas, P.; Dhaliwal, H.S. Uptake, distribution, and remobilization of iron and zinc among various tissues of wheat–Aegilops substitution lines at different growth stages. *Acta Physiol. Plant.* 2017, 39, 1-12.
95. Zeidan, M.S.; Mohamed, M.F.; Hamouda, H.A. Effect of foliar fertilization of Fe, Mn and Zn on wheat yield and quality in low sandy soils fertility. *World J Agric Sci* 2010, 6, 696–699
96. De Vita, P.; Platani, C.; Fragasso, M.; Ficco, D.B.M.; Colecchia, S.A.; Del Nobile, M.A.; Padalino, L.; Di Gennaro, S.; Petrozza, A. Selenium-enriched durum wheat improves the nutritional profile of pasta without altering its organoleptic properties. *Food Chem.* 2017, 214, 374–382.
97. Deng, X.; Liu, K.; Li, M.; Zhang, W.; Zhao, X.; Zhao, Z.; Liu, X. Difference of selenium uptake and distribution in the plant and selenium form in the grains of rice with foliar spray of selenite or selenate at different stages. *Field Crops Res.* 2017, 211, 165-171.
98. Chu, J.; Yao, X.; Yue, Z.; Li, J.; Zhao, J. The effects of selenium on physiological traits, grain selenium content and yield of winter wheat at different development stages. *Biol. Trace Elem. Res*. 2013, 151, 434–440.
99. Galinha, C.; Freitas, M.D.C.; Pacheco, A.M.G.; Coutinho, J.; Macas, B.; Almeida, A.S. Selenium supplementation of Portuguese wheat cultivars through foliar treatment in actual field conditions. *J. Radioanal. Nucl. Chem*. 2013, 297, 227–231
100. Singh, P.; Dhaliwal, S.S.; Sadana, U.S.; Manchanda, J.S. Enrichment of rice cultivars with Fe at different plant growth stages through ferti-fortification. *LS- Int. J. Life Sci.* 2013, 2, 91-96.