



## **SAFE UTILIZATION OF HEAVY METALS-POLLUTED SOILS FOR HEALTHY FOOD PRODUCTION**

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## **ABSTRACT**

The safe utilization of globally decreasing arable land polluted with heavy metals from increasing industrial activities was reviewed. Global industrialization and commercialization has caused soil to be inundated with various deleterious heavy metals with the attendant health implications to the sustainable development of man in the global environment. This paper considered the sources (both anthropogenic and geogenic) of these heavy metals in soil to understand the dynamism of the soil heavy metal pollution. It considers the temperate and tropical soil types and appropriately described the contamination patterns and the relevant soilspecific ways of alleviating and making the limited available land conducive for agriculture. It highlights the equilibrium dynamics between soil (rock) surface, heavy metals lability, soil solution, and the various strategies to sequester the labile heavy metals component of the soil solution which is the cardinal proportion that is bio-available for uptake by plants. It concluded by proffering smart-farming strategies based on the adaption of soil chemistry and soil microbiology principles for farming with particular reference to heavy metals-contaminated soils which can mitigate the accumulation of these heavy metals at toxic levels in the food chain.

**Keywords**: Soil, heavy metals, Bio-accumulation, Labile, Bio-uptake, Smart-farming. **INTRODUCTION** 

Heavy metals are a group of elements whose density is above 5  $g/cm<sup>3</sup>$  (Jannettoa & Cowl, 2023). Examples include Fe, Cu, Cd, Cr, Pb, Ni, V, and Zn. They have the property of existing in more than one oxidation state. Heavy metals exist in every sector of the environment (Briffa *et al*., 2020; Pujari & Kapoor, 2021) – they are present in the air, soil, and aquatic environment as particulate, complex with soil nutrients, and as dissolved ions (*Figure* 1). Each of these three sectors of the environment interacts with the other and as such not mutually exclusive to one another. That notwithstanding, the soil is regarded as the major reservoir of heavy metals (Ahmad *et al*., 2021; Tomaszewska et al., 2013; Wei *et al*., 2019). The metal ions are taken up by plants together with nutrients from where these heavy metals are transported up the food chain and eventually get to man in his diet (Du *et al*., 2019).



*Figure 1: Environment where heavy metals exist.*





Heavy metals are generally not required in our body systems except for a few of them, in particular, Cu, Co, Zn, Fe, Mn, and Mo which are needed in trace quantities for many of the body's biological functions (Mehr *et al.*, 2020; Witkowska *et al*., 2021). Hence, they are often referred to as essential trace nutrients and are obtained from our diets. Others have no recognized biological functions in the body. Excess of heavy metals in the body is deleterious to health and has been linked to many disease conditions including cancer (Witkowska *et al*., 2021). There is therefore the need to carefully regulate and be mindful of the quality and content of what we eat and the environment in which we live and cultivate our food crops, especially vegetables.

### **SOURCES OF HEAVY METALS IN THE ENVIRONMENT**

The presence of heavy metals' in the environment is attributed to two sources: Geogenic and Anthropogenic (Pujari and Kapoor, 2021). The geogenic source is linked to natural phenomena like rock formation (Pujari and Kapoor, 2021). Through the actions of weathering and climate, they are gradually released into the environment; especially soil which is the primary repository where they form complex with soil matter (Masindi *et al*., 2018). The proportion of soil heavy metals content is usually low. This is because the process of weathering is gradual and takes a lot of time in terms of decades and centuries to evolve (Kaninga *et al*., 2019). This process is characteristically slow and hence, the eventual heavy metals' concentration in the soil is substantial. This is further attributed to the fact that these heavy metals are strongly bound to the formative rock types in many cases (Kaninga *et al*., 2019). The more intractable culprit of heavy metals deposition in the soil is the anthropogenic source (C. Li *et al*., 2019). This is directly associated with man and his activities, especially in his unbridled quest for industrialization and commercialization (Das *et al*., 2023) . Prominent among these is his mining activities which directly deposit heavy metals onto the soil in the form of tailings (Kaninga *et al*., 2019). Tailings are waste produced from mining activities on a minefield and are rich in heavy metals. They are responsible for the sharp rise in heavy metals composition of soil within the immediate environment of minefields (Kaninga *et al*., 2019).

Other sources of heavy metals in the environment come from herbicides, pesticides, fertilizers, animal feed, and excretory waste from livestock farming (Ahmed and Al-Baidhani, 2022; Wuana and Okieimen, 2011). These products contain heavy metals stock from the source materials from which they were produced. For example, the potassium, phosphate, and sulphate fertilizer types have heavy metal contents originally from the source rocks from which these inorganic fertilizer types are produced. In contrast to the geogenic source, anthropogenic heavy metals are loosely bound onto soil matter. The tailings-soil mixture is loose (Kaninga *et al*., 2019). Thus, they would be expected to elute easily into the soil. Meanwhile, another source of heavy metals presence in the soil is from septic tank sewage (Oyem and Oyem, 2023). Septic tank bioremediation reactors are a veritable repository of heavy metals (Oyem and Oyem, 2023). Eventually, these heavy metals are also deposited on the soil as a consequence of septic tank maintenance work. Similarly, like the tailings, these loosely held heavy metals elute into the soil and water bodies through erosion. Unlike in geogenic source, the elution process is rapid spanning a matter of days to weeks (Kaninga *et al*., 2019). The United Nations Environment Programme (UNEP) gave the permissible limits for some heavy metals as shown in Table 1:







**Table 1**: Threshold and Permissible limits of heavy metals in soils.

Note: (er) and (hr) represent ecological and health risks respectively associated with higher concentrations above the permissible limit (Adagunodo *et al*., 2018; Tóth *et al*., 2016; UNEP, 2013).

# **SOIL PROPERTIES AND CHARACTERIZATION**

Soil is the surface component of the earth on which human activities are concentrated. It is the land on which man lives, works, and farms. Soil is made up of three types: sandy, clayey, and loamy (humus) soil. Humus soil is rich in silt and organic matter and so more suited for agriculture because of its high nutrient composition (Brussaard and Juma, 1996; Piccolo *et al.*, 2019). It is also intermediate of all the three soil types in its moisture-holding capacity. Soil is made up of inorganic and organic components which are generally classified as soil matter (Sparks, 2019). Heavy metals occur in soil usually in their oxide or hydroxide forms (Li *et al*., 2019). Others are in their sulphides (pyrites) e.g., FeS and CuS (Kaninga *et al*., 2019). The pyrites in the presence of air and water are oxidized to form sulphuric acids which confers acidity to soil solutions.

### **Factors Affecting Heavy Metals Content in Soil**

Several factors affect the distribution of heavy metals in soil. These could be summarized into three broad types: physical, physicochemical, and chemical (Zhang *et al*., 2020). Among the physical factors are the weather and climate of a region from a global perspective. Regions of the world are classified as temperate or tropical according to the degree of sunshine and humidity it experiences. Invariably, these impact the weather of the region. In temperate regions, humidity is higher and temperature conditions are low. Hence, soil organic matter (SOM) and its heavy metal content are somewhat tightly bound together. Elution of heavy metals is slow and concentrations in the soil matter (SM) are relatively high (Krol *et al*., 2020). In other words, the equilibrium dynamics of heavy metals between the soil matter and soil solution is shifted toward the former. Whereas, in the tropical regions where temperature conditions are high and sunshine intensity significant, soil heavy metals dynamics are shifted towards the soil solution as solubility increases.

A crucial physicochemical parameter that affects soil heavy metals content and composition is pH. This is defined as the negative logarithm of the hydrogen ion  $(H<sup>+</sup>)$ concentration. Soil pH ranges from acidic to basic depending on the amount of  $H^+$  or OH $\overline{\phantom{a}}$  ions present in the aqueous medium of a soil sample solution. Hydrogen ion concentration similarly affects the heavy metals dynamics between the soil surface and soil solution (*Figure 2*). Facts





in the literature are in agreement that increasing pH conditions favour the complexation and precipitation of heavy metals in soil (Oyem and Oyem, 2023). While acidic conditions (low pH values) result in the solubilization of heavy metals into their natural stable ionic forms. Soil pH also controls such processes as heavy metal chelate formation and cation exchange capacity (CEC) (Sinegani *et al*., 2015). The chemical nature of the composing soil which is directly connected to its founding rock is associated with the chemical composition of the heavy metals complex formed and by extension their solubility. Chlorides, sulphate, carbonates, and some hydroxyl salts are known to be insoluble or sparingly soluble in aqueous solutions. Therefore, it would be expected that heavy metal salts with these anions are likely to display similar insolubility. The equilibrium dynamics would be anticipated to shift in the direction of the soil surface (solid) in line with complex formation.

#### **Lability and Bioavailability**

Lability is the tendency or ease of a substance to go into a solution (to be solubilized). It depicts mobility – being mobile – especially from a stationary to a mobile phase. In chemistry, when a chemical substance is described as labile, it means it possesses the ability to readily transit from a static to a mobile phase. Soil heavy metals are often described by the term labile, or conversely, as immobile (Wood *et al*., 2016). The heavy metals bound to the solid surface (Rock source) of the soil are immobilized and are unavailable in the soil solution. This means they are complexed and strongly bound by chemical bonding to the rock substrate and are therefore unavailable in the soil solution phase.



Figure 2: Transition of heavy metals between the three soil phases.

The proportion of the eluted soil heavy metals which is available for dissolution in the soil solution is rightly known as the labile heavy metals. This is the portion of the source heavy metals that have been eluted from the rock source (solid phase) and are subsequently available in soil solution for dissolution into the soil solution from where they can be absorbed by plants. The labile phase therefore is the intermediate between the solid rock phase and the soil solution (*Figure 2*). However, it is the proportion (fraction) of the labile heavy metals that is available for uptake by plants (phyto-uptake) that is described as being bioavailable. Bioavailability is the fraction of the solubilized (labile) heavy metal (or nutrient) in soil solution that is available for uptake by plants.

Since plants are the direct beneficiaries of soil nutrients from soil solutions, this bioavailability can be renamed as phyto-availability. At this point, it is important to emphasize that not all the heavy metals in soil solution are automatically bioavailable and eventually end up in plant tissues (Li *et al*., 2022; Xu *et al*., 2022). The pH and chemical properties of soil act to mitigate and determine how much of these heavy metals are available for uptake eventually. Individual heavy metals have their pH-controlled precipitation ranges in aqueous solutions (Oyem and Oyem, 2022). On the other hand, the dissolved anionic components would also affect heavy metals' bioavailability proportion by way of complex formation (Kaninga *et al*., 2019). For example, heavy metal chlorides and especially carbonates would form an insoluble complex in the soil solution phase. They may even form chelates with soil organic matter. In essence, this reduces the labile concentration. Therefore, it must not be expected that all the labile heavy metals would be bioavailable. Specifically speaking, liability is not equivalent or synonymous with bioavailability.





### **Heavy Metal Content and Plant Speciation**

Man-related heavy metal pollution is responsible for the contamination of soil globally (Golia, 2023). Not less than 3500 tailing facilities are available globally, contributing between 5 -7 tonnes of tailings annually according to Kaninga *et al*., (2020). The uptake of heavy metals is not restricted to any particular plant species. For example, irrespective of which plant species are cultivated on a heavy metal dumpsite, there would always be a significant heavy metal uptake relative to the same plant species planted away from the environment of the dumpsite. What will be different is the heavy metals concentrations in the roots, stems, leaves, and fruits. These heavy metal concentration differences may not be unconnected with the complexation potentials of the various plant tissues (Ghuge *et al*., 2023; Xu *et a*l., 2022). Ordinarily, it could be expected that the heavy metals content of tropical plants should be foreseen to be high as a result of an anticipated heavy metal ion lability. However, this does not give a directly correlation high dumpsite heavy metal content and high plant heavy metal content; there are slight fluctuations owing to such intrinsic factors like pH and *in situ* solubility as well as soil anions all contribute to the resulting situation.

#### **HEAVY METALS AND HEALTH IMPLICATIONS**

Heavy metals do not form an essential component of nutrients for the growth and wellbeing of man (Mehr *et al*., 2020). If at all they do, like in the case of Fe, Cu, Mn, and Zn, they occur only in trace quantities in enzymes and co-enzymes in the body where they play vital roles in biological processes (Mitra *et al*., 2022; Witkowska *et al*., 2021). Any dramatic increase in the body's heavy concentration and speciation will result in birth deformations, cancer, and death (Mitra *et al*., 2022; Witkowska *et al*., 2021). Thus, since anthropogenic sources of heavy metals is the major contributor of heavy metals to the environment fuelled by industrial activities, man is at an increased risk of these heavy metals-related health issues. This threatens his sustainable existence and directly antagonizes the United Nations Sustainable Development Goals. Therefore, the issue of heavy metals pollution of soil for agriculture is an important one that requires global attention.

The effects of heavy metals on the human body depend on the level of exposure (Mitra *et al*., 2022; Witkowska *et al*., 2021). Chronic toxicity effects include multiple organ dysfunctions, endocrine disruption, peripheral and central neuropathy, kidney and liver damage, encephalopathy, visual defects, and anemia (Witkowska *et al*., 2021). Their presence in the body causes oxidative stress and the formation of reactive oxygen species (ROS) (Andr *et al*., 2021; Hajam *et al*., 2022).

### **Mitigation against Uptake and Bioavailability of Heavy Metals by Plants**

It is easy to suggest that plants should be planted in naturally free land away from industrial sites, but this does not take into account the fact that available arable land is fast diminishing globally as a consequence of urbanization and industrialization. Previously available acres and hectares of land are fast disappearing; there is competition for urban settlements and industrial areas. A case in study is the Niger Delta area in Nigeria. Other examples are the Amazon area of Brazil and mining fields in Zambia and the Democratic Republic of Congo (Kaninga *et al*., 2019). Consequently, more ingenious and scientific ways of food cultivation are therefore required for the sustainable growth and development of the people globally. Some of the recommended measures to be taken to achieve this are listed below:

- Locating farmlands away from mining sites;
- Soil analysis of proposed land for agriculture;
- Chemical analysis of irrigation water source;





- Screen fertilizers, pesticides, and herbicides for heavy metals content;
- Plant food crops away from the precincts of industrial areas;
- Introduce complexing agents where soil contains highly labile heavy metals;
- Control the bioavailable portion by shifting the equilibrium the labile phase and soil solution towards the rock surface/soil surface;
- Manage the proportion of bioavailable heavy metals in soil solution;
- Control soil pH.

The critical point between bioavailability and uptake of heavy metals is the immobilized fraction, since the lability of heavy metals tends towards its bioavailability. It should therefore make good sense to approach the control of the bioavailable portion by adopting measures that would stymie or reverse the lability of these heavy metals in soil solution thus rendering them immobile. This could be termed as immobilization. Immobilization aptly renders heavy metals unavailable for phyto-uptake. It can take the form of chemical, bioremediation, and phyto-immobilization.

#### **Chemical Immobilization**

This approach uses chemical substances to achieve immobilization of heavy metals in soil *(Li et al.*, 2022). Organic and inorganic chemical complexing agents can be used to immobilize heavy metals in soil. Such chemical entities bind with heavy metals to form insoluble motifs that are immobile and unavailable for uptake by plants. Calcification of soil in a process also known as liming involves the addition of calcium carbonate to soil (Olego *et al*., 2021). This method is also used to increase soil pH. It has been established that acidic conditions mobilize heavy metals into soil solution thereby rendering them bioavailable (Kaninga *et al*., 2019). Thus, liming increases the pH and causes complexation and precipitation of heavy metals.

$$
CaCO3 + H2O \rightarrow Ca2+_{(aq.)} + HCO3-_{(aq.)} + OH-_{(aq.)}
$$
 (1)

$$
M^{n+}{}_{(aq.)} + nOH^{\cdot}{}_{(aq.)} \rightarrow M(OH)_n
$$
 (2)

Equation (1) above is responsible for the increase in the pH of the soil solution; while equation (2) depicts (Kaninga *et al*., 2019) the formation of metal hydroxide precipitates which are immobile and thus not bioavailable. Meanwhile, the presence of  $Ca^{2+}$  ions in solution will cause cation exchange between the  $Ca^{2+}$  ions in soil solution and the soil surface-bound heavy metals (Filipek, 2014). As the soil pH increases and becomes more alkaline, and cation exchange capacity increases. More heavy metals are exchanged into the soil solution and forms precipitates with negatively charged anions and are immobilized. Meanwhile, cadmium is known to possess unique solubility even in high pH conditions, thereby, making  $Cd^{2+}$  more labile *(Filipek, 2014; Olego et al*., 2021). Organic compounds like acetates and others containing sulphur and nitrogen atoms like ethylene diaminetetraacetic acids (EDTA), citric, tartaric, and oxalic acids form chelates with heavy metals (Kaninga *et al*., 2019). This way, they immobilize heavy metals in soil solution and render them unavailable for bio-uptake.

### **Bioremediation**

Bioremediation uses microorganisms to "treat" heavy metals contaminated in soil through natural means (Ahmed and Al-Baidhani, 2022; Wuana and Okieimen, 2011). It is important to know that heavy metals are not biodegradable but they can be changed from one oxidation state to another which may be benign and less available for plant uptake. Soil microbial population is a positive indication of bioactivity (Kaninga *et al*., 2019). Microbes break down soil organic matter to release nutrients for plant growth and development (Eze *et* 





*al*., 2024). This process often terminates at stable products which are adducts of soil heavy metals (Ahmed and Al-Baidhani, 2022; Wuana and Okieimen, 2011).

## **Phytoremediation**

This is a form of bio-remediation which centres on the use of plants for bio-remediation of heavy metals in soil (Microbiome *et al*., 2022). It entails the use of certain plant processes and physical characteristics to achieve remediation. Other forms of plant-assisted phytoimmobilization include phyto-extraction, phyto-stabilization, and phyto-filtration (Microbiome *et al.*, 2022). **Phytoextraction** is concerned with the uptake of heavy metals from soil by plants' roots and their translocation to other parts of the plant. This method is attractive to green environmentalists. Such plant types generally known as hyperaccummulators possess the ability to absorb and accumulate heavy metals in certain tissues of the plants (Skuza *et al*., 2022). These can subsequently be safely disposed of afterward.

**Photostability** describes the process of immobilizing heavy metals in the soil and preventing their migration and bioavailability (Narayanan and Ma, 2023). In this method, plants break the direct transmission of heavy metals by wind and water erosion in the environment (Ahmed and Al-Baidhani, 2022; Wuana and Okieimen, 2011).

Phytofiltration is the use of plants' roots, shoots, and seeds to absorb or adsorb as the case may be, heavy metals from the environment and minimize their mobility (Shi *et al*., 2023).

### **SMART-FARMING PRINCIPLES**

Heavy metals are ubiquitous in the environment. They are certainly not biodegradable but can be transformed from one oxidation state to another which could be probably less toxic. Since the bioavailability of these heavy metals is cardinal for plant uptake and translocation, the smart thing to do is to evolve strategies to mitigate soil heavy metals bioavailability to plants. This way, the total heavy metals concentration in the soil would be more significant in an immobilized form (less labile) and would thereby pose fewer risks to man by transmission through the food chain. Besides adopting the earlier stated strategies of immobilizing these heavy metals, farming can be practiced by consequential approach through effective soil management. Consequential, in essence (Smart) farming requires that farmers first have their farmland analyzed for heavy metals and other pollutants; then, where it is established that the land is polluted by heavy metals, crops like tubers or Indian mustards (*Brassica juncea* L.), maize ( *Zea mays* L.), Willow (*Salix viminalis* L.), and Sunflower (*Helianthus annus* L.) (Ahmed and Al-Baidhani, 2022; Wuana and Okieimen, 2011) which are classified as hyperaccumulators of heavy metals can be temporarily cultivated. Some of these crops have roots that contain chemical by-products from microbial metabolism capable of forming complexes with heavy metals (Bai, 2022). This way, heavy metals are immobilized in their roots (rhizoids and rhizospores).

Another approach is by way of phytoremediation. This is akin to the hyperaccummulation strategy but differs in the sense of having these plants accumulate heavy metals in various plant tissues (Greipsson, 2014; Nedjimi, 2021). For instance, it is a usual practice to cultivate vegetable crops close to water bodies for ease of irrigation. However, vegetables accumulate heavy metals in their leaves which incidentally is the target for consumption by humans. Therefore the smarter thing to do would be to cultivate plant species that possess the ability to accumulate heavy metals in their roots and stems and avoid cultivating leafy vegetables from the onset. Rather, farmers can plant tubers on such soil since tubers are less accumulators of heavy metals (Kaninga *et al*., 2019). Similarly, farmers should avoid planting crops whose fruits are edible and at the same time, are unfortunately, phytoaccumulators of heavy metals on polluted soil (Hussain *et al*., 2021). In another vein, the





shifting cultivation method could be practiced in a way that allows for the cultivation of hyperaccumulating plant species over a farming season or two, to allow for the phytoextraction of heavy metals from such polluted soil. This is of course assuming there are alternate land available for farming. This should reduce the soil's heavy metals load over time. Alternatively, if the earlier-mentioned methods seem impracticable due to unavailable land, controlled liming can be practiced. This would increase soil pH and drive the equilibrium dynamics of heavy metals towards precipitation; thereby increasing the immobilized heavy metals fraction in the soil solution.

Finally, composting as a method of farming looks like a sensible farming option, that is, if you discountenance for a moment the problem of the production of greenhouse gases – (methane). This is because composting introduces the use of manure–organic fertilizer. Manure sure increases the humus content of soil in the farmland and by extrapolation the microbial community. Microbes carrying out their natural degradation activities break down soil organic matter to release available nutrients for uptake by plants at the same time producing molecules like formic, oxalic, citric, acetic, succinic, malic, and lactic acids which form complexes with heavy metals (Adeleke *et al*., 2017). This will reduce the bioavailable proportion of heavy metals available for uptake. Besides, some of these microbes can adapt reasonably to the heavy polluted environment by accumulating heavy metals in their cellular system (Oyem and Oyem, 2022, 2023). Microorganisms like *Bacillus*, *Klebsiella*, *Pseudomonas*, *Enterobacteria*, and *Microbacterium* fall in this category (Oyem *et al*., 2020; Shu and Huang, 2021). Although there is no clear-cut distinction about the difference in the heavy metals content between the inorganic and organic fertilizers, it would appear that organic fertilizers are more advantageous for use as fertilizers in this respect. Apart from the fact that inorganic fertilizers contain heavy metals from the source rock (raw materials), organic fertilizers are not associated with this problem. They rather contain microbial communities that are adapted to heavy metals bioextraction and accumulation as well as the production of metabolic end- and by-products that form immobilizable complexes with heavy metals. Evidence points to the fact that the lability of heavy metals reduces with organic matter content in soil (Angelova *et al*., 2013). Temperate and tropical soil types are reported to characteristically have high and low organic matter content as well as a corresponding high and low cation exchange capacities respectively. This is arising from the difference in their soil properties. Tropical soils are deficient in soil organic matter in contrast to soil from temperate regions (Kaninga *et al*., 2019). Hence, tropical soil have low cation exchange properties and is ineffective at mitigating heavy metals lability *(Kaninga et al*., 2019). Consequently, farmers in tropical regions could be advised on beneficial soil amendment practices like liming, and composting which are proven to reduce heavy metals lability in soil solution (Kaninga *et al*., 2019). This is drawing from the vital role of pH in heavy metals transport in soil solution and retention of heavy metals in soil thereby making them biounavailable for uptake. However, it is understandable that such liming practice increases soil pH (more alkaline) by introducing the OH ions in solution which translates to more negative charge on soil organic matter, and therefore, an eventual increase in cation adsorption with solubilized heavy metals ions (Oyem and Oyem, 2022). The already solubilized cations will also form complexes with aqueous carbonate, sulphates, and chloride anions at these pH conditions. Thus, these heavy metals would be sequestered and kept away from the soil solution and unavailable for bio-uptake by plants. For example, clay-rich soil (kaolinite) could benefit from the liming approach being naturally acidic. Which translates to a reduction in the number of negative sites on the clay molecules because of the interaction with more protons environment. There would be a high competition for the available negative sites on the clayey





soil for bonding between the H<sup>+</sup> ions and the solubilized heavy metals cations in the soil solution.

## **CONCLUSION AND RECOMMENDATION**

It is difficult to extract or remove heavy metals from the environment, especially soil, bearing in mind also that they are not bio-remediable. But it can certainly be by applying the knowledge and principles of soil science to limit their uptake by plants. The advantages of certain species of plants and microbes as well as chemical substances, complexing agents, and pH and apply them as agents of heavy metals sequestration in arable land to make them biounavailable for plant uptake could be taken. There is no gainsaying the fact that for man to ensure his sustainable existence, he must find a way of cultivating healthy food amidst the increasing challenges of industrialization and urbanization viz-à-vis the limited and diminishing farmland globally. This requires not only thinking smartly but also practicing smart-farming principles.

## **CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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