Global Impact of Non-essential Heavy Metal Contaminants in Industrial Cannabis Bioeconomy

Louis Bengyella (bengyellalouis@gmail.com)
Penn State: The Pennsylvania State University
Mohammed Q.O. Ali
University of Hail
Piyali Mukherjee
The University of Burdwan
Dobgima J. Fonmboh
University of Bamenda
John E. Kaminski
Penn State: The Pennsylvania State University

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Abstract

The intrinsic signatures of *Cannabis* species to bioaccumulate non-essential harmful heavy metals (HMs) are substantially determined by their high tolerance, weedy propensities, phenotypic plasticity attributes, and pedoclimatic stress adaptation in an ecological niche. The detection trends of HMs contaminants in cannabis products have reshaped the 2027 forecast and beyond for global cannabis trade valued at $57 billion. Consumer base awareness for the cohort of HMs contaminants viz., lead (Pb), mercury (Hg), arsenic (As), chromium (Cr), cadmium (Cd), and radioactive elements, and the associative dissuading effects significantly impact cannabis bioeconomy. On the premise that fiber hemp (*Cannabis sativa* L.) could be repurposed to diverse non-consumable products, concerns over HMs contamination would not significantly decrease fiber trade, a trend that could impact globally by 2025. The economic trend will depend on acceptable consumer risk, regulatory instruments, and grower's due diligence to implement agronomic best practices to mitigate HMs contamination in marketable cannabis-related products. In this unstructured meta-analysis study based on published literature, the application of *Cannabis* species in HMs phytoremediation, new insights into transportation, distribution, homeostasis of HMs, the impact of HMs on medical cannabis, and cannabis bioeconomic are discussed. Furthermore, a blueprint of agronomic strategies to alleviate HMs uptake by plant is proposed. Considering that one-third of the global arable lands are contaminated with HMs, revamping global production of domesticated cannabis requires a rethinking of agronomic best practices and post-harvest technologies to remove HMs contaminants.

1. Introduction

The 21st century rejuvenated interest in *Cannabis sativa* Linn, known as industrial hemp (when expressing tetrahydrocannabinol (THC) < 0.3%) or marijuana (THC > 0.3%) is predicted to grow to a $57 billion bioeconomy by 2025 (Reporterlinker 2019) even though growing the plant remains largely illegal worldwide. Exposure to air pollutants, domestic effluents, direct root absorption from the earth's crust, cross-contamination during the drying process, and post-processing adulteration with additives to enhance market value are the main sources of non-essential heavy metals (HMs) in cannabis products (Busse et al. 2008). Decision-making in industrial cannabis production must integrate the following: (1) that one-third of the global arable lands are contaminated (Tripathi et al. 2016) with HMs such as lead (Pb), chromium (Cr), arsenic (As), zinc (Zn), cadmium (Cd), copper (Cu), mercury (Hg), and nickel (Ni), (2) that *Cannabis* species have a high propensity to bioaccumulate HMs from their growing medium (Galić et al. 2019; Husain et al. 2019; Linger et al. 2005), and (3) that there is no market value for cannabis product contaminated with Hg, Cd, As, and Pb above the permissible threshold. This cohort of elements (As, Pb, Cd, Hg, Cr) are often with unknown biological purposes and toxic at higher concentrations in plants (Fig. 1; Hajar et al. 2014). While deficiency and excessive uptake of beneficial elements in cannabis is phenotypically expressed, hyperaccumulation of HMs in the roots and above-ground tissues is associated with no detectable morphological changes (Galić et al. 2019; Linger et al. 2005). This suggests that the cultivation of cannabis should be accompanied by HMs monitoring at all growth stages. Interestingly, a comparative gene expression analysis for known HMs transporter in six cannabis genotypes (Fedora 17, Felina 32, Ferimon, Futura 75, Santhica 27, and USO 31 expressing THC < 0.3%) grown on HMs contaminated soil, and two commercial soils (Miracle-Gro Potting Mix® and PRO-MIX Mycorrhizae High Porosity Grower Mix®) did not uncover major significant differential expression for HMs transporter genes such as *phosphate transporter PHT1:1* and *PHT1:4*, *heavy metal transporter 3 (HMA3)* and *vacuolar cation-proton exchanger (CAX)* genes (Husain et al. 2019). From this study, it is tempting to hypothesize that domesticated cannabis genotypes have an evolved pedoclimatic stress adaptation in their ecological niche that enhanced their propensity to function as HMs accumulators by constitutively expressing HMs transporters. In this light, HMs contamination levels in cannabis products are positively correlated to the degree of plant exposure to the metals in a given ecological niche that could severely affect end-users. In this unstructured meta-analysis study based on published literature, the application of *Cannabis* species in HMs phytoremediation (Fig. 1, 2), new insights into the transportation, distribution, and homeostasis of HMs in the cannabis plant (Fig. 3), the impact of HMs on medical cannabis (Fig. 4), and the bioeconomy (Fig. 5) are discussed. We proposed novel blueprint agronomic strategies to mitigate HMs uptake at the farm level. We discuss the direct impact of HMs-contamination in a hypothetical scenario by 2025 should cannabis stakeholders fail to address the issue in marketed cannabis products.

2. Materials And Methods

2.1 Unbiased database search strategy and synthesis

An unstructured review was performed on HMs contamination in cannabis based on available data in published literature (from Medline, Scopus, Google Scholar, and CINAHL) and gray literature in book chapters and unindexed sources, including local and global agencies entries such as the FAO, and WHO in February–May 2021. Keywords for the unstructured search were *"*cannabis HMs contaminant*"*, *"*cannabis trace metals*"*, *"*hemp HMs contaminant*"*, *"*hemp trace metals*"*, "cannabis phytoremediation of HMs", "hemp phytoremediation of HMs", *"*cannabis mercury toxicity", *"*cannabis proteins and chelators*"* and *"*hemp proteins and chelators*"*. Key MeSH terms used included "hemp bioaccumulation of metals*"*, *"*hemp bioaccumulation of HMs*"*, *"*metals in cannabis smoke*"*, *"*metals in hemp smoke*"* and "harmful effects of heavy metals in cannabis and hemp". A refined search was performed using the aforementioned keywords except that the word "metal" was replaced either by arsenic, cadmium, lead, and mercury, and cannabis (or hemp) was replaced by *Cannabis sativa* L. After reading the abstract for relevance, the most appropriate articles were fully reviewed and synthesized. The overarching data set of 25 articles (Additional information S1) were consolidated with the objectives of the study as follows: i) the application of cannabis in phytoremediation, ii) fate of HMs in cannabis, iii) medical impact of HMs in cannabis, iv) agronomic strategies to mitigate HMs uptake, and v) impact of HMs in cannabis bioeconomy.

3. Results And Discussion

3.1 Cannabis mediated phytoremediation of heavy metals contaminants

The average cost of remediating HMs contaminant soil using plants is \$37.7/m^3 (Wan et al. 2016), a lucrative and cheaper option to other remediation technologies. This led to the search for plant species having traits for HMs bioaccumulation and tolerance capabilities. We discussed the inherent features of cannabis to remediates radioactive metals, HMs, the mechanism of transport, and the impact of this bioaccumulation trait in the cannabis business.

3.1.1 There is a high likelihood that radioactive cannabis ends up with consumers: Increasing detection of HMs load in *Cannabis sp*ecies on one hand emerged as the ultimate answer to land remediation efforts owing to its unique morphological characteristics such as stem length, fast growth at the vegetative stage, root area and leaf surface, high photosynthetic activity, fewer nutrient requirements for survival, and shorter life cycle (~ 180 days). *Cannabis species* exhibits a great geo-demographic diversity showing prominence in the wild and cultivated lands (Mura et al. 2004) and on soil pH 5–7 which are excellent attributes for phytoremediation. The use of plants to remove, transfer, stabilize and destroy contaminants in the soil and groundwater (Fig. 1) is called phytoremediation. *Cannabis* species are endowed with stress-tolerant genes which ensure in part their phenotypic and chemotypic plasticity as a mechanism for adaptation in an ecological niche. Cannabis species act as a hyper-accumulator of radioactive elements, toxins, pesticides, and polycyclic aromatic hydrocarbons such as chrysene and benzo[a]pyrene through the fundamental processes of phytoaccumulation, phytovolatilization, and phytodegradation in their leaves (Campbell et al. 2002; Greipsson 2011; Morin-Crini et al. 2018). When cannabis was grown in emulated Chernobyl conditions with radiocesium (Cs-137), radioactivity was detected in all plant tissues as well as retting water, fiber, seed oil, and biofuel which could potentially end up in the hands of consumers (Vandenhove and Van Hees 2005). Akin to the above study, maximum absorption, and distribution of strontium (Sr-90) was 45%, 45%, and 15% in roots, stem, and leaves, respectively (Hoseini et al. 2012). The extensive rhizosphere of cannabis owing to its long root system (~ 2.4 m below the ground level), naturally resistant to pests, thus, obviating the need for pesticides gives cannabis species an extra edge over other plants used for phytoremediation. With this high propensity to bioaccumulate radioactive material from the soil, it is obvious that cannabis used in phytoremediation (or cannabis that is erroneously grown on radioactively contaminated soil) cannot find its place as animal feed, human food, supplements nor textile. Thus, impeding the cannabis bioeconomy. Nonetheless, repurposing radioactive cannabis biomass for electricity and ethanol production could be a possibility to salvage grower's investment, even though poor oxidation stability in biodiesel production has been reported (Li et al. 2010).

3.1.2 Non-essential heavy metal contaminated cannabis ends up with consumers: While selenium (Se) is a beneficial element in plants, excess in human results in nausea, vomiting, nail discoloration, nail brittleness, nail loss, hair loss, fatigue, irritability, and foul breath odor (MacFarquhar et al. 2010). *C. sativa* sequestrates Se mainly in leaf vasculature and seed embryos, with predominant Se speciation in C

– Se – C forms (57 – 75% in leaf and more than 86% in seeds) (Stonehouse et al. 2020). Equally, cannabis seed extracts contain selenomethionine and methyl-selenocysteine which are excellent dietary Se sources, highlighting the implication of cannabis in phytoremediation as well as biofortification. Cannabis species follows a unique genotype-dependent pattern for accumulating non-essential HMs as evident from various studies: For example, when grown in moderate Cd levels of 17 mg/kg soil showed seasonal changes in photosynthetic performance whereas extreme levels above 800 mg/kg caused significant loss of vitality and biomass (Girdhar et al. 2014). The cannabis strain, Zenit (THC < 0.3%) had a high iron accumulation property (1859 mg/kg) compared to other varieties (Mihoc et al. 2012) while another study indicated that the Tygra variety accumulated metals as follows Fe > Mn > Zn > Cr > Cu > Ni > Cd (Zielonka et al. 2020). Interestingly, when these data were correlated with bioavailability in soil, Cd and Cr were accumulated the most while Fe was absorbed and transported to the aboveground tissues to the least and stored particularly in plant inflorescences (Mihoc et al. 2012; Zielonka et al. 2020). Using cannabis genotypes viz., Fedora 17, Fibrol, Futura 75, and Santhica (expressing THC < 0.3%) grown on acid and alkaline soil (Galić et al. 2019) displayed differential accumulation of Pb, Hg, Cd, and As (Fig. 2). From these studies, we postulate that cannabis exhibits bioaccumulation preferences for HMs which is genotype-dependent as well as growing medium pH-dependent (Fig. 3) irrespective of their nutritional requires. This thesis is supported by the apparent constitutive expression of HMs transporters genes viz., *PHT1:1*, *PHT1:4*, *HMA3*, and *CAX* genes (Husain et al. 2019). It is tempting to suggest that cannabis has evolved the HMs accumulation mechanism which is not dependent on the growing medium but the availability of HMs in the medium, type of heavy metal, plant genotype, and medium pH.

3.1.3 Insights into the molecular mechanism of HMs phytoremediation in cannabis: Differential gene expression has been observed during phytoremediation of HMs in cannabis. Metal cation uptake is routed through four steps in the cannabis plant starting from metal uptake through the root system, loading into the xylem vessels, translocation, chelation, and sequestration during trafficking to the phloem. The influx of metal cations into the root occurs via symplastic and apoplastic pathways wherein metal trafficking ZRT-YRT-like proteins, yellow stripe-like transporters (YSL), and natural resistance-associated macrophage proteins (NRAMP) play a critical role (Vert et al. 2002). The HMs loading into xylem vessels occurs via HMA2 and/or HMA4 proteins (Park and Ahn 2017), and sequestration results from the binding of chelating proteins and transporters (Uraguchi et al. 2009). Heavy metals trafficking from xylem to phloem is mediated by *PHT1:1*, *PHT1:4*, and heavy metal ATPase and cation exchanger 2 (Wong and Cobbett 2009). Recently, Ahmad et al. (2016) identified two important HMs responsive genes, *glutathione-disulfidereductase* (*GSR*) and *phospholipase D-α* (*PLDα*) in *C. sativa* that are overregulated by reactive oxygen species (ROS) produced under stress. In another study, an increase in phytochelatin and DNA content was observed when *C. sativa* was subjected to heavy metal stress conditions (Citterio et al. 2003). The cannabis genome consists of 54 GRAS transcription factors (involved in growth and development) that regulate 40 homologous GRAS genes under cadmium stress (Ming-Yin et al. 2020). Thus, we suggest the application of reverse genetics to silence HMs transporters in the developmental process of next-generation domesticated cannabis. This approach has the potential to mitigate the intrinsic phytoremediation propensity, ensure consumer safety, and boost cannabis safety and its bioeconomy.

3.2 The fate of non-essential heavy metals in cannabis trichome, seed, and consumers

Cannabis reproductive structures such as seed and flower are arguably highly valued on the market for phytocannabinoids, flavonoids, terpenoids, rich protein sources, and omega-6 and omega-3 oil-rich in a desirable range between 1:2 and 1:3 (Callaway 2004). Understanding the fate of HMs homeostasis in these reproductive structures is thus critical for consumer safety as more than 500 different compounds characterized in *Cannabis* species are used for several medical interventions (Alves et al. 2020). Plants often counter the destructive effects of HMs by: (i) inactivating the HMs and preventing them from forming a complex with metal chelators such as phytochelatins (PCs) and metallothioneins, and (ii) compartmentation of HMs in idioblasts, vacuoles, and cells walls (Harada et al. 2010; Mazen and El Maghraby 1997). Plants, therefore, rely on low-molecular-weight proteins, the metallochaperones or chelators (such as spermine, spermidine, putrescine, nicotianamine, glutathione, phytochelatins, and other organic acids), metallothioneins, phenylpropanoid compounds (such as flavonoids and anthocyanins), amino acids (proline and histidine), stress-responsive phytohormones and even heat shock proteins (Dalvi and Bhalerao 2013) to effectively counter HMs. Glandular trichomes in cannabis species are microscopic protrusion of variable sizes on flower and leaf surfaces that often-entrap phytocannabinoids (Fig. 3) could potentially play a critical role in HMs homeostasis.

High accumulation of metals in trichomes (Sarret et al. 2006), their role in sequestration and compartmentalization of HMs have been reported (Harada et al. 2010). Long and short glandular trichomes of *Nicotiana tabacum* (tobacco) accumulate and excretes HMs at the tips of trichomes cells (Harada et al. 2010). For instance, Cd and Zn are expelled at the tip of trichomes cells as calcium-crystal precipitates (Sarret et al. 2006). Putative cysteine-rich pathogenesis resistance proteins (PR) such as osmotin, thaumatin-like proteins, non-specific lipid transfer proteins (nsLTPs), and metallocarboxypeptidase inhibitors in tobacco trichomes were shown to be sequestrating agents of Cd (Harada et al. 2010). Since trichome apparently is one of the exit points of HMs in the narcotic tobacco plant, it could be interesting for cannabis breeders to incorporate trichome HMs metabolism in their breeding program as trichome quality is a determining factor in the market value of cannabis flower. Akin, this creates an avenue to investigate which of the HMs exit the cannabis plant at the tip of trichome cells.

On the other hand, cannabis seed is valuable on the essential oil market. Contamination of seeds with Cd at 1.3–4.0 ppm (Mihoc et al. 2012) and Cr at 15.2–15.25 ppm (Eboh and Thomas 2005) have been reported, making it possible to postulate that vertical transmission and storage of HMs in cannabis reproductive tissues is apparent. A total of 181 proteins have been identified in cannabis seed (Aiello et al. 2017). Two major storage cannabis seed proteins identified are the legumin-type globulin edestin and globular-type albumin constituting 67–75% and 25–37% of total cannabis protein, respectively (Aiello et al. 2017). These proteins are void of enzymatic activities but have high Zinc–metal binding capacity

(Wang and Xiong 2018) an indication that they serve as zinc sequestration and storage-hub in the reproductive tissues of cannabis. While these two seed storage proteins have not been reported in trichomes, one might be tempted to ask whether cannabis seed storage proteins play a role in entrapping and sequestering non-essential Hg, Cr, Cd, As, and Pd akin to Zn? It could be interesting to investigate the interactions of HMs with metallothionein and phytochelatins at the trichome level to gain insights into their potential to form complexes that could be transferred to end-users of cannabis products.

3.3 Medical implications of regulated heavy metals in cannabis

The current trends at which non-essential HMs is been detected in cannabis products (Saltiola 2020; Wakshlag et al. 2020) had failed to dissuade human interest in the crop fibers and therapeutic uses despite concerns of accumulation in the body of end-users. Cannabis, like other crops, richly contains essential heavy metals such as iron, cobalt, copper, manganese, molybdenum, and zinc which are required for biochemical and physiological processes (Briffa et al. 2020) but toxic at higher concentrations (Singh et al. 2011). Evidence-based concerns over Cd, Pb, Hg, As, and Cr contaminations encountered during the cultivation and post-harvest processing (Gauvin et al. 2018) have emerged as a major drawback to the global use of cannabis species in medicine. Also, premeditated adulteration of cannabis products for market profit as in the case of Leipzig, Germany that resulted in acute poisoning of 150 people (Busse et al. 2008) is an inhibitive factor for medical utilization in several countries. The high amount of HMs contamination in cannabis can cause various health problems because these elements are rarely metabolized, thus, accumulates in specific areas of the human body (Fig. 4).

The most common mechanism of HMs toxicity in the human body is via the production of reactive oxygen species (ROS) and free radicals which damage either enzymes, proteins, lipids, and nucleic acids resulting in carcinogenesis and neurotoxicity (Engwa et al. 2019). Cannabis consumed in combustive form represents the greatest danger to human health. Using tobacco, it was shown that less than one percent of Hg remains in the ash after combustion (“smoking”), while elemental mercury (Hg°) is carried in the smoke (Andren and Harriss 1971). Furthermore, smoking any form of contaminated cannabis introduces the whole mercury load in the biomass into the lungs where 75–85% of Hg is absorbed and retained within 40 hours (Siegel et al. 1988), a scenario more likely for Cd, Cr, As, and Pb. Interestingly, most smoke from unfiltered cannabis products is rich in aluminum, Cr, Cu, Pb, and Hg (Gauvin et al. 2018). Furthermore, analysis of HMs in the smoke of cannabis (THC > 0.3%, marijuana) revealed the presence of selenium (Se), Hg, Cd, Pb, Cr, Ni, and As (Moir et al. 2008).

A recent study showed that NatureDry© lyophilized FINOLA® hemp juice grown on fine-sandy moraine soil in central Finland contained minute concentrations of Cd, Hg, and Pb (Saltiola 2020), but, sufficient to trigger a long-term chronic effect. Chronic toxicity effects of HMs often damage and alter the functioning of organs such as the brain, kidney, lungs, liver, and blood, which lead to muscular, physical, and neurological disorders associated with Parkinson disease, Alzheimer disease, multiple sclerosis, muscular dystrophy and cancer (Engwa et al. 2019; Jaishankar et al. 2014). In essence, chromium III (Cr^{3+}) and inorganic arsenic (As^{3+}, arsenite; As^{5+}, Arsenate) abundantly generates different free radicals including superoxide ($O_2^{\bullet-}$), nitric oxide ($NO^{\bullet}$), hydrogen peroxide (H_2O_2), peroxyl radical ($ROO^{\bullet}$) and dimethylarsinic peroxyl radicals ($(CH_3)_2AsOO^{\bullet}$) (Liu and Shi 2001; Pi et al. 2003; Rin et al. 1995) responsible for oxidative stress and cause cellular damages *in vivo* (Fig. 1). Non-essential cadmium (Cd^{2+} ions) promotes apoptosis, DNA methylation, and DNA damage (Engwa et al. 2019). Besides HMs ROS-mediated harmful effects, it was shown that the smoke from cannabis contains HCN, NO, NOx, and polycyclic aromatic hydrocarbons, which are toxic to human health more than tobacco (Moir et al. 2008). Lead (Pb) causes neurological toxicity in three stages *viz.*, (i) inhibits N-methyl-d-aspartate receptor, (ii) block the neuronal voltage-gated calcium (Ca^{2+}) channels, and (iii) reduce the expression of brain-derived neurotrophic factor (Neal and Guilarte 2013). Hence, consumption of HMs contaminated cannabis above permissible levels might lead to severe medical conditions in the long term (Fig. 4). Thus, this could dissuade new medical and recreational consumers of cannabis products impeding the cannabis bioeconomy worldwide from achieving the predicted $57 billion trade value by 2027.

3.4 Blueprint agronomic strategies to mitigate non-essential HMs in cannabis product

Atomic absorption spectrometer and inductively coupled plasma mass spectrometry (ICP−MS) have emerged as the method of choice to detect and quantify HMs in cannabis products in the United States. With the prevailing evidence that cannabis species have the propensity to uptake HMs from any growing medium, efforts to shield consumers from HMs should occur principally at the farm level through best agronomic practices. This is because one-third of global arable lands are contaminated with non-essential HMs (Tripathi et al. 2016). Agronomic practices must improve and adopt diverse strategies that mitigate bioaccumulation of HMs in cannabis. Important agronomic practices are herein discussed:

3.4.1 Primary agronomic best practices base on site selection: Lowering post-harvest losses should be prioritized by cannabis growers since HMs awareness is growing within the consumer base. For instance, the Business and Professions Code (BPC 2019) of the State of California, USA have set limits for Cd, Pb, Ar, and Hg per gram of inhalable cannabis products (ICP) and other cannabis products (OCP) as follows: Cd (0.2 μg/g ICP and 0.5 μg/g OCP), Pb (0.5 μg/g ICP and 0.5 μg/g OCP), Ar (0.2 μg/g ICP and 1.5 μg/g OCP) and Hg (0.1 μg/g ICP and 3.0 μg/g OCP). These values suggest that outdoor growers must perform their due diligence in choosing their outdoor cultivation sites. The following blueprints can be adopted to avoid post-harvest losses caused by HMs:

i) Select cultivation sites away from industrialized zones, zones with mining activities), zones with contemporary volcanic activities (Siegel et al., 1988), and consult the soil conservation service for HMs data.

ii) Perform air quality test for HMs emanating from industrially polluted air-To this effect, analyses on invasive weeds growing on the selected site could provide clues for soil quality and HMs content.

iii) Perform irrigation water test, soil test, and soil pH test before and during cannabis Soil pH is very critical for HMs bioaccumulation in cannabis At pH > 7.0 bioaccumulation of HMs from the soil in decreasing order is Cu > Cr > Cd > Mo > Hg > Zn > Ni > Co > As > Pb while at pH < 7.0 the pattern is as follows Zn > Cd > Cr > Ni > Hg > Cu > Mo > As > Co > Pb (Galić et al. 2019). By exploring the data in Galić et al. (2019) we found that mercury accumulates more in the leaf (~ 0.015 ppm) and roots (0.038 ppm) of cannabis in acid soil more than in basic soil (Fig. 2).

iv) Monitor the crop at all development stages, notably at the vegetative phase as cannabis draws a large number of minerals to maintain its fast growth rate.

v) Use only fertilizers, grow selected variety with certified seeds, and use only pesticides with a certificate of analysis stating HMs-free.

3.4.2 Advanced agronomic practice-based on-site management: Laboratory research must be integrated with agronomic practices to deliver instruments that can mitigate uptake of HMs. We proposed the following blueprints:

i) Avoid the use of arbuscular mycorrhizae (AM): Previous studies show that AM enhanced the translocation of Cd, Ni, and Cr (VI) from the root to the shoot of *C. sativa* (Citterio et al. 2005). In cultivation practice where *C. sativa* was fertilized with sewage sludge and phosphogypsum, AM was detected (Zielonka et al. 2020). Akin, the interaction of AM and sunflower (*Helianthus annuus* L.) on heavily contaminated soil was shown to significantly promote shoot phytoextraction of Cd, Pb, Cu, Cr, Zn, and Ni (Zhang et al. 2018). Previously, it was shown that the interactions of AM with plant *Lygeum spartum* and *Anthyllis cytisoides* in the presence of either Pb or Zn stimulated the plant growth in direct proportion to the amount of Pb and Zn added to the soil (Díaz et al. 1996). Taken together with this evidence, it is tempting to suggest that cultivation practices of cannabis for grains and cannabinoids should completely avoid the use of AM.

ii) Avoid the use of Achromobacter: Another trigger for increased HMs uptake in cannabis is associated with *Achromobacter sp*. strain AO22 that had been shown to concomitantly enhanced plant growth accumulation of Cd and Zn in fiber crop plant; sunn hemp (*Crotolaria juncea*) (Stanbrough et al. 2013).

iii) Field monitoring: Farmers must perform a robust soil test after heavy torrential rainfall and This is applicable for farming sites located in areas where snowfall and snow melting activities are common.

iv) pH modification of chemigation, and irrigation water: Cannabis is acidophilic (~ 5.56–7.and the uptake of Pb and Hg in plants occurred at pH below 6.Thus, ensuring pH stays above 6.5 in all chemigation practices can mitigate Pb and Hg absorption from the soil (Azevedo and Rodriguez, 2012). This approach heavily depends on the soil test results for HMs. Unlike Pb and Hg, the highest absorption of Cd in perennial ryegrass (*Lolium perenne* L), Cocksfoot (*Dactylis glomerata* L), lettuce (*Lactuca sativa* L), and watercress (*Rorippa nasturstium-aquaticum* L) was observed at pH 5.0–7.0 (Hatch et al. 1988).

Thus, while pH modification might confer HMs mitigation control, the uniqueness of cannabis biology requires similar experiments to be performed.

v) Coupling ozone water treatment with water softener system: Ozone water treatment could help oxidized HMs in irrigation water and coupling ozonized system with a water softener system, could help remove oxidized forms of the HMs before they are delivered to the cannabis crops.

3.5 Impact of heavy metals contamination on cannabis bioeconomic by 2025

Relaxation on regulatory laws governing industrial cannabis production had generated fortunes to many industrialized nations, notably the United States. For instance, the industrial hemp- cannabidiol (CBD) market contributed $4 billion to the United States economy in 2020, forecasted and valued at $16 billion by 2025 (Kristen 2019) while at the same period the entire hemp industry is expected to generate $26.6 billion (Reporterlinker 2019).

Since 21st -century consumers generally exhibit high demand for quality and health benefits for products they buy (Sajdakowska et al. 2018), we took the case of the United States of America to illustrate how increasing consumer awareness of HMs contamination in hemp could affect total estimated retail revenue and found divergent pattern as follows. From Hemp Industrial Daily (HID) data (Fig. 5a), we used the yearly prediction upper and lower limits of estimated retail sales to generate average estimated revenue and differential growth (ΔG) as follows:

$$\Delta \mathrm{G} = L + \frac{(U - L)}{N}$$

Where ΔG – is differential growth over 5 years based on HMs dissuading impact on consumers

U – upper estimate retail sales

L – lower estimate retail sales and N – number of years covered by the prediction

Based on the average estimated retails (Fig. 5b) assuming that consumers are less aware and concern about HMs contaminated CBD-related products, an exponential economic return valued at about $10.3 billion by 2024 is expected, a margin decreased of $1.5 billion than predicted by Hemp Industrial Daily. This economic boom is only possible should the hemp industry retain the current consumer base, leverage consumer enthusiasm and raise awareness for new beneficial CBD-related products, and prioritized consumer health within 2021 to 2025. By considering the differential growth (ΔG) in a scenario where the consumer-base become aware of HMs contaminants, develops resentment and fewer new consumer are attracted, the CBD total retail sales will slump to about $9.7 billion (Fig. 5b). This represents a margin decrease of $2.1 billion less than predicted by Hemp Industrial Daily at $11.8 billion. Although the cannabis CBD market had developed faster than the fiber market, consumer awareness for

HMs contamination could trigger a dramatic repurposing of HMs contaminated crop for fibers-related products at the farm level, causing a paradigm-shift in fiber production.

Interestingly, it has been shown that HMs pollution in industrial hemp does not have any significant influence on fiber properties such as fineness and tensile strength of single fiber bundles (Linger et al. 2005). Based on mean values for HMs in fibers (Pb = 2.8 ppm and Cd = 0.8 ppm) and in seeds (Pb = 0.8 ppm and Pb = 1.8 ppm) from Linger et al. (2005), and mindful of the Öko-Tex-Initiative-2000 for textile contamination set for Pb (0.2–1.0 ppm), Ni (1.0–4.0 ppm) and Cd (0.1 ppm) will disqualify the use of most industrial hemp fibers produced in the USA to be used in the European Union textile industry. This economic upheaval can be avoided by applying the proposed agronomic blueprints and developing agronomic technologies such as breeding for heavy metal sensitive cannabis genotypes.

Based on these factors: (1) consumer-base awareness for HMs contaminated cannabis, and (2) development of hempcrete and textile derivatives market, we forecast that fiber retail trade will soar over the cannabis oil market by 2023, and significantly contribute towards the total estimated retail sales (Fig. 5C). This scenario will force consumable CBD-related products to enter a stationary phase in economic return while the global cannabis bioeconomy will continuously grow as multiple governments slowly relax production laws on cannabis species.

For the hemp industry to experience a global boom, information gaps between cannabis research, production, and the consumer-base must be bridged by implementing some of these blueprints:

i. New hemp consumers should be attracted via reliable, transparent, and regulated marketing.
ii. Efforts towards building consumer confidence should be intensified by testing, certifying, labeling, and branding cannabis products as “*heavy metal-free*” specifying the actual concentration of HMs such as As, Pb, Hg, Cr, and Cd against their permissible levels. Importantly, studies have shown that consumers often rely on label displayed ingredients, expiration date, health information, and environmental attributes in the purchasing-process (Prentice et al. 2019).
iii. Hemp education should be intensified at all levels spear-headed by top-tier universities.
iv. Heavy metal monitoring at the field level and appropriate repurposing of hemp crop should be promoted over the 0.3% THC threshold values which define whether a cannabis plant should be classified as hemp or marijuana.
v. New farmland in developing countries having low-level environmental pollution could be used for cannabis-essential oil production or invest in hydroponics cropping system.
vi. The cannabis industry must invest in research that seeks to understand consumer perception of a quality product.
vii. Promote hemp research on heavy metal metabolism and breed for the following cannabis strains: a) heavy metal sensitive, b) heavy metal tolerant, and c) heavy metal resistant varieties and enable knowledge transfer to growers.

Conclusion Of The Matter And Future Directions

The intrinsic signatures of *Cannabis* species to bioaccumulate heavy metals (HMs) from the earth's crust are substantially determined by their high tolerance, weedy propensities, phenotypic plasticity, and adaptation in an ecological niche. Although HMs accumulation in cannabis seems to be useful for phytoremediation, it does pose a threat from the consumer-base. Application of agronomic best practices such as the choice of cannabis seed varieties, abiding by the industry standards, and choice farmland can critically mitigate HMs contamination. The choice for farmland should include soil pH, nutrient levels, pesticides, microbial communities especially *A. mycorrhizae*, and heavy metal content. It would be in the interest of growers to avoid fire outbreaks near their farms since their crops could absorb chemicals from the fire. At the retail level, growers must disclose information on the soil type based on data from soil conservation services and such transparency should be made available to consumers when requested. Cannabis plants grown for land remediation should not be repurposed for human and animal consumption which might dissuade consumers in the long-term and trigger a slump in the global cannabis trade.

Declarations

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Competing Interests:

The authors have declared that no competing interests exist.

Author contributions:

Conceptualization, LB.; Methodology, LB.; formal analysis, LB.; writing–original draft preparation, LB.; MQOA, PM, and DFJ.; writing – review and editing, LB., and JEK.; supervision, LB and JEK. All authors have read and agree to the published version of the manuscript.

Data Availability:

All data supporting the findings of this study are available within the article.

Ethics Approval:

No ethical approval was required except authors were above 21 years in handling the cannabis plant.

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Additional Information

Additional Information S1 is not available with this version.

Figures

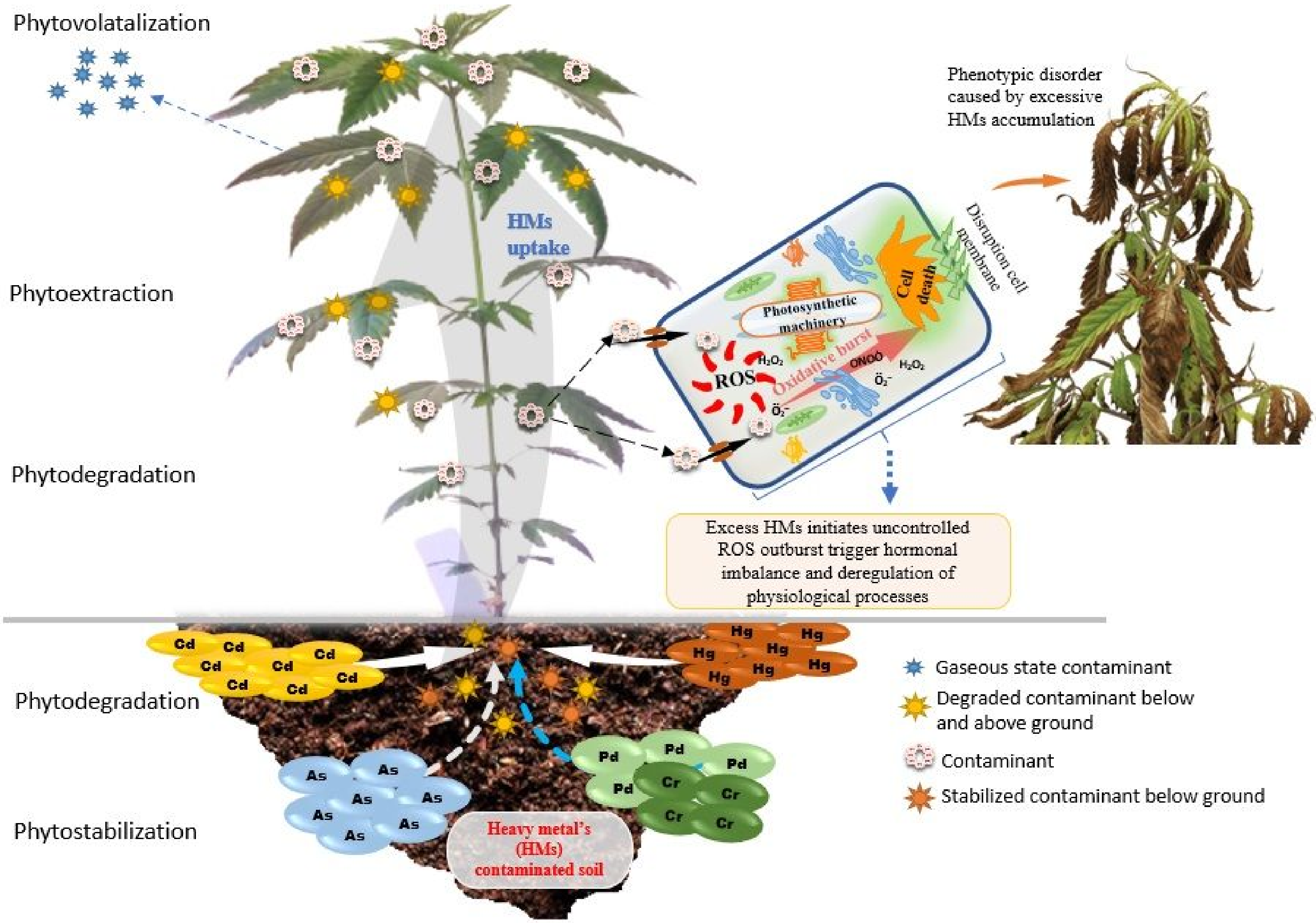

Figure 1

Bioaccumulation and distribution of heavy metals (Cd, As, Hg, Cr, and Pb) in the cannabis plant. The constitutive uptake of HMs is associated with no phenotypic alterations at the moderate levels. Excessive accumulation and stabilized contamination in the plant triggers an advent of oxidative outburst manifested by severe leaf and stem disorder.

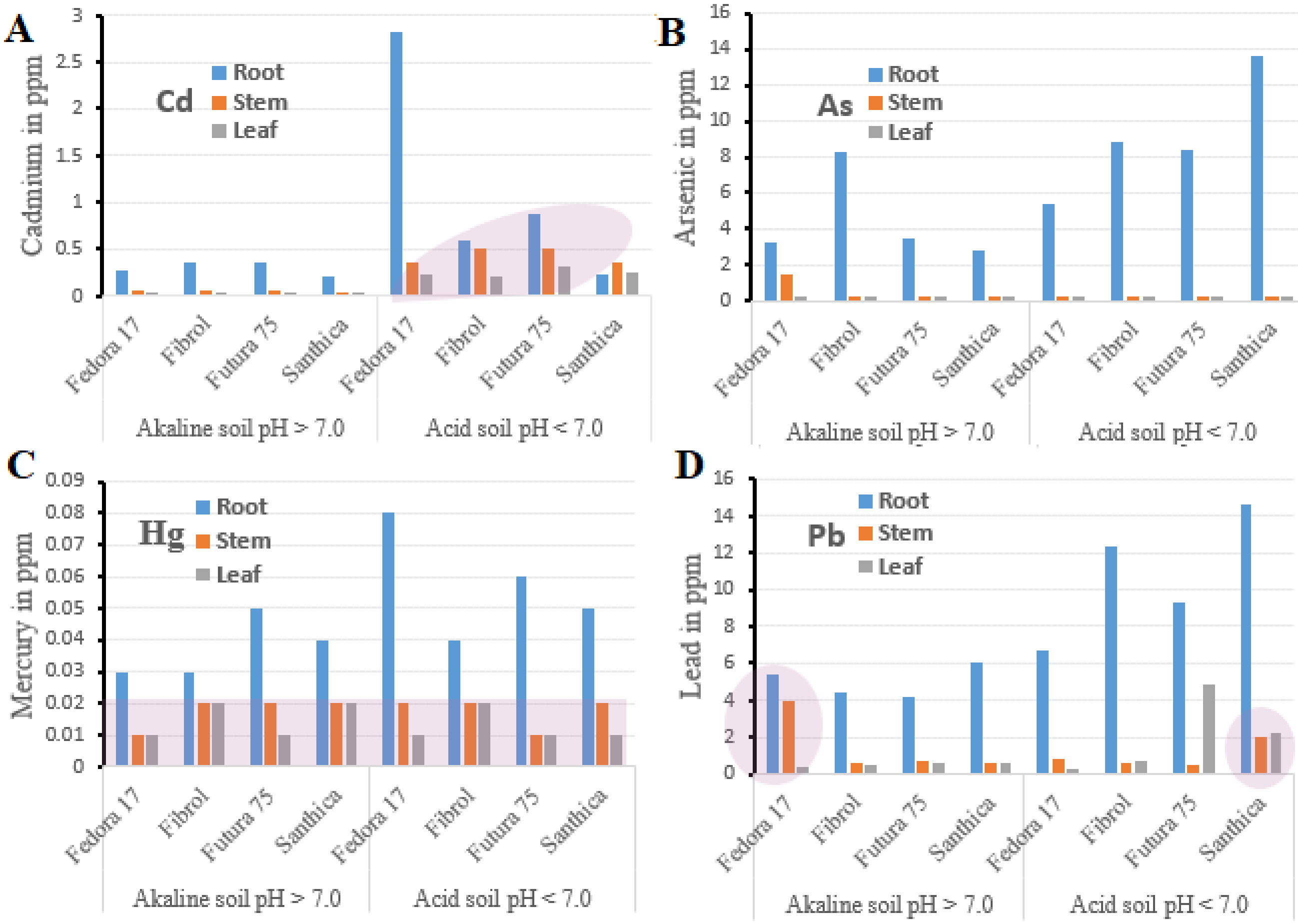

Figure 2

Effect of pedoclimatic pH on bioaccumulation of cadmium (Cd), arsenic (As), mercury (Hg), and lead (Pb) in hemp varieties. This graphic representation was produced by mining mean quantitative data ($P < 0.05$) generated in Galić et al. (2019).

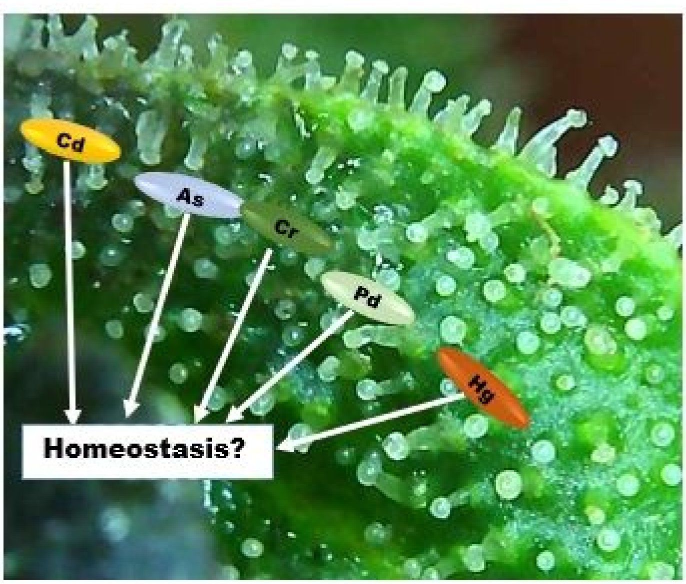

Figure 3

Example of cannabis gland visualized with a stereoscope at 1000X showing glands bearing resin of cannabinoids in a Sour-diesel strain of marijuana (THC > 0.3%). The homeostasis of heavy metals at the level of cannabis trichome is still unknown.

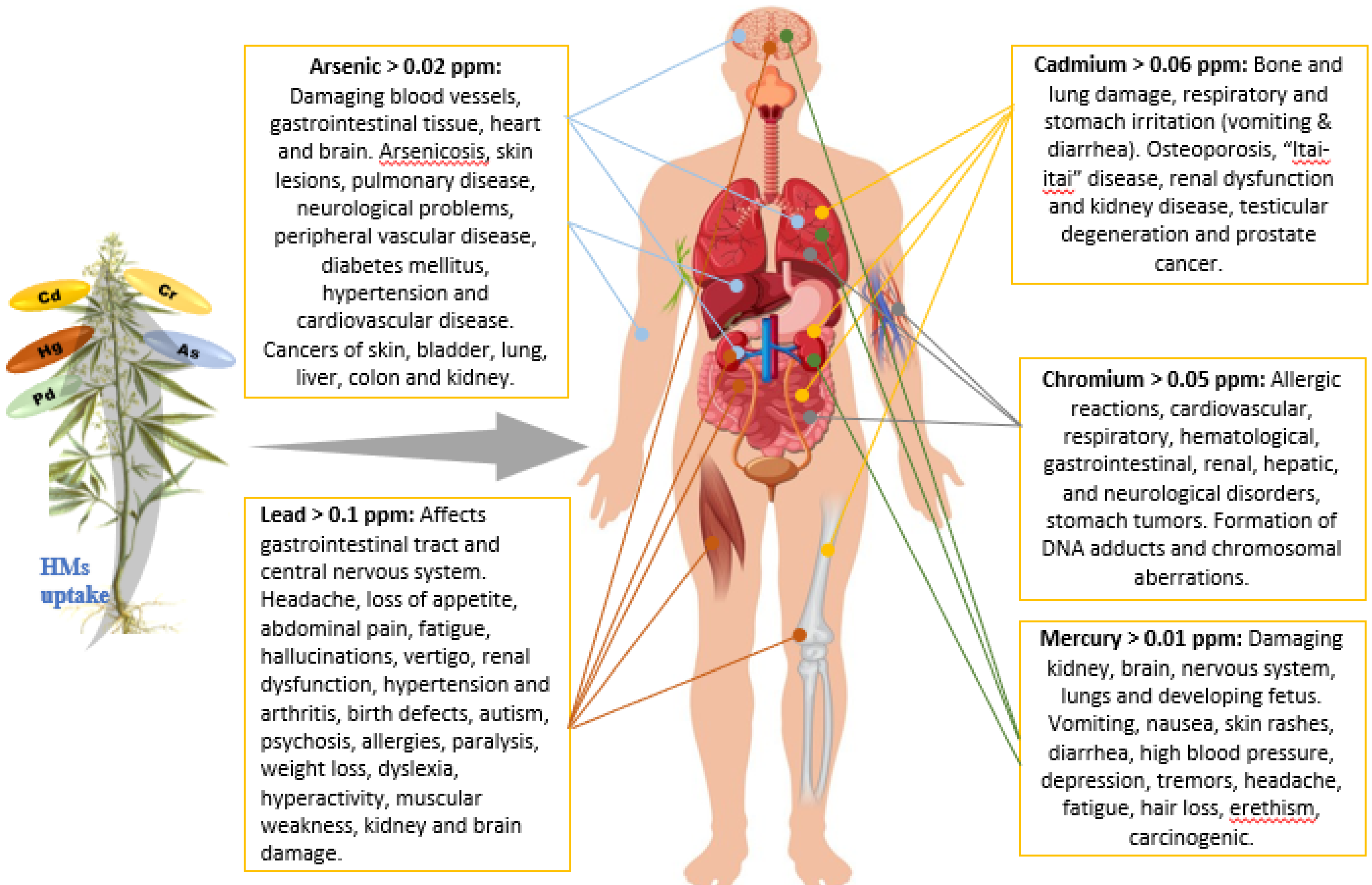

Figure 4

Typical effects of non-essential heavy metals above the permissible level on the human body. Hypothetically, the accumulation of HMs below the permissive levels represents a long-term risk factor for several chronic medical conditions.

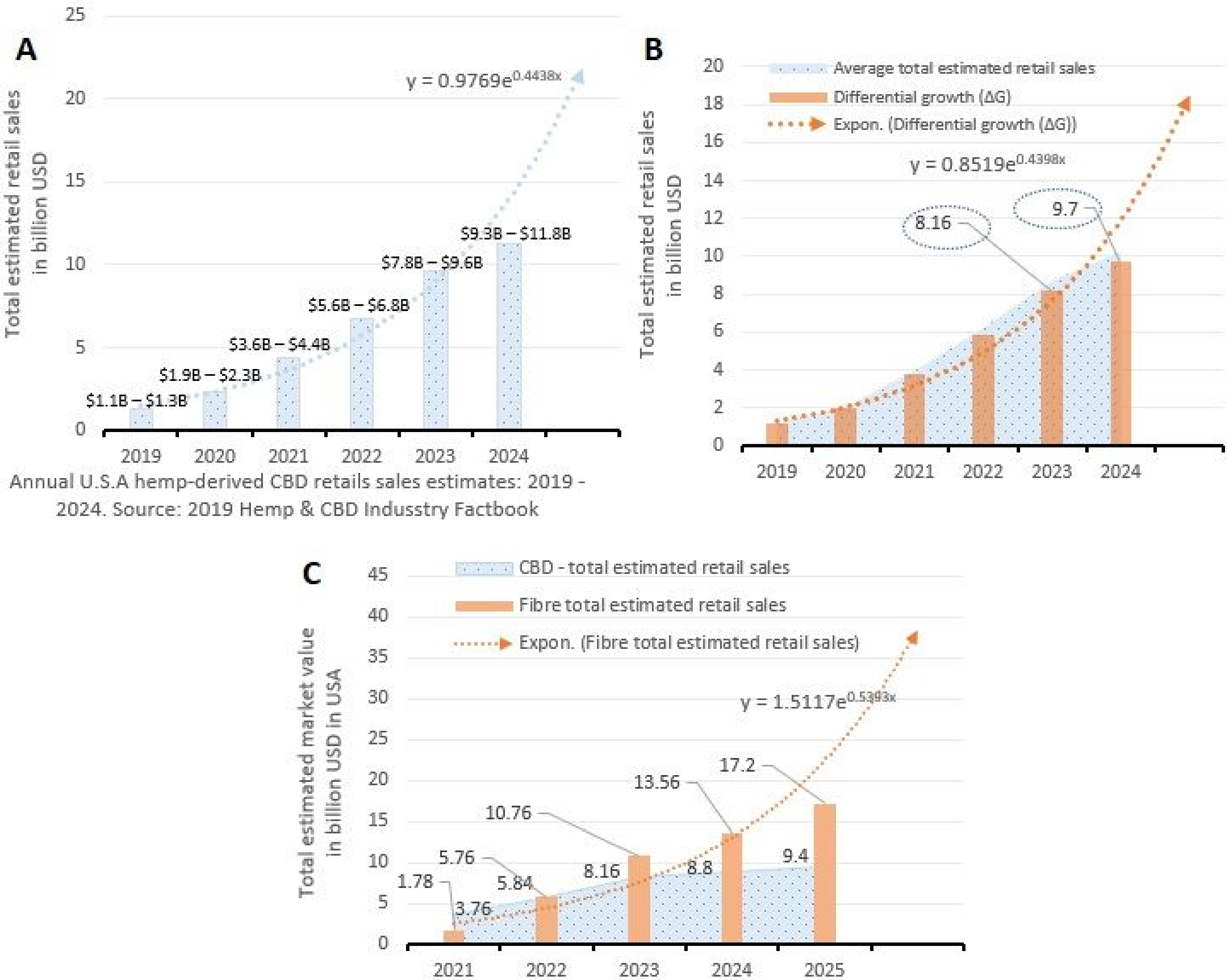

Figure 5

Forecasting unforeseen effects of heavy metals and mycotoxins on industrial hemp. A) Hemp Industry Daily predictions on estimated hemp-derived CBD sales for 2019-2024. B) Unforeseen repercussion based on differential growth on total estimated hemp-derived CBD sales for 2019-2024 in situations of consumer aversion caused by HMs contamination awareness. C) Prediction on the total estimated market value for fibers should mitigation strategies to counter HMs contamination in hemp-derived CBD fails forcing growers to shift production to hemp fibers. All dotted lines are trend lines of the displayed phenomenon.