



## Review

# Pharmaceuticals in Agricultural Soils as Emerging Non-Conventional Agrochemicals: Environmental Fate, Plant Uptake and Food Safety Implications

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## Highlights

- Pharmaceuticals act as emerging non-conventional agrochemicals in agricultural soils.
- Wastewater reuse, biosolids, and manure are primary drivers of pharmaceutical contamination in agroecosystems.
- Plant uptake of pharmaceuticals raises concerns for food safety, antimicrobial resistance, and One Health.

## Abstract

Pharmaceutical contamination in agricultural environments has become an increasing concern at the intersection of environmental sustainability, food security, and public health. The growing reuse of reclaimed wastewater (RWW), the application of biosolids, and intensive livestock production practices have contributed to the continuous release of pharmaceutically active compounds into agricultural soils worldwide. Although these substances are not intentionally applied in crop production systems, their persistent presence and biological activity have led to their recognition as emerging non-conventional agrochemicals. Once introduced into agroecosystems, pharmaceuticals may undergo sorption, degradation, and transformation, as well as interactions with soil microorganisms, while still remaining potentially available for plant uptake and transfer into the food chain. Various pharmaceutical classes, including antibiotics, anti-inflammatory drugs, antidepressants, antiepileptics, and hormones, have been detected in soils and edible crops at variable concentrations, depending on environmental conditions, soil properties, and plant physiological characteristics. In this context, this narrative review aims to analyze the origin of this contamination in agricultural soils, the physicochemical mechanisms that determine the environmental persistence of pharmaceuticals, as well as their absorption by plants, and the consequent impact on food security and the One Health model. It further proposes pharmaceuticals as a novel class of non-conventional agrochemicals unintentionally entering food production systems and discusses current regulatory challenges, mitigation strategies, and future research priorities needed to support sustainable agricultural management and safer resource reuse practices.



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## 1. Introduction

Agricultural systems are increasingly exposed to a diverse range of emerging contaminants driven by urban expansion, industrialization, and intensive farming [1–3]. Pharmaceuticals are among the most concerning of these pollutants due to their continuous environmental release, biological activity at low concentrations, and potential impacts on ecosystem integrity and human health [4,5]. Despite being designed for targeted therapeutic use in humans and animals, significant fractions are excreted unmetabolized or as active metabolites [6,7]. They ultimately reach agricultural ecosystems through treated wastewater, biosolid applications, livestock manure, and improper disposal [6,8,9].

In regions facing water scarcity, reclaimed wastewater (RWW) represents a valuable alternative water source capable of supporting agricultural productivity while simultaneously recycling nutrients and reducing freshwater demand [10,11]. However, this practice also introduces complex mixtures of pharmaceuticals and personal care products into agricultural soils [7,10,12,13]. Conventional wastewater treatment plants are not specifically built to filter out pharmaceutically active compounds; consequently, a fraction of these contaminants persist through treatment processes and is discharged into receiving waters or retained in sewage sludge [9]. As a result, agriculture soils receiving RWW or organic amendments can act as environmental sinks for pharmaceutical residues [5]. Repeated irrigation with RWW may progressively increase pharmaceutical concentrations in soil, thereby enhancing their persistence and potential availability for plant uptake [10].

In addition to RWW, the recurrent application of organic fertilizers, such as biosolids and animal manure, represents another important contributor to the increased concentration of pharmaceutical-derived contaminants in agricultural environments [14–17]. Intensive animal production frequently relies on veterinary medicines, particularly antibiotics. Because these compounds are often only partially metabolized, substantial amounts are excreted by livestock and subsequently introduced into soils fertilized with manure [15,16], posing ecological and food safety concerns while also contributing to the dissemination of antimicrobial resistance (AMR) [17].

The characteristics and physicochemical properties of the soil, such as pH, organic matter content, composition, humidity, and microbial activity, strongly influence the processes that pharmaceutical products can undergo once they reach the cultivated land (sorption, degradation, transformation, leaching, and interactions with microorganisms) [4,16,18–21]. It should be noted that some of pharmaceuticals exhibit considerable environmental persistence and may remain bioavailable for plant uptake over extended periods [4]. The frequent detection of antibiotics, antidepressants, and hormones in vegetables, cereals, and fruits grown in contaminated environments highlights how edible crops can act as direct vectors for human exposure to these drugs [13,16,21]. The effectiveness of absorption varies greatly between cultivated species [13,21,22].

Among pharmaceutical contaminants, antibiotics are of particular concern because of their role in the emergence and spread of bacterial resistance. Antibiotic-contaminated soils can act as reservoirs of resistant microorganisms and resistance genes, promoting the transfer of antibiotic resistance via environmental and human interfaces [17,21,23]. This dynamic perfectly illustrates the One Health concept: environmental quality, animal health, and human health are inextricably linked [24,25].

While pharmaceutical pollution in aquatic environments is well-documented, less attention has been directed toward agricultural soils and food crops. Existing reviews frequently focus on specific contamination sources [2,4], individual pharmaceutical classes [16,26], or wastewater reuse practices [10,11,13], while fewer studies integrate the entire soil-plant-food continuum. Furthermore, pharmaceuticals are rarely discussed as agrochemical contaminants.

To address this gap, this review conceptualizes pharmaceuticals as a novel class of emerging, non-conventional agrochemicals. We critically examine their primary sources in agricultural soils, the mechanisms driving their persistence and plant uptake, and their broader One Health implications. Finally, we discuss current regulatory blind spots and mitigation strategies to guide more sustainable agricultural management.

## 2. Sources of Pharmaceuticals in Agricultural Soils

Pharmaceuticals enter agricultural systems through multiple anthropogenic pathways, primarily through wastewater reuse and organic waste recycling. Driven by global water scarcity and circular economy initiatives, these inputs have intensified dramatically, turning agricultural soils into prominent reservoirs for active compounds [2,4,10–13,16,26].

### 2.1. Wastewater Irrigation

RWW plays an increasingly important role in sustaining agricultural production, particularly in arid and semi-arid regions [27,28]. Beyond serving as an alternative water source, RWW also provides beneficial nutrients for agricultural production [28]. However, municipal wastewater typically contains complex mixtures of pharmaceuticals originating from households, hospitals, and industrial activities [29–31]. As conventional wastewater treatment plants do not completely remove these compounds, numerous pharmaceuticals persist in treated effluents [29].

Frequently detected compounds include antibiotics, analgesics, anti-inflammatory drugs, antidepressants, beta-blockers, antiepileptics, lipid regulators, and hormones [16,31]. Local usage patterns, treatment efficiency, and seasonal shifts dictate the exact chemical profile [14,32]. Continuous irrigation may lead to the gradual accumulation of persistent residues such as ampicillin, ibuprofen, and fluoxetine in the soil matrix [10,31]. The resulting exposure risk is heavily influenced by the irrigation method; while surface sprinklers maximize direct contact between contaminants and plants, drip irrigation can significantly mitigate the contamination of edible tissues [13,33].

### 2.2. Biosolids and Sewage Sludge Application

Sewage sludge generated during wastewater treatment processes is frequently stabilized and applied to agricultural soils as biosolids due to its high organic matter and nutrient content [34]. However, many pharmaceuticals (particularly hydrophobic and ionizable compounds) strongly sorb to sludge particles during water treatment. As a result, biosolids often contain much higher concentrations of these contaminants than treated liquid effluents [4].

Compounds frequently detected in biosolids include antibiotics, hormones, antidepressants, anti-inflammatory drugs, and antiepileptics [16,29,35]. Repeated sludge amendment may result in cumulative pharmaceutical loading. In addition, transformation products generated during sludge stabilization processes may remain biologically active and contribute to environmental risks [35,36].

### 2.3. Livestock Manure and Veterinary Pharmaceuticals

Modern livestock production relies heavily on veterinary drugs for disease management and growth promotion [15,17,33,37]. Because animals excrete a substantial proportion

of these drugs (unmetabolized or as active metabolites) through urine and feces, applying raw or poorly composted manure to fields represents a direct pathway for pharmaceutical inputs into agricultural soils [4,16]. Antibiotics commonly detected in manure-amended soils include fluoroquinolones, sulfonamides, tetracyclines, lincosamides, and macrolides [16]. Continuous manure application may promote the accumulation of resistant bacteria and antibiotic resistance genes (ARGs) in soils, contributing to the dissemination of AMR across environmental and food production systems [16,17,23,33,36,38].

The environmental persistence of veterinary pharmaceuticals varies considerably according to compound properties [4,16], manure storage conditions, and soil management strategies. Some compounds may strongly sorb to soil particles, while others remain mobile and potentially available for plant uptake or groundwater contamination [2,4].

#### *2.4. Aquaculture and Additional Emerging Sources*

Aquaculture production systems also contribute to environmental pharmaceutical contamination using antibiotics, antiparasitics, and veterinary drugs in fish farming operations [39,40]. Agricultural systems can also receive pharmaceutical waste, accumulated in aquaculture sediments and from discharges into surrounding aquatic environments [41].

Pharmaceutical contamination also originates from landfill leachate, urban runoff, hospital discharges, and even atmospheric deposition [8,20,25]. While these pathways generally contribute less directly than wastewater irrigation or manure application, they collectively increase the overall environmental burden of pharmaceutical contaminants in agroecosystems, complicating environmental monitoring [37,42].

### **3. Pharmaceuticals as Emerging Non-Conventional Agrochemicals**

Traditionally, agrochemicals are defined as substances intentionally applied within agricultural systems to enhance crop productivity, including fertilizers, pesticides, herbicides, fungicides, and plant growth regulators [43,44]. However, the chronic, unintended influx of pharmaceuticals into farming systems effectively constitutes what recent literature increasingly conceptualizes as a new class of non-conventional agrochemical contaminants [1–3,26,45]. This designation serves as a scientific framework rather than a formal policy or regulatory reclassification.

Although pharmaceuticals are not designed for agricultural applications, their continuous presence in agroecosystems enables them to influence biological and ecological processes in ways that resemble conventional agrochemicals. Similar to many agricultural inputs, pharmaceuticals are repeatedly introduced into the environment, remain biologically active at low concentrations, may persist in soils for extended periods, and can affect both soil microbial communities and plant physiological processes [46]. Consequently, their presence has the potential to influence soil-plant-microbe interactions despite their unintended entry into agricultural systems [47], requiring ecotoxicological risk assessments and legislative framework, which are currently lacking.

Different pharmaceutical classes may affect agroecosystem functioning through distinct mechanisms. Antibiotics can disrupt soil microbial community composition and suppress beneficial taxa involved in nutrient transformation and rhizosphere functioning [47]. Endocrine-active compounds may interfere with plant signaling pathways, while certain non-steroidal anti-inflammatory drugs (NSAIDs) and psychoactive drugs have been associated with phytotoxic responses under defined exposure conditions [46]. Classifying pharmaceuticals as non-conventional agrochemicals highlights a critical regulatory gap. Unlike traditional pesticides, which are subject to rigorous environmental risk assessments before being introduced to the market, pharmaceuticals may enter the soil through wastewater reuse and sludge application, common practices in the circular economy, without any

comprehensive analysis of their long-term influence on food security [48,49]. Recognizing this reality is the first step towards creating a structure suitable for the future management of this type of waste in agricultural systems. This requires policies that promote the assessment of the persistence of pharmaceutical products, their absorption by plants, and the consequent spread of AMR, with a rigor similar to that applied to conventional pesticides.

#### 4. Environmental Fate and Persistence of Pharmaceuticals in Soil

The environmental behavior and impacts of pharmaceuticals in soil are governed by complex physical, chemical, and biological processes that influence mobility, persistence, bioavailability, and potential plant uptake [50]. When introduced into agricultural ecosystems, these compounds may undergo sorption, degradation, transformation, and interactions with soil microorganisms. In addition to the physicochemical properties of pharmaceutical compounds, environmental and soil properties significantly influence these processes [20]. Therefore, understanding the interactions between pharmaceuticals and agricultural soils is essential for assessing ecological risks, food safety concerns, and the long-term sustainability of wastewater reuse and organic fertilization practices.

##### 4.1. Sorption and Mobility

Sorption includes several mechanisms, such as adsorption on mineral surfaces, partitioning into soil organic matter, ion exchange reactions, hydrogen bonds, and electrostatic interactions [20]. It is a process that directly controls the mobility, persistence, degradation potential, and bioavailability of pharmaceuticals to plants, thereby determining their environmental fate in soils.

The physicochemical characteristics of the compound, such as hydrophobicity (log Kow), ionization constant (pKa), molecular mass, polarity, and aqueous solubility, as well as the properties of the soil, determine the degree of sorption of pharmaceutical compounds [4,20].

In parallel, soil properties such as organic matter content, clay mineralogy, pH, cation exchange capacity, moisture content, ionic strength, and temperature play a decisive role in determining sorption behavior [18,20,37,50].

Hydrophobic compounds typically exhibit a strong affinity for soil organic matter, which reduces their mobility in the soil profile while potentially increasing their long-term persistence. Polar pharmaceuticals tend to remain in the soil solution phase, which increases their mobility and likelihood of leaching into groundwater or being taken up by plants [20,50].

Ionizable pharmaceuticals display particularly complex behavior because their charge state is governed by soil pH relative to their pKa. Under specific conditions, cationic forms may strongly interact with negatively charged clay minerals, whereas anionic forms often exhibit greater mobility due to weaker sorption interactions, depending on soil composition and chemistry [20].

Distinct pharmaceuticals exhibit contrasting sorption patterns in soils. Fluoroquinolone antibiotics are frequently characterized by strong sorption due to cation exchange and complexation with soil components [50], whereas compounds such as carbamazepine generally display higher mobility because of their neutral structure and moderate hydrophobicity [51].

##### 4.2. Degradation and Transformation Processes

The degradation of pharmaceuticals in soils occurs through a combination of biological, chemical, and photochemical processes [4]. Although abiotic processes can also play a major role depending on environmental conditions, microbial degradation is generally

thought to be the main mechanism responsible for pollutant dissipation in agricultural conditions [52].

#### 4.2.1. Microbial Degradation

Numerous microorganisms, including algae, bacteria or fungi, can biodegrade various pharmaceutical compounds [53,54]. Soil bacteria, particularly members of the Actinobacteria, play a central role in pharmaceutical transformation [55]. These microorganisms may degrade pharmaceutical compounds through co-metabolic pathways associated with other substrates, or by direct metabolism, using them as carbon or energy sources. Direct metabolism is commonly carried out by native soil microorganisms, such as *Pseudomonas* and *Acinetobacter*, which can degrade structurally simple pharmaceuticals, such as paracetamol [56]. In contrast, co-metabolism occurs through the action of highly specific enzymes such as cytochrome P450 and other monooxygenases that fortuitously degrade pharmaceuticals present at trace concentrations [57]. Several environmental parameters influence microbial degradation efficiency, including microbial diversity, nutrient availability, oxygen status, soil moisture, temperature, pH, contaminant concentration, and exposure time [4,22,58]. In addition, the physicochemical properties of pharmaceuticals, such as molecular structure, solubility, sorption potential, bioavailability also control the efficiency of biodegradation [4]. In general, biodegradation is favored by environmental conditions that promote microbial activity and hindered by strong sorption of pharmaceuticals to soil particles and by the presence of highly recalcitrant compounds [18,26,59,60].

Aerobic environments promote faster breakdown rates for a variety of pharmaceutical classes; nevertheless, degradation kinetics vary significantly depending on chemical structure. Some pharmaceuticals, including ibuprofen and acetaminophen, are generally easily biodegradable, but substances like carbamazepine, fluoxetine, and fluoroquinolone antibiotics are well known for their environmental persistence [61].

Bacteria, such as *Pseudomonas*, *Bacillus*, and *Sphingomonas*, play an essential role in the degradation of compounds like sulfamethoxazole, ibuprofen, diclofenac, and carbamazepine. These microorganisms are capable of transforming antibiotics, anti-inflammatory drugs, and antiepileptics into less persistent metabolites through the action of their oxygenases, hydrolases, and cytochrome P450 enzymes [12,22,54]. Fungi, such as *Trametes* and *Phanerochaete*, also contribute significantly to the attenuation of pharmaceutical residues in soils, including antibiotics, analgesics, and endocrine-disrupting chemicals. Their degradative capacity is largely attributed to the secretion of extracellular oxidative enzymes, such as laccases, lignin peroxidases, and manganese peroxidases, and are characterized by the substrate specificity and the ability to degrade recalcitrant pharmaceuticals that are less susceptible to bacterial metabolism [4,62].

Actinobacteria, including *Streptomyces*, *Rhodococcus*, and *Nocardia*, are particularly effective in the degradation of persistent pharmaceuticals, such as antibiotics, anti-inflammatory drugs, analgesics, and endocrine-disrupting drugs. These microorganisms possess diverse catabolic pathways and encode a wide range of degradative enzymes, including oxygenases, hydrolases, cytochrome P450 monooxygenases, and other enzymes capable of transforming complex organic compounds [4,22,55]. Their metabolic versatility, combined with the ability to colonize heterogeneous environments and tolerate environmental stress, makes Actinobacteria promising candidates for bioremediation strategies aimed at reducing pharmaceutical residues in soil [54,59].

The ability of soil microorganisms to degrade pharmaceutical contaminants varies according to both the microbial taxa and the chemical structure of the target compounds. Although many degradation mechanisms are shared among microorganisms, specific bacterial and fungal genera have been associated with the transformation of particular

pharmaceuticals through distinct enzymatic pathways. Table 1 summarizes representative soil microorganisms reported to degrade pharmaceutical compounds, the principal reactions and enzymes involved, and examples of pharmaceuticals susceptible to microbial transformation in soil environments.

**Table 1.** Representative soil microorganisms involved in pharmaceutical degradation, associated degradation reactions, enzymes, and pharmaceutical compounds degraded, compiled from [53–55,62–65].

| Microorganism                      | Group                     | Pharmaceutical(s) Degraded                           | Main Reactions                           | Key Enzymes                      |
|------------------------------------|---------------------------|------------------------------------------------------|------------------------------------------|----------------------------------|
| <i>Pseudomonas</i> spp.            | Bacteria (Proteobacteria) | Sulfamethoxazole, diclofenac, ibuprofen, paracetamol | Oxidation, hydroxylation, cleavage       | Oxygenases, hydrolases           |
| <i>Bacillus</i> spp.               | Bacteria (Firmicutes)     | Diclofenac, ibuprofen, tetracycline                  | Hydrolysis, oxidation                    | Esterases, oxidoreductases       |
| <i>Sphingomonas</i> spp.           | Bacteria (Proteobacteria) | Carbamazepine, sulfamethoxazole                      | Oxidation, ring cleavage                 | Monoxygenases                    |
| <i>Rhodococcus</i> spp.            | Actinobacteria            | Diclofenac, sulfamethoxazole, triclosan              | Hydroxylation, oxidation, mineralization | Cytochrome P450, oxygenases      |
| <i>Arthrobacter</i> spp.           | Actinobacteria            | Antibiotics, analgesics                              | Hydrolysis, oxidation                    | Hydrolases, oxidoreductases      |
| <i>Streptomyces</i> spp.           | Actinobacteria            | Carbamazepine, antibiotics, NSAIDs                   | Oxidation, hydroxylation                 | Cytochrome P450, oxygenases      |
| <i>Phanerochaete chrysosporium</i> | Fungi                     | Carbamazepine, diclofenac, antibiotics               | Oxidation, dealkylation                  | Lignin peroxidase, Mn-peroxidase |
| <i>Trametes versicolor</i>         | Fungi                     | Diclofenac, ibuprofen, sulfamethoxazole              | Oxidation, dehalogenation                | Laccase, peroxidases             |
| <i>Pleurotus ostreatus</i>         | Fungi                     | Antibiotics, analgesics                              | Oxidation, hydroxylation                 | Laccases, peroxidases            |

Microbial degradation of pharmaceuticals in soil reduces the concentrations of these contaminants and mitigates their environmental impact. Continuous exposure to pharmaceuticals can lead to microbial adaptation, resulting in the development of metabolic pathways and enzymatic systems capable of transforming or mineralizing these contaminants. Consequently, biodegradation rates may increase, particularly for pharmaceuticals introduced into the environment through irrigation with RWW or by the application of manure or biosolids [59].

Understanding the environmental factors controlling degradation, as well as microbial adaptation, and persistence of pharmaceuticals in soils, makes it possible to predict the risk of exposure to and accumulation of these contaminants while simultaneously devising strategies to reduce pharmaceutical pollution in agricultural environments.

#### 4.2.2. Abiotic Transformation

Abiotic degradation refers to the transformation of chemical compounds through physical and chemical processes that occur independently of biological activity. In soils, the main abiotic transformation mechanisms include hydrolysis, oxidation–reduction reactions,

and photodegradation. Pharmaceuticals present in surface soils may be transformed by sunlight-driven processes, especially in dry circumstances that increase light penetration and decrease shielding by water or organic matter [4].

However, abiotic transformation does not necessarily result in detoxification. The resulting transformation products are frequently still poorly defined, and their toxicity and environmental fate remain insufficiently understood [66]. Some metabolites may retain biological activity or perhaps exhibit more toxicity or persistence than their parent substances.

#### 4.3. Persistence and Accumulation in Agricultural Soils

Persistence and accumulation in agricultural environments refer to the long-term survival and successive build-up of chemical or physical pollutants in the topsoil layer. Several publications claim that the persistence of pharmaceuticals in soil settings is highly variable and depends on both molecular structure and environmental factors [4,22,67]. Environmental half-lives have been reported to range from hours to months and, in some cases, may extend to years under conditions that limit degradation processes.

Repeated inputs from practices such as irrigation with RWW, application of animal manure, or biosolids amendment may lead to pseudo-persistence. In such situations, the continuous introduction of pharmaceuticals exceeds their degradation rates, resulting in gradual accumulation within agricultural soils even when individual compounds are not inherently highly persistent [68]. This accumulation is environmentally relevant because persistent pharmaceuticals may remain bioavailable for plant uptake, modify soil microbial community structure, alter enzymatic activity, and contribute to the selection and maintenance of AMR. In addition, they may be transported to adjacent compartments such as groundwater systems.

Long-term accumulation is further modulated by agricultural management practices, irrigation frequency, cropping systems, soil amendments, and climatic conditions. Arid and semi-arid environments, characterized by limited microbial activity and reduced degradation capacity, may be particularly prone to accumulation phenomena. Diclofenac, tetracycline and fluoroquinolone antibiotics, carbamazepine, and various antidepressants are among the substances commonly found to be persistent in the environment, since pharmaceutical compounds are continuously introduced into municipal wastewater through human and veterinary excretion [6,67].

As previously discussed, pharmaceutical concentrations in soil depend on various factors. Consequently, pharmaceuticals are detected over a wide range of concentrations, spanning several orders of magnitude, from  $\text{ng kg}^{-1}$  to  $\text{g kg}^{-1}$ . Municipal biosolids, widely used as additives in agricultural soils, can contribute in significantly higher pharmaceutical loads than RWW, with certain highly persistent compounds such as triclosan, triclocarban, and fluoroquinolone antibiotics reaching very significant levels shortly after intensive biosoil application. The importance of these inputs is reflected in accumulation estimates reported in the literature. Santos et al. (2026) reported that the average annual load of contaminants of emerging concern accumulated into agricultural soils through RWW irrigation is  $129.4 \pm 88.5 \text{ g ha}^{-1}$ , with pharmaceuticals representing the predominant fraction [16]. Similarly, Nguyen et al. (2023) reported pharmaceutical concentrations ranging from  $0.048 \text{ ng g}^{-1}$  to  $1420.76 \text{ mg kg}^{-1}$ , highlighting the large variability observed across compounds and environmental settings [32]. Among the different pharmaceutical classes, antibiotics are frequently detected at the highest concentrations due to their frequent use in veterinary medicine and their strong adsorption to soil particles [32]. Carbamazepine, one of the most frequently detected pharmaceuticals in agricultural soils, is characterized by high persistence and resistance to biodegradation. Consequently, it frequently exhibits

high soil–plant accumulation factor values, raising concerns regarding its environmental persistence and potential transfer through the food chain [12].

A critical limitation in current environmental risk assessments is the assumption that pharmaceutical “degradation” equates to complete mineralization or reduced ecological risk. Relying solely on the disappearance or dissipation of the parent compound can provide a false sense of safety [26]. Lower parent concentrations do not guarantee lower risks, as incomplete mineralization often leaves reactive intermediates that are as persistent, biologically potent, or even more toxic than the original drugs [16,26,60]. These transformation products can sometimes accumulate in edible crop tissues at concentrations exceeding those of the parent compound itself [16].

Specific transformation pathways yield distinctly hazardous byproducts. For example, rather than fully mineralizing to CO<sub>2</sub>, the microbial transformation of carbamazepine in soil generates epoxide and hydroxy intermediates that are highly persistent, prolonging environmental exposure [26]. The photocatalytic degradation of diclofenac generates reactive quinone-imines and persistent halogenated transformation products that can induce greater oxidative stress than the parent compound itself [60]. Furthermore, antibiotic biotransformation products often retain their antimicrobial structural properties and potency, and can maintain continuous selective pressure for AMR within soil microbial communities [59].

Detecting pharmaceutical metabolites and transformation products in agroecosystems is highly challenging due to their trace concentrations, severe matrix interferences (e.g., amino acids, chlorophylls), and a lack of analytical standards specific to plant and soil metabolism. To overcome these barriers and accurately assess environmental and human health risks under circular agriculture practices, it is essential to employ advanced high-resolution mass spectrometry combined with non-target and suspect screening approaches to comprehensively identify these unknown compounds [16].

#### 4.4. Influence of Soil Properties on Pharmaceutical Fate

The physicochemical and biological properties of soils strongly influence the environmental fate of pharmaceuticals in agroecosystems, affecting their transport, degradation, sorption, and bioavailability [69]. Acidity is one of these relevant factors, and soil pH is an important element since it affects the ionization state of many pharmaceuticals [68]. Even minor pH changes can significantly affect sorption affinity, mobility, and breakdown routes, especially for ionizable molecules such as antibiotics and nonsteroidal anti-inflammatory drugs [4].

Soil organic matter generally enhances sorption capacity by providing binding sites for hydrophobic interactions. While this can reduce mobility, it may also decrease bioavailability to microorganisms, thereby slowing degradation and prolonging persistence.

Soil texture and mineral composition also play a major role in pharmaceutical retention. Clay-rich soils are characterized by a higher sorption potential, since they have a large specific surface area and cation exchange capacity. Consequently, antibiotics such as tetracyclines and fluoroquinolones tend to form strong associations with clay minerals, as their molecular structures facilitate cation exchange, surface complexation, and cation bridging [70].

Sandy soils generally exhibit lower organic matter content and lower cation exchange capacity than clay-rich soils, resulting in lower sorption and greater contaminant mobility, which can increase leaching potential and pharmaceutical availability for plant uptake. In contrast, clay-rich and organic matter-rich soils retain pharmaceuticals more efficiently through adsorption, cation exchange, and surface complexation processes [18–20]. To understand these dynamics, it is crucial to consider the specific physicochemical properties of the compounds, such as their dissociation constants (pKa) and lipophilicity (log

Kow), in relation to soil pH. Because many pharmaceuticals contain ionizable functional groups, their charge state (cationic, anionic, or zwitterionic) at a given soil pH frequently overrules their lipophilicity ( $\log K_{ow}$ ) in determining sorption. A comprehensive review covering 137 studies, 106 pharmaceutical compounds, and 212 soil materials reported average sorption coefficients ( $K$ ) ranging from only  $0.0915 \text{ L kg}^{-1}$  for anionic sulfonamides (which are typically negatively charged at agricultural soil pH and thus highly mobile) to  $84725.5 \text{ L kg}^{-1}$  for zwitterionic norfloxacin, highlighting the strong influence of both pharmaceutical speciation and soil properties on contaminant retention [71]. Likewise, experimental studies have shown that sorption varies markedly even within the same pharmaceutical class according to soil characteristics. For example, metformin exhibited  $K$  values ranging from 2.1 to  $332 \text{ L kg}^{-1}$ , whereas erythromycin ranged from 6.25 to  $845 \text{ L kg}^{-1}$  depending on soil organic matter content, pH, and texture [19].

Importantly, stronger sorption does not necessarily imply lower environmental risk. While coarse-textured soils may increase short-term exposure through enhanced mobility and potential plant uptake, fine-textured soils enriched in clay and organic matter may promote long-term persistence and pseudo-persistence under repeated applications of RWW, biosolids, or manure, maintaining pharmaceuticals as a continuous source of exposure within agroecosystems [18,20,68,71].

In addition to physicochemical properties, biological factors strongly influence pharmaceutical degradation. Microbial activity, which largely determines biodegradation rates, is strongly influenced by soil moisture and temperature. Higher moisture levels and temperatures generally promote biodegradation processes, whereas cold or dry conditions reduce microbial activity and increase pharmaceutical persistence.

The rhizosphere constitutes another important factor affecting pharmaceutical fate in soils. The study by Zambelli et al. [72], conducted under both field and laboratory conditions, demonstrated that root exudates, microbial community shifts, and localized changes in pH and redox conditions can either enhance or inhibit degradation processes, as well as modify the availability of pharmaceuticals for plant uptake.

#### 4.5. Pharmaceuticals and Soil Microbial Communities

Pharmaceutical contamination can significantly affect soil microbial communities by altering their structure, diversity, and functional capacity. Antibiotics are of special concern because they can exert selective pressure on microbial populations and promote the development and dissemination of AMR [24]. Multiple studies have shown that exposure to pharmaceuticals in soil systems can lower microbial diversity, affect community composition, inhibit critical soil enzymes, disrupt nitrogen cycling mechanisms, and affect soil respiration dynamics [4,60,67].

Beyond these general changes, recent evidence provides deeper insights into specific microbial alterations. For instance, irrigation with pharmaceutical-contaminated water has been shown to alter the human pathobiome within the soil, potentially selecting for pathogenic communities. Furthermore, these microbiome alterations are not confined to the soil matrix; they can trigger cascading ecological effects across agricultural food webs, including disruptions of insect-endosymbiont dynamics (e.g., in aphids) [73]. Additionally, prolonged exposure to low concentrations of antibiotics may enhance horizontal gene transfer, boosting the presence and spread of ARGs among soil microbial communities in agricultural settings [74].

These microbial changes have broader environmental implications because resistance determinants and resistant bacteria may be transferred through agricultural products, water irrigation, livestock systems, and ultimately to human populations [75]. Consequently,

pharmaceutical contamination in soils represents a significant ecological and public health concern from a One Health perspective.

## 5. Plant Uptake and Translocation of Pharmaceuticals

The uptake of pharmaceuticals by edible crops is a growing concern within the context of pharmaceutical contamination in agroecosystems. The absorption of pharmaceutical residues by plant crops and their accumulation in edible tissues generally result from contaminated soils or irrigation with RWW, conditions that create a potential channel for human dietary exposure [37]. The extent of plant uptake is governed by a complex interplay between pharmaceutical physicochemical properties, soil characteristics, environmental conditions, and plant physiological traits. A mechanistic understanding of these processes is essential for assessing food safety risks and informing sustainable agricultural management strategies.

### 5.1. Mechanisms of Plant Uptake

Plants absorb pharmaceuticals predominantly through root absorption from soil solution or irrigation water, a process largely driven by passive transport mechanisms associated with water uptake and transpiration stream. Once in the rhizosphere, chemicals may enter plant tissues via two main mechanisms [76].

The apoplast constitutes the continuous extracellular compartment of plants, comprising cell walls, intercellular spaces, and xylem vessels. In the apoplastic pathway, pharmaceuticals move through cell walls and intercellular spaces without crossing plasma membranes. This route is generally more relevant for hydrophilic compounds that can diffuse through aqueous extracellular compartments [77]. In contrast, the symplastic pathway entails movement from cell-to-cell via plasmodesmata after crossing the plasma membrane and entering root cells. It is more likely for lipophilic substances with the right molecular size and membrane affinity to pass through biological membranes and be transported through this route.

After root uptake, pharmaceuticals may be translocated through the xylem to aerial plant parts, including stems, leaves, fruits, and grains, depending on their mobility and physicochemical properties. However, it is crucial to differentiate between uptake pathways demonstrated experimentally under controlled conditions and the actual accumulation inferred in real agricultural ecosystems, where bioavailability is heavily constrained.

### 5.2. Factors Influencing Pharmaceutical Uptake

Pharmaceutical absorption by plants is a complex process influenced by several inter-related factors related to compound properties, soil characteristics, and plant physiology [4]. Thus, pharmaceutical properties strongly influence uptake and translocation potential, including molecular size, hydrophobicity, water solubility, ionization state, and polarity. Compounds with moderate hydrophobicity and appropriate molecular dimensions typically exhibit enhanced membrane permeability and translocation efficiency. Neutral species are more readily absorbed than ionized forms because they may traverse biological membranes more easily [78].

As aforementioned, soil characteristics also play a critical role in determining pharmaceutical bioavailability. Low organic matter content, low sorption capacity, sandy soil texture, favorable pH conditions, and enhanced soil moisture can improve the availability of pharmaceuticals for plant uptake [20]. In contrast, substantial sorption to soil organic matter or clay minerals may significantly reduce bioavailable fractions and limit root uptake. Because of these complex soil dynamics, a critical distinction must be made regarding the source of uptake evidence. Much of the foundational data demonstrating high pharmaceutical accumulation comes from hydroponic systems or greenhouse pot experiments using

artificially spiked substrates. These laboratory studies tend to significantly overestimate plant uptake compared to real field conditions, where strong soil binding severely limits the fraction of pharmaceuticals actually available to roots. In addition to soil characteristics, plant physiological traits also influence pharmaceutical uptake and accumulation. Differences in root morphology, transpiration rate, lipid composition, growth stage, and metabolic activity contribute to variability in pharmaceutical accumulation among species. Fast-growing leafy vegetables with high transpiration rates typically exhibit greater pharmaceutical accumulation potential than many fruit crops due to increased mass flow of water and solutes [16].

### 5.3. Translocation and Distribution Within Plants

Variations in the uptake and accumulation of pharmaceutical pollutants relate to biotic parameters such as the plant species, cultivar, variety, genotype, and the plant's physiological stage. In general, following root uptake, pharmaceuticals migrate through vascular tissues, especially the xylem, to above-ground organs. The effectiveness of internal transport is determined by compound mobility, chemical interactions with plant tissues, and transpiration-driven flows [79]. Once absorbed, pharmaceuticals can be translocated to shoots, leaves, and fruits through the xylem or phloem. Their accumulation in edible plant tissues may subsequently lead to dietary exposure of humans and livestock through consumption of contaminated crops [10,16,79]. A common accumulation pattern found in the literature is roots > leaves/stems > fruits/seeds [70–82]. Roots are frequently the predominant accumulation site due to direct contact with contaminated soil and increased sorption to root tissues [83].

Nevertheless, considerable translocation to aerial parts has been observed for some pharmaceutical classes, notably those with higher mobility within plant vascular systems. Leafy tissues often show greater quantities because transpiration allows for continuous upward transport of water and dissolved contaminants [84]. In contrast, fruits and seeds frequently have lower levels of pharmaceutical residues due to limited xylem transport into reproductive organs, but residues have been measured in crops such as tomatoes, lettuce, cucumbers, peppers, strawberries, and cereals [85–88].

### 5.4. Crop-Specific Uptake Patterns

Pharmaceutical uptake and accumulation vary significantly between crop varieties, reflecting changes in physiology, morphology, and growth dynamics. Available evidence indicates that crop-specific accumulation patterns are primarily governed by differences in root architecture, transpiration demand, growth cycle, and other physiological traits, together with the physicochemical properties of individual pharmaceuticals [13,76,82]. Although field data on the uptake of pharmaceuticals by cultivated plants and their accumulation in edible parts are scarce, some authors report that leafy vegetables, including lettuce, spinach, cabbage, and culinary herbs, often exhibit the greatest potential for accumulation due to high transpiration rates and rapid biomass development [16]. Consequently, leafy vegetables are generally regarded as the crop group with the highest potential for pharmaceutical accumulation and dietary exposure.

Field investigations further illustrate these differences. Ben Mordechay et al. [88] demonstrated that the distribution of pharmaceuticals within the water–soil–plant continuum is highly dynamic and crop-dependent. Their results showed the following concentrations: banana ( $19.0 \pm 22.7 \text{ g ha}^{-1}$ ), avocado ( $6.3 \pm 4.2 \text{ g ha}^{-1}$ ), tomato ( $3.9 \pm 5.9 \text{ g ha}^{-1}$ ), citrus fruits ( $3.3 \pm 5.8 \text{ g ha}^{-1}$ ), leafy vegetables ( $1.0 \pm 1.4 \text{ g ha}^{-1}$ ), carrot ( $0.7 \pm 0.7 \text{ g ha}^{-1}$ ) and potato ( $0.4 \pm 0.6 \text{ g ha}^{-1}$ ).

Compounds such as antibiotics, carbamazepine, sulfamethoxazole, and triclosan are frequently detected in these crops, both under real and spiked conditions [16]. Root vegetables, including carrots, radishes, potatoes, and beets, may accumulate pharmaceuticals directly in edible tissues through close and prolonged contact with contaminated soils [12,89]. This exposure pathway is particularly relevant for food safety considerations, as contaminants are retained in harvested organs.

Cereal and staple crops such as rice, wheat, and maize generally demonstrate moderate uptake capacities. Pharmaceutical residues are often more concentrated in roots and vegetative tissues than in grains, although measurable levels have still been detected in edible portions under certain conditions. For example, de Santiago-Martín et al. [90] detected four of the twenty-five pharmaceuticals in corn grains from an extensive agricultural land: acetaminophen (8.4–27.5 ng/g, dry weight), nicotine (0.03–1.2 ng/g, dry weight), ibuprofen (0.2–1.1 ng/g, dry weight), and carbamazepine (0.04–0.4 ng/g), even if these pharmaceuticals were present in the lowest concentrations in the irrigation water (less than 100 ng/L of paracetamol and 100–250 ng/L of nicotine, ibuprofen and carbamazepine). Margenat et al. [91] detected lincomycin (0.60–3.4 ng/g, wet weight), ciprofloxacin (8.0–34 ng/g, wet weight) and azithromycin (0.55–10 ng/g, wet weight) in lettuce leaves grown in a greenhouse using soil fertilized with manure. Depending on the type of horticultural product, it is believed that fruit crops exhibit less accumulation in edible fruits due to limited translocation to reproductive tissues. However, persistent pharmaceuticals, including carbamazepine and some antibiotics, may be present in low concentrations, depending on levels of environmental exposure.

Taken together, these findings indicate that leafy vegetables and root crops generally represent the crop groups with the greatest potential for pharmaceutical accumulation under contaminated agricultural conditions, whereas fruit crops and cereal grains tend to accumulate lower concentrations in edible tissues [16,76,88]. Nevertheless, prolonged irrigation with RWW or repeated biosolid and manure applications may increase pharmaceutical residues even in crops generally considered less susceptible [16,50,88]. Therefore, crop selection should be considered together with soil properties and agricultural practices when assessing pharmaceutical transfer through the soil–plant continuum and the associated risks to food safety.

### 5.5. Plant Metabolism and Transformation

Understanding the interactions between plant metabolites and environmental xenobiotics, including pharmaceuticals from treated wastewater and biosolids, is critical due to their increased exposure and possible impact. Plant metabolites, including alkaloids, polyphenols, flavonoids, saponins, and terpenes, are recognized not only for their bioactive properties but also for the fundamental roles they play in plant defense, growth, and development, allowing significant interactions with xenobiotics [92]. So, plants can metabolize pharmaceutical compounds through enzymatic pathways analogous to xenobiotic detoxification systems in other organisms. The biotransformation of the original compounds in plant tissues is a consequence of a series of chemical processes, namely oxidation–reduction, hydrolysis, and conjugation reactions [82]. The final products of these reactions may be different from the original pharmaceutical compounds regarding toxicity, mobility, and environmental persistence. Nevertheless, current knowledge regarding the fate and toxicological relevance of plant-derived pharmaceutical metabolites remains limited [93]. It should be noted that the degradation or disappearance of the reactants in these reactions does not guarantee the existence of complete detoxification. The metabolites formed may have biological activity, also contributing to human exposure to these contaminants through the consumption of plant tissues [94].

## 6. Food Safety Implications and Human Exposure

The increasing detection of pharmaceutical residues in edible crops has raised concerns regarding food safety and long-term human exposure [16]. Although pharmaceuticals detected in agricultural products are generally present at low concentrations, continuous dietary intake may contribute to chronic exposure scenarios whose health implications remain insufficiently understood.

Circular economy practices, including the use of RWW for irrigation and the application of biosolids or animal manure to agricultural soils, provide important environmental, economic, and societal benefits. However, the increasing reliance on RWW irrigation and organic waste recycling in agriculture further emphasizes the need to better understand and assess the transfer of pharmaceutical contaminants through the soil–plant–food continuum [95].

### 6.1. Food Safety and Human Health

The recent European Union (EU) directive on water reuse (Regulation (EU) 2020/741) establishes quality criteria for the use of reclaimed water for irrigation. Nevertheless, these criteria focus primarily on conventional physicochemical and microbiological parameters, such as biological oxygen demand, chemical oxygen demand, pH, total suspended solids, and microbial indicators, without specifically addressing pharmaceutical contaminants [96].

Human exposure to pharmaceuticals through crop consumption depends on multiple factors, including contaminant concentration in edible tissues, dietary habits, consumption frequency, body weight, and the physicochemical properties of individual compounds. Because these physicochemical properties vary greatly, pharmaceuticals cannot be treated as a single uniform group; rather, they must be evaluated based on their distinct profiles of persistence, mobility, and toxicological risk. Antibiotics and antimicrobials are among the most abundant pharmaceutical classes in sludge and sludge-amended soils, and reviews repeatedly identify them as major agricultural soil contaminants [67,97]. Apart from antibiotics, the pharmaceutical pollutants most frequently detected in agricultural soils and crops are antiepileptics (e.g., carbamazepine), antidepressants (e.g., fluoxetine and sertraline), NSAIDs (e.g., diclofenac and ibuprofen), hormones (e.g., estradiol and ethinylestradiol), lipid regulators, and beta-blockers [11,98,99]. Carbamazepine was detected in 98% and 90% of the irrigation water and soil samples, respectively, and in all plant organs (i.e., roots, leaves, and fruits), indicating a high potential for food-chain transfer [11].

The occurrence of pharmaceutical residues in edible crops largely reflects their prevalence in agricultural soils and irrigation water. Antibiotics, anticonvulsants/antiepileptics, psychiatric drugs, NSAIDs/analgesics,  $\beta$ -blockers, and stimulants such as caffeine are among the most frequently detected classes in food crops [10–12,98]. A 2025 review of field-grown edible plants found that antibiotics, psychiatric drugs, NSAIDs, and caffeine together accounted for more than half of all detected pharmaceuticals. Among the 28 compounds reported in at least three studies, 15 were antibiotics, five were psychiatric drugs, three were NSAIDs, two were analgesics, one was a  $\beta$ -blocker, one was a diuretic, and one was caffeine [16].

Antibiotics are the contaminants that present the higher risk. The presence of antibiotics in agroecosystems is a known driver of AMR: there is evidence that antibiotic residues exert selective pressure in agricultural soils, leading to the proliferation and long-term persistence of ARGs within the soil microbiome; more, these soil-borne ARGs can be mobilized and transferred to the plant microbiome, colonizing crop tissues [17,23,25,38,47]. It has been demonstrated that *rmtB*-positive bacteria in agricultural soils can be transmitted in swine farms and their environments, and that these ARB or ARGs can be acquired by humans through the food chain [74,75].

Apart from antibiotics, the pharmaceuticals that pose the greatest threat are diclofenac and other NSAIDs, hormones, and psychotropic/antiepileptic drugs. NSAIDs, especially diclofenac, are among the most threatening pollutants because they are common in irrigated soils and waters, often poorly removed, and can drive high acute ecological risk [98,100]. Meanwhile, hormones present a completely different risk profile; they exhibit lower mobility but are critical from a chronic-risk perspective, as estrogenic compounds have repeatedly been identified as decisive contributors to long-term ecological effects even at low concentrations [100]. Similarly, psychiatric and antiepileptic drugs, especially carbamazepine and venlafaxine, are persistent, frequently detected, and can exceed ecological risk thresholds in aquatic systems [31].

Leafy vegetables and root crops are generally considered particularly susceptible to pharmaceutical accumulation because of their greater uptake potential and frequent consumption with minimal processing [89,97].

Table 2 highlights the main pharmaceutical classes detected in agricultural soils and edible crops, together with their principal food safety concerns.

**Table 2.** Major pharmaceutical classes detected in agricultural soils and edible crops and their main food safety concerns, based on data obtained by [35,94,97,101].

| Pharmaceutical Class    | Representative Compounds                      | Main Agricultural Source | Main Crop Types Affected | Potential Food Safety Concern        |
|-------------------------|-----------------------------------------------|--------------------------|--------------------------|--------------------------------------|
| Antibiotics             | Sulfamethoxazole, Ciprofloxacin, Tetracycline | Wastewater, manure       | Leafy vegetables, roots  | AMR                                  |
| Anti-inflammatory drugs | Diclofenac, Ibuprofen                         | Wastewater irrigation    | Vegetables, cereals      | Chronic low-dose exposure            |
| Antidepressants         | Fluoxetine, Sertraline                        | Wastewater, biosolids    | Leafy vegetables         | Neurotoxicity concerns               |
| Antiepileptics          | Carbamazepine                                 | Wastewater irrigation    | Leafy vegetables, fruits | High persistence and bioaccumulation |
| Hormones                | Estradiol, Ethinylestradiol                   | Manure, sludge           | Vegetables               | Endocrine disruption                 |
| Beta-blockers           | Atenolol, Metoprolol                          | Wastewater               | Cereals, vegetables      | Cardiovascular and metabolic effects |

While the detection of these residues in edible tissues confirms the exposure pathway, assessing the actual human health risk requires quantifying this dietary exposure. Human health risk is typically evaluated by calculating the Estimated Daily Intake (EDI). This EDI is then compared to the Acceptable Daily Intake (ADI) or Tolerable Daily Intake (TDI) to derive a Risk Quotient (RQ) [102]. Although current literature generally indicates that the Hazard Quotient (HQ) for individual pharmaceuticals consumed via crops remains below the threshold of immediate concern ( $RQ < 1$ ) for the general adult population, vulnerable groups, particularly infants and children, face significantly higher risks due to their lower body weight and proportionally higher dietary intake of specific foods [4,35].

Estimated food exposure levels are often found to be below accepted daily intake guidelines for certain pharmaceuticals in current risk evaluations. However, there is significant uncertainty in these assessments [102]. Existing toxicological frameworks are primarily designed for single compounds and may not adequately account for chronic low-dose exposure to complex pharmaceutical mixtures. Agricultural soil and RWW often contain multiple contaminants simultaneously, including pharmaceuticals, personal care

products, heavy metals, pesticides, and microplastics, creating the possibility of additive or synergistic effects [94,103].

One of the principal concerns associated with long-term exposure is the potential for subtle biological effects that may not be immediately detectable through conventional toxicological approaches. Chronic exposure to trace concentrations of pharmaceuticals has been associated with endocrine disruption, alterations in gut microbiota composition, reproductive toxicity, developmental effects, immunological disturbances, and neurological impacts [67,104]. Hormonal compounds and endocrine-active drugs are especially concerning since they can have biological effects even at very low concentrations. Antibiotics represent a particularly important pharmaceutical class within food safety discussions due to their potential role in AMR dissemination [41,105]. Soils exposed to antibiotic residues act as reservoirs of resistant microorganisms and ARGs. In this way, fresh produce contaminated with resistant bacteria may contribute to the transfer of AMR into the food chain. This risk is especially relevant for vegetables consumed raw, like leafy greens and fresh herbs, where limited food processing may reduce the removal of pharmaceutical residues and resistant microorganisms [102,106,107].

Currently, regulatory frameworks addressing pharmaceutical residues in plant-derived foods are scarce [108]. Existing legislation primarily focuses on veterinary drug residues in animal-derived products and pharmaceutical contamination in aquatic environments, leaving a critical regulatory void for crop-based agriculture. The lack of standardized monitoring guidelines and maximum residual limits (MRLs) for pharmaceuticals in edible plants indicates a significant regulatory gap that needs urgent attention. Future food safety protocols should incorporate assessment of cumulative and long-term exposures, mixture toxicity, and AMR. A multidisciplinary approach, integrating agronomy, toxicology, and public health, will be essential for understanding the full implications of pharmaceutical contamination within agricultural systems.

## 6.2. Mitigation Strategies

The mitigation of pharmaceutical residues in agricultural and environmental matrices needs a multifaceted approach [3,48]. Current literature emphasizes three primary domains of intervention: treatment at the wastewater source, management of biosolids and manure in agriculture, and field-scale remediation to reduce exposure. A strong consensus across recent studies underscores that no single method is sufficient; rather, integrating removal, containment, and managed reuse strategies yields the most effective mitigation [67].

Advanced wastewater treatment represents the most empirically supported strategy for intercepting pharmaceutical residues before they enter soils and irrigation networks. Comparative reviews consistently indicate that activated carbon (AC) adsorption, advanced oxidation processes (AOPs), and membrane separation technologies significantly outperform conventional biological treatments for persistent compounds, though each presents distinct operational trade-offs [5,30,109]. AC adsorption is widely feasible and relatively simple to operate; however, the subsequent management of spent sorbents, which retain the transferred contaminants, remains a logistical challenge. AOPs effectively degrade refractory pharmaceuticals via reactive radical species, yet they can generate toxic by-products and often result in substantial energy and chemical costs. Membrane technologies (reverse osmosis, nanofiltration, and membrane bioreactors) offer robust barriers against compounds, but retentate disposal and capital costs are the main disadvantages of this technology [109].

Regarding agricultural inputs, evidence strongly supports the pre-treatment of biosolids and manure prior to land application. Mitigation must focus on lowering residue concentrations and limiting direct contact with food systems. Promising manure-treatment

strategies include composting, anaerobic digestion, and hybrid bioprocesses, which can be further optimized by integrating newer microbial or enzymatic degradation systems [110].

At the field scale, mitigation strategies primarily function to reduce contaminant transport, bioavailability, and crop uptake. Although quantitative data at this scale are less robust compared to wastewater treatment, precision irrigation, biochar amendments, and biological remediation consistently emerge as vital, eco-friendly complementary measures [2,5,32,69,99]. A recent review highlights the rapid evolution of soil remediation technologies for pharmaceuticals, focusing on the efficacy of bioremediation, advanced adsorption, AOPs, with a growing focus on hybrid systems and artificial intelligence [111].

Precision delivery systems, such as drip irrigation, minimize direct plant contact and manage exposure pathways by aligning water quality with specific soil properties and crop types [13]. The application of biochar amendments can substantially attenuate pharmaceutical concentrations in both soil and irrigation water; however, its removal efficacy is highly compound-specific and dose-dependent, rather than universal [32]. Additionally, phytoremediation and bioremediation strategies (like constructed wetlands, microalgae systems, rhizosphere degradation, and microbial breakdown) offer cost-effective mitigation. Nevertheless, their performance is intrinsically tied to local environmental parameters, soil characteristics, and the specific contaminant profile [4,32].

### 6.3. Monitoring Pharmaceuticals in Agricultural Soils

Current literature indicates that routine monitoring occurs across wastewater influent and effluent, sludge, reclaimed-water irrigation systems, and agricultural soils [16,112,113]. As an instance, the RISMEAU dataset is an open-access scientific database focused on evaluating the environmental impacts of applying urban sewage sludge and agricultural manure as fertilizers to soil, including 33 pharmaceutical substances and biocides and AMR indicators [113].

Wastewater monitoring is the most established part of the evidence base. Studies measured pharmaceuticals in influent and effluent wastewater, then linked those profiles to soils irrigated with reclaimed water or to sludge destined for land application [114]. Soil monitoring is less standardized but highly feasible. Field studies successfully track pharmaceutical persistence from the surface down to 1.5 m deep [115]. Furthermore, analytical technology is no longer a barrier. Current methods reliably detect nanogram-per-gram (ng/g) concentrations in soil, making routine surveillance entirely possible [35].

Despite this technical capacity, the literature does not report legally binding soil limits for drugs. Environmental safety is instead estimated using predicted no-effect concentrations (PNECs) and RQs [114,115]. A cross-country human health risk assessment of emerging organic contaminants, including pharmaceuticals, calculated the risk-based threshold concentrations in biosolids and soils, but these and other published numeric values act as temporary standards [112]. In contrast, pesticide regulations enforce strict maximum soil concentrations, exposing a major regulatory gap for pharmaceuticals.

The 2021 EU Zero Pollution Action Plan formally recognizes pharmaceuticals as a critical environmental threat, even though they still lack legally binding numeric limits for these compounds in soil. Instead of setting strict soil thresholds, the framework aims to prevent contamination at the source and during treatment [116]. According to the 2026 Mid-Term Review, the EU is on track to meet its 2030 goal of reducing veterinary antimicrobial sales by 50%, a success that directly cuts the volume of residues entering agricultural soils through manure. Furthermore, the review points to the newly proposed Soil Monitoring Law as a critical next step, which will finally establish a harmonized surveillance framework to track diffuse pollution and emerging contaminants in European soils [117].

## 7. One Health Perspective and Antimicrobial Resistance

The occurrence of pharmaceuticals in agricultural soils must be interpreted within the broader context of the One Health paradigm, which recognizes the links between environmental quality, animal welfare, and human health [22]. Pharmaceutical contamination represents a particularly relevant One Health issue because contaminants introduced into water and soil circulate across ecological systems and affect human populations through crop consumption [118].

Among pharmaceutical classes, antibiotics are of particular concern because of their role in the development and dissemination of AMR [104,105]. The extensive use of antibiotics in livestock production has resulted in continuous environmental inputs through wastewater effluents, manure application, and biosolid amendments [24].

Agricultural soils receiving these inputs may thus serve as environmental reservoirs for antibiotic residues, resistant bacteria, and resistance genes. Even low environmental concentrations of antibiotics may exert selective pressure on soil microbial communities, promoting the survival and proliferation of resistant bacteria. Continuous exposure to sublethal antibiotic doses may also promote horizontal gene transfer mechanisms involving plasmids, integrons, and transposons, facilitating the spread of resistance determinants among environmental microorganisms [24,75].

The rhizosphere represents a particularly important interface within agroecosystems because intense microbial activity surrounding plant roots may enhance interactions between contaminants, soil microorganisms, and resistance genes. Pharmaceutical contamination may alter rhizosphere microbial composition, disrupt ecological balance, and influence nutrient cycling processes essential for soil fertility and plant productivity [72,74].

Fresh produce cultivated in contaminated soils may become contaminated with resistant microorganisms either through direct uptake, surface deposition, or interactions with contaminated irrigation water and soil particles. Vegetables consumed raw therefore represents a potential pathway for transferring resistant bacteria from environmental reservoirs to humans [75,102,106].

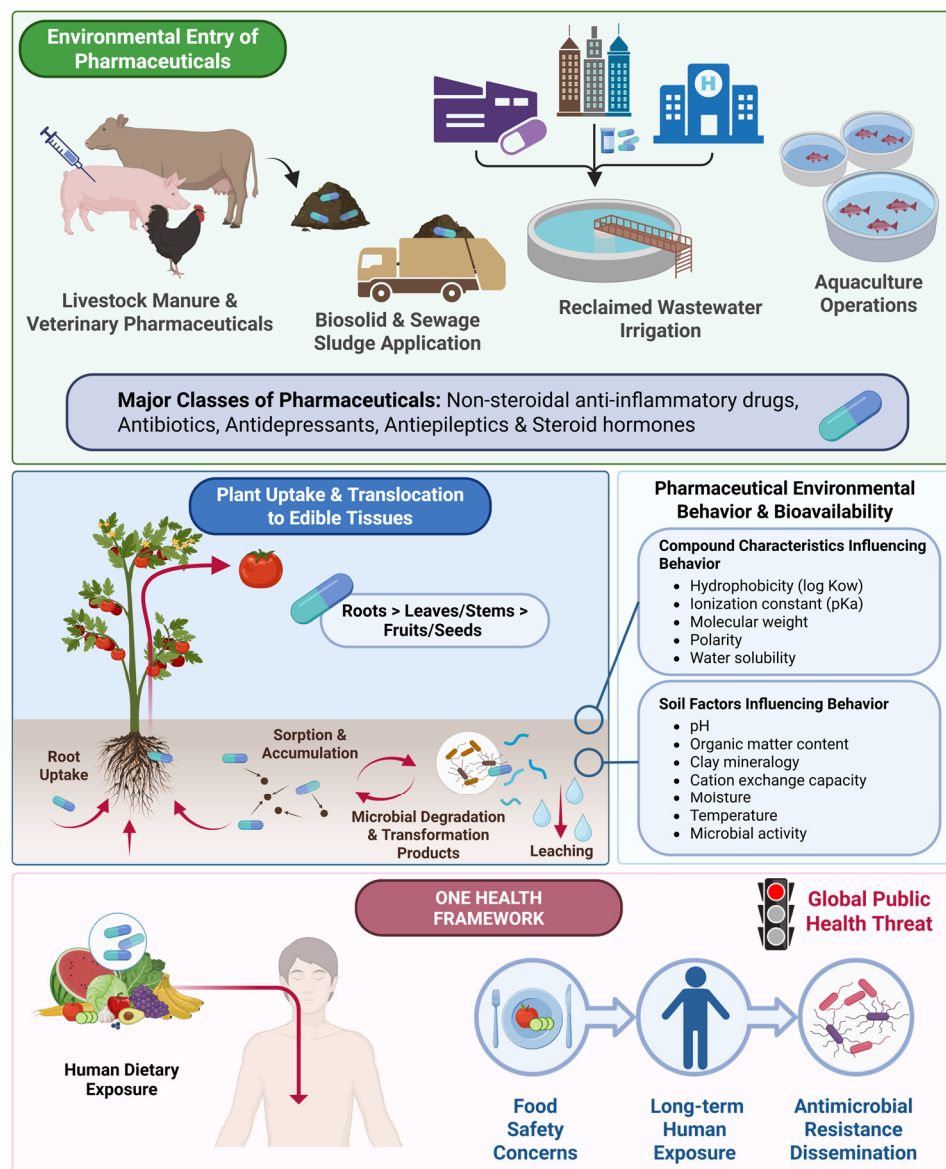
The environmental dissemination of AMR is increasingly recognized as one of the most serious global public health threats. The World Health Organization has repeatedly emphasized the importance of environmental compartments in resistance transmission dynamics [119]. Agricultural systems receiving pharmaceutical contaminants may therefore contribute to the maintenance and spread of AMR, highlighting the need for integrated mitigation strategies.

From a One Health perspective, the assessment of pharmaceutical contamination in agricultural systems requires the integration of environmental, agricultural, and public health indicators. Environmental monitoring should include pharmaceutical concentrations in soils and irrigation water, the occurrence of transformation products, and the presence of AMR determinants. Agricultural indicators should encompass pharmaceutical residues in crops, crop-specific uptake patterns, and changes in soil microbial communities and ecosystem functions. Public health considerations should include dietary exposure assessments and surveillance of AMR trends. Integrating these indicators would support a more comprehensive evaluation of pharmaceutical contamination across the soil–plant–food continuum and facilitate the development of evidence-based management and regulatory strategies.

The One Health framework requires coordinated action across environmental management, human and veterinary medicine, agriculture, and regulatory authorities [118]. Mitigating pharmaceutical contamination and AMR in agroecosystems demands a cohesive solution that incorporates advanced wastewater remediation and sustainable agronomic practices with public health and food safety. The One Health approach is also useful for identifying the implications of chronic pharmaceutical exposure in agroecosystems, beyond

AMR [25]. Pharmaceutical contaminants disrupt non-target biota and destabilize agroecosystem biodiversity, creating direct human exposure via the food web and water supply. Consequently, pharmaceutical contamination in agriculture should be regarded not only as an environmental issue but also as a significant food safety and public health concern.

Figure 1 summarizes the major sources, environmental fate, plant uptake pathways, and One Health implications of pharmaceutical contamination in agricultural systems.



**Figure 1.** Conceptual overview of pharmaceutical contamination in agroecosystems. Created in BioRender. dias, C. (2026) <https://BioRender.com/igplu7q> (accessed on 9 July 2026).

## 8. Conclusions

Pharmaceutical contamination in agricultural soils has emerged as an important environmental and food safety concern associated with wastewater reuse, biosolid application, and intensive livestock production. Through their continuous introduction into agroecosystems, these biologically active compounds behave as emerging non-conventional agrochemicals capable of influencing soil processes, plant physiology, and microbial communities.

Current evidence demonstrates that several pharmaceutical classes persist in agricultural soils and may be transferred to edible crops, with uptake and accumulation largely determined by compound physicochemical properties, soil characteristics, and plant phys-

iology. Although reported concentrations in food products are generally low, critical uncertainties remain regarding chronic exposure, mixture toxicity, transformation products, and the dissemination of AMR. Scientists can easily detect pharmaceutical pollution across water and soil, but regulators lack the legal standards to act on these findings. In particular, the absence of legally binding soil quality standards limits the translation of monitoring data into enforceable environmental protection measures. Consequently, soil systems remain comparatively under-regulated relative to aquatic environments, where governance structures are more established.

The increasing adoption of circular economy practices and water reuse strategies in agriculture reinforces the need for integrated risk assessment frameworks capable of balancing environmental sustainability with food safety and public health protection. In this context, the One Health framework provides a valuable perspective for understanding the interconnected environmental, agricultural, and human health implications of pharmaceutical contamination. Overall, the literature supports a multi-faceted basis to effectively mitigate this contamination. This involves wastewater treatments at the source, biosolid and manure processing prior to agricultural reuse, and field interventions (biochar application and precision irrigation) to manage residual exposure. For optimal management, interventions must be adjusted to the unique matrix of wastewater quality, specific pharmaceutical loads, prevailing soil conditions, and the intended agricultural end-use.

Future research should prioritize long-term field-scale mass balance studies, identification and monitoring of transformation products, assessment of mixture toxicity under environmentally realistic exposure scenarios, crop-specific uptake and translocation studies conducted under field conditions, improved dietary exposure assessment methodologies, and investigations into the persistence and transmission pathways of ARGs within agricultural systems.

Ultimately, pharmaceuticals should no longer be regarded solely as aquatic contaminants but recognized as relevant agroecosystem pollutants requiring systematic integration into sustainable agricultural management and environmental regulatory policies.

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