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Pollution of Soil by Pharmaceuticals: Implications for Metazoan and Environmental Health

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Abstract

The use of pharmaceuticals has grown substantially and their consequential release via wastewaters poses a potential threat to aquatic and terrestrial environments. While transportation prediction models for aquatic environments are well established, they cannot be universally extrapolated to terrestrial systems. Pharmaceuticals and their metabolites are, for example, readily detected in the excreta of terrestrial organisms (including humans). Furthermore, the trophic transfer of pharmaceuticals to and from food webs is often overlooked, which in turn highlights a public health concern and emphasizes the pressing need to elucidate how today's potpourri of pharmaceuticals affect the terrestrial system, their biophysical behaviors, and their interactions with soil metazoans. This review explores the existing knowledge base of pharmaceutical exposure sources, mobility, persistence, (bio)availability, (bio)accumulation, (bio)magnification, and trophic transfer of pharmaceuticals through the soil and terrestrial food chains.

1. INTRODUCTION

The US Environmental Protection Agency (EPA) and the EU Water Framework Directive (WFD) have established a list of priority pollutants that pose a challenge to aquatic organisms and overall water body health (1–3). This list currently excludes many commonly consumed contaminants of emerging concern, such as pharmaceuticals, that are now routinely reported to occur in surface waters at concentrations of picogram to microgram per liter (4, 5). Some pharmaceuticals have been included on the WFD watch list but have not yet been regulated (6). Since 2017, the global pharmaceutical market has grown annually by 5.8% (7, 8), and the consumption of antidepressants, antidiabetic drugs, and cholesterol-lowering agents has doubled over the past two decades (9, 10). The presence of pharmaceuticals in the environment has attracted growing concern, with over 130 pharmaceuticals detected in surface waters in Germany and global numbers exceeding 600 (11). Despite the potential impact of pharmaceuticals on the environment, the lack of comprehensive field occurrence data limits our understanding of their sources, transport, transformation, and effects in soils, including their potential transfer within food webs. Some 60% of European soils are considered unhealthy, which triggered a soil protection proposal by the European Commission to establish a watch list of priority substances linked to soil contamination (12). Pharmaceuticals and their transformation products are released into the environment via point (a defined source) or nonpoint (a diffuse source) dispersal routes. Major point sources include wastewater, sewer misconnections, storm flow vents, and direct dumping (e.g., of waste, packaging, unused medications). The most prominent source is the discharge from wastewater treatment plants (WWTPs) serving households, businesses, hospitals, schools, and pharmaceutical manufacturing sites, among other places. Importantly, modern WWTPs are not designed to remove pharmaceuticals completely. Major nonpoint discharges to water are likely to come from land leaching and surface runoff, where pharmaceutical contamination in soils or from other non-sewer-connected surfaces is washed out following storm events. Pharmaceutical contamination routes to and through soil are different from and less studied than the water routes.

Secondary wastewater treatment using activated sludge/biosolids is the dominant process for pharmaceutical residue removal, and this medium provides an environment that promotes (bio)transformation and sorption, as well as the horizontal/vertical exchange of antibiotic resistance genes (13). Following deactivation, digestion, and thermal treatment, this sludge by-product can still contain pharmaceutical residues, and large proportions of this material are often used as an agricultural soil fertilizer (e.g., in the United Kingdom this can be as much as 87% or 3.2 million tonnes) (12, 14). Exacerbating the issue, treated wastewater is also used to irrigate soils, especially where drought pressures on water resources exist, and the impact of pharmaceutical release via this route needs to be investigated in more detail (15). A further route to soil (13) is the diffuse dispersal of manure, slurry, or natural fertilizers containing animal excreta. Notably, the release of active pharmaceutical ingredients from veterinary medicines is estimated to significantly exceed the equivalent release from human drug applications (16). An additional source of pollutants is derived from the utilization of reclaimed water to irrigate recreational areas, such as golf courses (17). The notion that active pharmaceutical ingredients in reclaimed water are readily taken up by plants and in turn enter the biological food chain underlines how intricate pathways contribute to the permeation of pharmaceuticals into the environment (18).

Upon the release of these agents into the environment, their biological activity can adversely affect nontarget wildlife, thereby compromising ecosystem health (19). The deleterious impact of active pharmaceutical ingredients on aquatic organisms has been studied in fine detail. For example, extensive organ damage was inflicted on fish exposed to the antiepileptic agent carbamazepine and the β-blocker metoprolol (19), and sexual characteristics in male fish and the behavior of perch

were altered following a challenge with synthetic estrogen 17α-ethinylestradiol and psychotropic oxazepam, respectively (20). Equivalent research that focuses on the impact on the terrestrial habitat is, however, still in its infancy. One of the early examples that highlighted an unintended impact on terrestrial organisms was the sudden drastic decline in vulture populations in India. This decline was attributed to the vulture's consumption of cattle that had been treated (off-label) with diclofenac, a nonsteroidal anti-inflammatory painkiller. The bioaccumulation of diclofenac caused kidney failure in vultures, resulting in a 95% decline in vulture population within a decade (21).

Expert advice and routine testing ensure that pharmaceuticals in drinking water do not exceed concentrations considered to be above the danger threshold, at least in terms of the current knowledge pertaining to the no observable effects on human health (22). Residual levels of antibiotics and antibiotic resistance genes can enter the environment through WWTPs and manuring, thus posing an indirect but potentially severe threat to human health (23). The consumption of active pharmaceutical ingredients and antibiotics through meat and plant-derived food sources is generally considered to pose a negligible risk to human health (24); however, the occurrence of acute (high level) or chronic (low level) exposures needs to be taken into account, especially concerning foods derived from commercial croplands with a long history of irrigation or amendment by wastewater with limited regulation. This notion stresses the urgent need to fully understand the movements and accumulation characteristics of these contaminants (in isolation and as mixtures).

2. OCCURRENCE OF PHARMACEUTICALS IN SOIL

Many traditional pharmaceuticals, including nonsteroidal anti-inflammatory drugs, antibiotics, cardiovascular medicines (β-blockers/diuretics), psychostimulants, antihypertensives, estrogens and other hormones, and antiepileptic drugs, have been administered for several decades (25). Their omnipresence in soils and biosolids, including their potential bioactivity and potency, even at low concentrations, has been documented (25). Notable drugs of concern include antibiotics that foster microbial resistance, such as diclofenac, which displays acute toxicity, and 17β-estradiol, which induces endocrine disruption (26–28). However, other antibiotics (e.g., trimethoprim and sulfadiazine), antimicrobials (e.g., triclosan), nonsteroidal anti-inflammatory drugs (e.g., ibuprofen and diclofenac), and antiepileptic drugs (e.g., carbamazepine) are now commonly detected in soils around the globe, varying from microgram per kilogram (e.g., ibuprofen and trimethoprim) to milligram per kilogram (e.g., triclosan and sulfadiazine) levels (29–32).

One of the main routes of toxic pollutant exposure to humans is via ingestion, and soil is a prominent source (33). Public concern and research efforts have centered around heavy metals and polycyclic aromatic hydrocarbons, two diverse groups of pollutants pervasive in soils. Predicting the source and fate of these contaminants is surprisingly challenging due to their geographical redistribution through stormwater runoff and groundwater circulation, but also complicated by the application of treated water and/or sewage sludge. The most frequently detected pharmaceutical classes in soil samples often include analgesics, anti-inflammatories (in particular, the nonsteroidal anti-inflammatory drugs), antibiotics, and psychiatric drugs, but their abundance varies spatially and temporally (19). For example, erythromycin, carbamazepine, fluoxetine, and diphenhydramine were ranked as the most commonly detected pharmaceuticals across several sites in the United States during summer 2003 (34), while in 2018 the most frequent drugs were carbamazepine, primidone, *N*,*N*-diethyl-meta-toluamide (DEET), and caffeine (35). In contrast, soils sampled in mainland China in 2008 contained mainly triclocarban, 4-nonylphenol, salicylic acid, and oxytetracycline (36). The same report warned of the potentially high risk that triclocarban poses to soil macroinvertebrates, exemplified by the sensitivity of the earthworm *Eisenia fetida* with an LC_{50} of

40 mg/kg soil and a predicted no-effect concentration of only 40 μg/kg. Similar environmental levels of triclosan were observed in sludge samples from Europe (Norway at 32 mg/kg and Ireland at 25 mg/kg) and the United States (up to 30 mg/kg) (14, 37, 38). Crucially, the exposure of pharmaceuticals, especially antibiotics, may also alter the microbial community in the receptor soil system, posing additional pressure on fundamental ecological functions, but may also challenge human health if edible products are consumed from the contaminated soil (39).

2.1. Pharmaceutical and Soil Properties Governing Transportation in Soil

The intricate movement of pharmaceutical and personal care products (PPCPs) in soil, encompassing the transportation, transformation, degradation, and uptake by plants and soil organisms, is governed by complex physicochemical properties, initial compound concentrations, and soil characteristics. Properties such as polarity, octanol-water partition coefficient (log K_{ow}), and solid–water distribution coefficient (log K_d) dictate the ability to move within the soil matrix (40). In addition, (non)polarity-based interactions, ionization, cation bridging, and retention in stagnant pore water can also influence a pollutant's behavior in the soil environment (41). Notably, reactive structures, such as triazine rings and amino groups, amplify the sorption affinity of lamotrigine relative to carbamazepine, augmenting their ability to form hydrogen bonds with functional groups on soil surfaces, in particular polar soil organic matter (42). Higher mobilities in the soil can contribute to an increase in microbial utilization and plant uptake, but this is interdependent with soil quality (43). The following paragraph explores the influence of soil organic matter and dissolved organic matter in interstitial or pore water on the movement of pharmaceuticals, thereby elucidating the intricate dynamics at play in this critical environmental context.

Soil properties, including the active mineral component, organic matter, pH, ionic strength, porosity, temperature, and humic acid, all contribute to the mobility of PPCPs. The chemistry and structure of the active surface area are critical and multimodal retention is likely through combinations of hydrophobic interactions, size exclusion, ion exchange, and cation bridging, among others (44). Pharmaceuticals exhibit diverse soil absorption patterns that are influenced primarily by the soil's organic content and base cation saturation. Metoprolol and atenolol, for example, interact with soil via hydrogen bonding or anion exchange (45, 46). Research conducted on arable soil revealed that drug movement in soil is reduced as organic content increases, which is aggravated when soils are amended with biosolids (45). This phenomenon might arise due to the interactions between drug molecules and soil organic matter, which are most pronounced at lower drug concentrations (47). Although most soil particles can absorb compounds present at environmental levels, pollutant mixtures may compete for absorption sites (42). However, certain nonsteroidal anti-inflammatory drugs, such as naproxen and ibuprofen, display significant differences in absorption behavior when introduced into soils as an individual drug or as part of a drug cocktail (48). That these drugs can interact with soil cations, thereby potentially affecting their movement within the soil (48), highlights how soil characteristics can affect the absorption and retention of drugs, particularly when multiple pollutants are present. However, a recent report involving 13 different soil types suggested that the sorption rate of atenolol, metoprolol, and carbamazepine is not determined solely by the soil matrix (49). These contradictory findings highlight the need for further detailed research, focusing in particular on how different soil types drive the movement and changes in the biochemical characteristics of pharmaceuticals.

A previous report concluded that wastewater-irrigated soil suffered from higher mobilities of weakly acidic drugs due to the change in pH after irrigation, while the application of biosolids to arable land increased the content of soil organic matter and therefore supported the retention of pharmaceuticals (45). The level of acidity influences the modalities (nonionic, anionic, cationic, and/or zwitterionic) of PPCPs, where pH affects the ionic strength of pharmaceutical

sorption across different sorbates and sorbents, concluding as bell-shaped (e.g., sulfamethoxazole), negative (e.g., irbesartan), and positive (e.g., citalopram) relationships (46). Indeed, a large portion of previously studied PPCPs (mostly acids) presented an increment in sorption rate as pH increased (46, 50, 51). Other authors noted comparable increases in immobility and proposed that these were the consequence of substances binding to the dissolved organic matter of wastewater (52), but hydrophobic interactions alone cannot account for the observed diversity in drug movements within the geophysical soils and biosolids (40). Barron et al. (40) also suggested that in the absence of highly curated mechanistically derived models [including the influence of (bio)transformation on persistence], machine learning could be employed to model the behavior of PPCPs in soil. Higher mobilities increase the possibility of PPCPs entering the groundwater, which in turn can have a wider impact.

The increased use of antibiotics and the development of multiresistant bacteria present a serious threat to human and animal health (53, 54). Antibiotics, which are complex molecules with diverse functional groups, can be categorized on the basis of their mechanism of action and may include the inhibition of cell wall synthesis, the alteration of cell membranes, protein synthesis inhibition, nucleic acid synthesis inhibition, and metabolic/anticompetitive antagonism (55). Soil, traditionally considered a rich source of antibiotics, antibiotic-resistant bacteria, and antibiotic resistance genes, is influenced by both natural and anthropogenic processes. Modern activities, particularly the accelerated use of antibiotics in health care and livestock, introduce these substances into aquatic systems through hospital and pharmaceutical industry wastewaters, uncontrolled drug disposal, and aquaculture (56). The application of manure and sludge as fertilizers, coupled with reclaimed water for irrigation, further contributes to the dissemination of antibiotics and antibiotic resistance genes in soil (57). Environmental concentrations of antibiotics can display pseudopersistence due to their continuous release and intrinsic persistence, with some antibiotics (e.g., penicillin) degrading easily and others [e.g., fluoroquinolones (ciprofloxacin), macrolides (tylosin), and tetracyclines] exhibiting higher persistence, and thus remain in the environment for extended periods and accumulate to higher concentrations (58, 59). Sulfonamides are mobile yet persistent, and tetracycline, which is consumed globally, is a prevalent antibiotic observed in agricultural soil likely due to its chelation ability with metals (60, 61). Levels of terrestrial contaminations correlate with manure application in agriculture and wastewater discharge into surface water (62). Antibiotic adsorption rates can vary widely and are broadly grouped by their class and are dependent on the matrix (63). One notable example is the broad-spectrum synthetic fluoroquinolone antibiotic ciprofloxacin, which exhibits a high K_d of 54,600 L/g in soil at pH 5.03 (64). Antibiotics exhibit, often as zwitterions, diverse sorption mechanisms, including charge interactions such as cation exchange, cation bridging, electrostatic attraction, and electrostatic repulsion. Hydrophobic interactions are more prominent when nonionized antibiotic structures dominate within the appropriate pH range (46). Multiple sorption mechanisms concurrently govern antibiotic partitioning behaviors in soil and aquatic environments, with irrigation and rainfall facilitating their entry into the underground and surface water through soil infiltration and surface runoff, and subsequent migration is heavily dependent on adsorption and partition behaviors (63).

Citalopram [1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-5-phthalancarbonitrile] is a selective serotonin reuptake inhibitor that is frequently used to manage depression, anxiety, and obsessive-compulsive disorders. Citalopram is one of the most abundant psychiatric pharmaceuticals detected in influents but also effluents of WWTPs (65). Reports have identified significant variations in the sorption (250–1,838 $cm^3\ g^{-1}$) (40, 65) and K_d (210–25,000 $cm^3\ g^{-1}$) (66) values of citalopram in treated sludges, which underscores the importance of the source and property of the recipient sludge and challenges the efficacy of fixed K_d models for contaminants (66). Its K_d value is also positively correlated with pH, base cation saturation, sorption complex saturation,

and soil salinity but negatively correlated with hydrolytic acidity. Other physiochemical properties of the soil are thought to contribute to citalopram's behavior (67). Standard WWTPs remove only a fraction of citalopram, which can be detected in over 80% of effluents in Europe (68). This finding raises concerns about exposure risks to agricultural land if effluent from WWTPs is routinely employed for irrigation or fertilization (68). Even if an additional gamma radiation step is introduced, only 13.5% of citalopram is biodegraded by WWTPs, with a further 6.7% subjected to adsorption and 1.9% to hydrolysis. It is relatively stable once absorbed onto sediments and sludges (69). Notably, these percentages fluctuate depending on specific treatment scenarios, temperatures, and initial influent concentrations. Understanding the intricate interplay between physicochemical factors is crucial for developing effective strategies to manage the environmental impact of citalopram and similar pharmaceutical contaminants in wastewater.

2.2. Transformation and Fate of Pharmaceuticals in Soil

The types, combinations, and extent of biotic and abiotic transformation processes pivotally shape the fate of pharmaceuticals in soil systems. Transformation can render a drug less harmful to soil systems or generate a new, potentially more toxic substance, thereby posing a novel environmental health threat (e.g., norfluoxetine was 50% more toxic than the parent compound in Spirotox and Thamnotoxkit F toxicity tests) (70, 71). Research suggests that photodegradation of target pollutants is elevated nearer to the surface of wastewater, with geographic location acting as a major driver (higher latitudes tend to result in an increase in photodegradation rate) (72). Other factors, such as suspended solids and turbidity, impede photolysis by reflecting incident photons and direct photodegradation. To date, only a few studies have focused on the photodegradation of pharmaceuticals, and most have focused primarily on the parent drugs (72, 73). Photodegradation rates in soil are significantly lower than those observed in water samples, attributed to limited light penetration through the solid matrix (restricted to the top 0.5-mm layer) and the presence of carbonates inhibiting photolysis (72, 73). Soil structure, moisture, and the quality/quantity of organic compounds can influence photolysis of dissolved organic matter, potentially generating free radicals. These free radicals typically reside in the soil surface layer and may interact with other emerging contaminants, which in turn may contribute to further transformation or degradation. Furthermore, it has been hypothesized that triplet state organic matter can be transported by water and migrate to lower soil horizons following irrigation (74).

Modern metabolism-guided drug discovery efforts tend to design pharmaceuticals with reduced metabolic intrinsic clearance in order to resist common biotransformation processes for an optimization of metabolic stability (75). This in turn has the potential to cause a long-lasting toxicological impact on the environment. Bacterial biodegradation is an acknowledged route of xenobiotic elimination; however, the bacterial species and pathways responsible for the biodegradation of pharmaceuticals within terrestrial ecosystems await to be defined and studied in detail (27). As with photodegradation, the detailed mechanisms that underlie the biodegradation of certain drugs, particularly in the context of specific microorganisms or catalysts, have not been fully explored. Recent reports have linked bacteria inoculated with activated sludge to the pharmaceutical degradation processes in biofilms (76, 77). Although the identified bacterial isolates were able to transform specific drugs (including carbamazepine and triclosan) under laboratory conditions, it remains uncertain whether these microorganisms can effectively degrade pharmaceuticals in soils at environmental concentrations and conditions. The transformation of pharmaceuticals is of course a multidimensional entity, and various degradation processes occur in parallel, which results in a potentially diverse mixture of substances (78–80). These observations highlight the necessity to further study the potential environmental impact of secondary compounds within the soil environment.

Researchers have long been aware that the environmental transformation and degradation (half-life) of an antibiotic is interwoven with its molecular structure and (a)biotic physicochemical characteristics (81, 82). Amoxicillin, for example, is easily biodegraded, with a half-life of 0.43 days in field soil (83, 84). More persistent antibiotics are ofloxacin, tetracycline, and norfloxacin, with estimated half-lives in paddy soil subjected to a repeated amendment with biosolids of 2.0, 2.2, and up to 3.7 years, respectively (85). A pot design study that compared the dissipation rates of various antibiotics in a rice–wheat system revealed that fluoroquinolones persist longer than other antibiotic classes, including macrolides and tetracyclines (85). Once biosolid application was suspended, macrolides and tetracyclines were rarely detected within 2 years, but fluoroquinolone concentration was reduced to only 50% after 1 year, decreasing a further 20% the following year. Repeated biosolid amendments inhibited soil microorganisms and microbial activity, but microbial degradation emerged as a principal mechanism for fluoroquinolone dissipation (86, 87). In contrast, the dissipation of tetracycline varied, but differences between treatments diminished. The findings suggest that aged residual forms of tetracyclines may accumulate in soils over time. The same experiment was also set up with two biosolids with varying metal content, which revealed that the presence of heavy metals modulated microbial activity and enhanced the adsorption and catalyzed the degradation of tetracyclines (88). The reduced mobility of tetracyclines may be due not only to enhanced adsorption but also to their ability to chelate with metals (89). Different biosolid-amended soils exhibited diverse antibiotic residues over 1–2 years, suggesting that microbial activity can recover over time. Crucially, not all antibiotics behave in the same manner. For example, fluoroquinolone residues in soils with high heavy metal loading remained elevated, possibly due to their lower bioavailability and stronger chelation with heavy metals (90). Also, antibiotics are rarely present in isolation.

Carbamazepine, a pharmaceutical that has been studied in some detail in terms of its impact on the terrestrial ecosystem, is removed by WWTPs at varying rates in different treatment processes with no variation across the seasons (49, 91). In soil, carbamazepine undergoes a transformation from the primary intermediates (10,11-dihydro-10-hydroxycarbamazepine and carbamazepine-10,11-epoxide) via secondary intermediates (acridone-*N*-carbaldehyde and 4-aldehyde-9-acridone) to acridine (92). The insertion of oxygen into the most reactive site facilitates the formation of hydroxyl derivatives, namely 10,11-dihydro-10-hydroxycarbamazepine and carbamazepine-10,11-epoxide, which suggests that at least some terrestrial biodegradation processes are enzymatically mediated. Indeed, similar epoxides (as well as additional intermediates) are generated when polycyclic aromatic hydrocarbons are metabolized by cytochrome P450 oxidation (93), which highlights their toxic potential to biological systems. Likewise, acridine, one of the final metabolites in this pathway, inhibits DNA repair and cell growth (92, 94). The lower hydrophobicity of carbamazepine-E (compared to that of carbamazepine) results in weaker sorption and higher mobility in the terrestrial environment, making it more likely to travel to deeper soil layers, and therefore poses a threat to the entire soil system, including groundwater (95). Other studies observed additional intermediates that are not covered here (27, 49, 96). Several potential pathways have been proposed in which endophytic fungus (*Aspergillus niger*) and bacteria (*Rhizobium radiobacter* and *Diaphorobacter nitroreducens*) transform carbamazepine into carbamazepine-E (97), 10,11-dihydro-10-hydroxycarbamazepine, and acridine, and certain flowering plants (e.g., the reed *Phragmites australis*) generate intermediates *cis*-10,11-dihydroxy-10,11-dihydrocarbamazepine and *cis*-2,3-dihydroxy-2,3-dihydrocarbamazepine (73). These findings highlight the critical need to elucidate the transformation pathway of pharmaceuticals in terrestrial compartments, as metabolites of carbamazepine might benefit from higher mobility and toxicity more than the parent compound would.

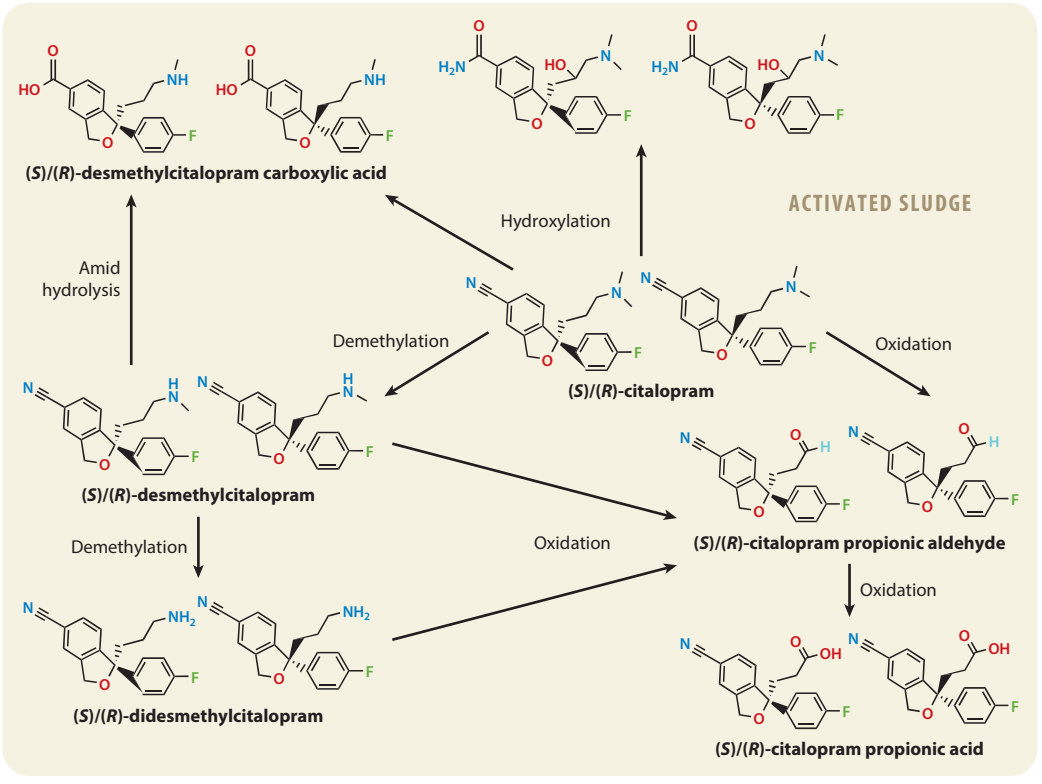

Figure 1

The complex biodegradation of citalopram in activated sludge can encompass numerous mutually nonexclusive hydrolysis, methylation, hydroxylation, and/or oxidation processes.

Citalopram does not seem to be prone to biodegradation either in the laboratory or in greenhouse experiments (98), and among the major psychiatric drugs, it has the longest dissipation half-life (223 days), which is extended to 311 days when applied with other antidepressants (98). Less than 50% of citalopram was observed to transform into its metabolite *N*-desmethylcitalopram (**Figure 1**), perhaps explaining why this compound remains in the terrestrial system and threatens the quality of soil health and agricultural products (99). Indeed, citalopram occurs in different environmental matrices, including sludges and agricultural soils (99). However, to date most publications have focused on the parent compound only and neglected the metabolized derivatives generated via oxidative reactions (hydroxylation, oxidation, and *N*-demethylation), nitrile hydrolysis, or amide hydrolysis (100).

3. PHARMACEUTICALS AND SOIL TROPHIC LEVELS

The natural ecosystem is inherently complex, and organisms find their position within the expansive framework of a food web. This interconnectedness implies that pharmaceutical compounds may also transfer horizontally across trophic levels. However, investigating the risks of such exposure poses challenges due to ethical, scientific, and practical constraints on direct approaches. Bioaccumulation models have therefore become instrumental in assessing the environmental and biological hazards associated with a spectrum of commercial chemicals, ranging from metals to pesticides, and persistent organic pollutants (101). The paradigm of environmental pollution has

recently expanded to encompass pharmaceuticals, leading to investigations into the occurrence and trophic transfer of drugs, including carbamazepine and roxithromycin (102, 103). Most of the advances have been achieved within the aquatic environment, particularly piscivorous food chains. Concerning the terrestrial ecosystems, attention has centered predominantly around plant communities and their accumulation of pollutants within food webs. Here, the bioconcentration factor is a powerful metric that facilitates the evaluation of the bioaccumulation potential of drugs, offering insights into plant uptake mechanisms under hydroponic conditions. Hydroponic experiments serve as rapid screening tools to identify priority drugs with a high potential for plant uptake, particularly as pharmaceuticals desorbed in pore water enhance the availability for plant uptake (42). However, translating findings from hydroponic research to real environments proves challenging given the intricate interplay with soil properties. The discrepancies between the calculated bioconcentration factor from hydroponic and soil studies emphasize that the bioavailability of certain drugs can potentially be significantly lower in a soil matrix, which in turn highlights the need for an improved understanding of the complex processes that govern the uptake of pharmaceuticals by plants in natural settings.

PPCPs accumulate in the edible tissues of plants grown on contaminated soils. Triclosan and triclocarban, for example, are easily absorbed by the roots and subsequently transported to leaves and fruiting bodies. Carbamazepine, in particular, accumulates in common vegetables such as celery and zucchini (104–106). The potential for root uptake is linked to the chemical property of a drug. While we know that the uptake of neutral PPCPs by roots is positively correlated with the hydrophobicity of the molecule (107), less is known about uptake dynamics of acidic/basic PPCPs (43, 108). Humans who consume daily root and leaf vegetables grown on commercial land are estimated to reach 0.09–3.81% of the acceptable daily intake for a single compound (41). Exceptions are triclosan, lamotrigine, and the metabolites of carbamazepine, which have the potential to exceed the threshold of toxicological concern (109). Our limited knowledge base pertaining to the human health risks that are derived from the consumption of plant foods restricts our ability to predict the impact of any indirect ingestion of pharmaceuticals.

3.1. Trophic Transfer of Pharmaceuticals by Plants

Field data support the notion that antibiotic resistance genes are distributed throughout the soil–plant continuum (47). The concentration of most antibiotic resistance genes decreases as they transition from soil to fruit, with some dilution factors ranging from 100- to 1,000-fold (110). The concentration and composition of antibiotic resistance genes in the edible parts of plants are strongly influenced by the antibiotic resistance genes input from the soil and the type of recipient crop. Certain antibiotic resistance genes, such as *tetM*, *mecA*, and *blaOXA-58*, serve as indicators of anthropogenic water and soil pollution (111). Treated wastewater seems to affect the soil and plants less than the amendment with biosolids and manure. Results from a study that utilized ^{14}C-carbamazepine, ^{14}C-carbamazepine metabolites, or both demonstrated that carbamazepine and its metabolites were taken up by all plant tissues of three edible vegetables (celery, carrot, and bok choy) (104). However, carbamazepine accumulation varied between tissues, suggesting that the extent of carbamazepine uptake is influenced by physiological properties of the crop. As exemplified by the bioaccumulation of carbamazepine, the consumption of vegetables subjected to organic fertilization, particularly through sewage sludge amendment, poses an additional exposure risk to primary consumers. This transmission is, however, not unidirectional but can further spread to surrounding water courses through agricultural runoff events and affect the resident wildlife. This source can therefore result in the indirect transmission of pharmaceuticals to terrestrial metazoans.

3.2. Trophic Transfer of Pharmaceuticals by Metazoans

Most drugs undergo a rapid transformation and elimination, thus explaining why most pharmaceuticals that occur in the environment are below the predicted no effect concentration. However, despite efficient removal, any incessant flow of pharmaceuticals into terrestrial environments risks the removal capacities of local soil systems to saturate over time. Elevated concentrations of heavy metals in soil, for example, bioaccumulate in the macroinvertebrate earthworm, and the subsequent predation by birds (e.g., black-tailed godwits) resulted in elevated heavy metal concentration in their unhatched eggs (112). The biomagnification of toxic substances by earthworms and the resultant (potentially transgenerational) secondary poisoning by feeding on them highlight an additional (indirect) route of exposure. Regulatory bodies/agencies rely primarily on models to predict the bioaccumulation of chemicals in water-respiring organisms. These models ignore, at large, the differences between aquatic and terrestrial organisms, variations in the biomagnification of certain drugs, but also the transfer of contaminants to other organisms (113). The biomagnification and trophic magnification factors partly address this shortfall, as they take dietary exposure into account and are adaptable for both air-respiring and water-respiring systems (114). Persistent organic pollutants can be trophically amplified from the primary producers, via detritivores and primary/secondary consumers, to the apex predator (113), which highlights that certain terrestrial food chains may experience elevated levels of organic compounds. Thus, specific and accurate models are required to study the accumulation of contaminants of emerging concerns in terrestrial invertebrates and organisms higher up in food chains. That said, the determination of trophic magnification factors is impractical when focusing on lower levels of the food chain, due to their trophic position and the presence of trace concentrations of certain drugs (115). Also, most models designed to generate trophic magnification factors are too simplistic in design (101), mainly due to the lack of relevant field studies and data collections that are needed to develop robust biomagnification models of the terrestrial environment.

Accepting that terrestrial organisms release a substantial quantity of active antibiotics into the environment leads to the notion that they contribute significantly to the propagation of antimicrobial resistance within communities, especially through the food chain (116). Limited information is available regarding the mode of introduction of antimicrobial resistance by animals; possible vectors include arthropods, rodents, and wild birds (117), but the specific pathways of gene exchange and the impact of manure or feed treatment remain poorly understood.

Human populations face chronic exposure to animal-derived antibiotic resistance genes through direct contact with animals or via the consumption of animal products. Manure application to soil introduces antibiotics into terrestrial systems, exposing animal populations to antibiotic resistance genes and antibiotic-resistant bacteria through the food chain and environmental pollution. In low- and middle-income countries, the use of unprocessed animal and human waste as fertilizer creates conditions conducive to the horizontal transfer of antimicrobial resistance genes, and this is exacerbated by the widespread release of antibiotic resistance genes into the environment. Although gene movement between hosts is extensive, attempts to qualitatively or quantitatively track these genes in vivo have proven challenging. Surveillance programs must expand their focus beyond pathogenic antibiotic-resistant bacteria to also include the antibiotic resistance genes they carry. This is in particular pertinent given the dynamic nature of gene movement and the potential alterations during the passage through intermediate hosts (110). While some data concerning antibiotics are available, field data that focus on pharmaceuticals are, at large, missing, even though pharmaceuticals have been predicted to accumulate in food webs (19).

3.3. Impact of Climate Change on Pharmaceuticals in Soil

Global climate change, driven by natural phenomena, human activities, or both, can significantly affect the occurrence, transportation, and transformation of toxicants (118). This aspect is of importance given that climate change is predicted to cause an additional 250,000 deaths annually between 2030 and 2050 (119). Many diseases are sensitive to climate variations and can therefore exacerbate the spread of bacterial and vector-borne diseases in humans, animals, and plants. Furthermore, the climate change–derived (re)emergence of diseases may contribute to the increased prevalence of pharmaceutical use. In recent years, several comprehensive reviews have established the ecotoxicological impact of pharmaceuticals on aquatic environments within the context of climate change (120–122). However, to what extent this global phenomenon can be extrapolated to the terrestrial environments has been neither established nor directly studied.

Climate change has been linked to shifts in pharmaceutical usage, particularly β-blockers, angiotensin-converting enzyme inhibitors, statins, salicylates, antiplatelets, and vasodilators, as well as various antidepressants, antipsychotics, and sedatives (123). Without proper management and regulation, these pharmaceuticals pose persistent threats to soil health. Once introduced into terrestrial systems, they can leach into surrounding water bodies through surface runoff or groundwater. Extreme precipitation events, which are modeled to become more prevalent due to climate change, can augment the transport of contaminants into water bodies. Moreover, climate change may increase the frequency of macropore and overland flow events due to the surpassing of soil infiltration capacities (124, 125). In addition, drier summers prolong the periods of high soil moisture deficits, increasing soil surface hydrophobicity and runoff during intense rainfall, while flood events have already been demonstrated to amplify water body contamination by pesticides (126). The impact of climate change on plant uptake of chemical contaminants is currently difficult to predict, suggesting that current regulatory models may inadequately assess the potential impact of climate change on human exposure from plant residues (123).

Climate change is also anticipated to influence the transport and fate processes that determine the persistence and form of contaminants in environmental compartments (127). The biodegradation and transformation of chemical pollutants are expected to increase, but the sequestration of contaminants might decline due to the projected decrease in soil organic carbon, as discussed in Section 2.1 (128). To what extent climate change will affect pathogen behavior, viability, and fate in the environment, as well as the stability and mobility of (disease) genes of public health concern, is currently not known yet poses a significant challenge for future generations.

4. CONCLUSION

The irrigation of soil with wastewater and the amendment with biosolids are often overlooked sources of secondary environmental pollution. Pharmaceuticals, when introduced into terrestrial environments through wastewater irrigation, can undergo a range of combined and complex transportation and transformation processes (**Figure 2**). The extent and specifics of these transformations depend not only on their physicochemical properties and concentrations but also on soil properties, such as organic and metal content, as well as pH, temperature, porosity, saturation, and pH. It is crucial to note that antibiotics and antibiotic-resistant bacteria, often present in wastewater, demand additional attention concerning their transportation and transformation within the terrestrial system and the food chain. A better understanding of the intricate dynamics of how these components move and change is needed for the comprehensive assessment of environmental and human risks.

Previous reports have identified pharmaceutically active compounds and their metabolites in human excreta following the consumption of a diet consisting of fresh products that had been

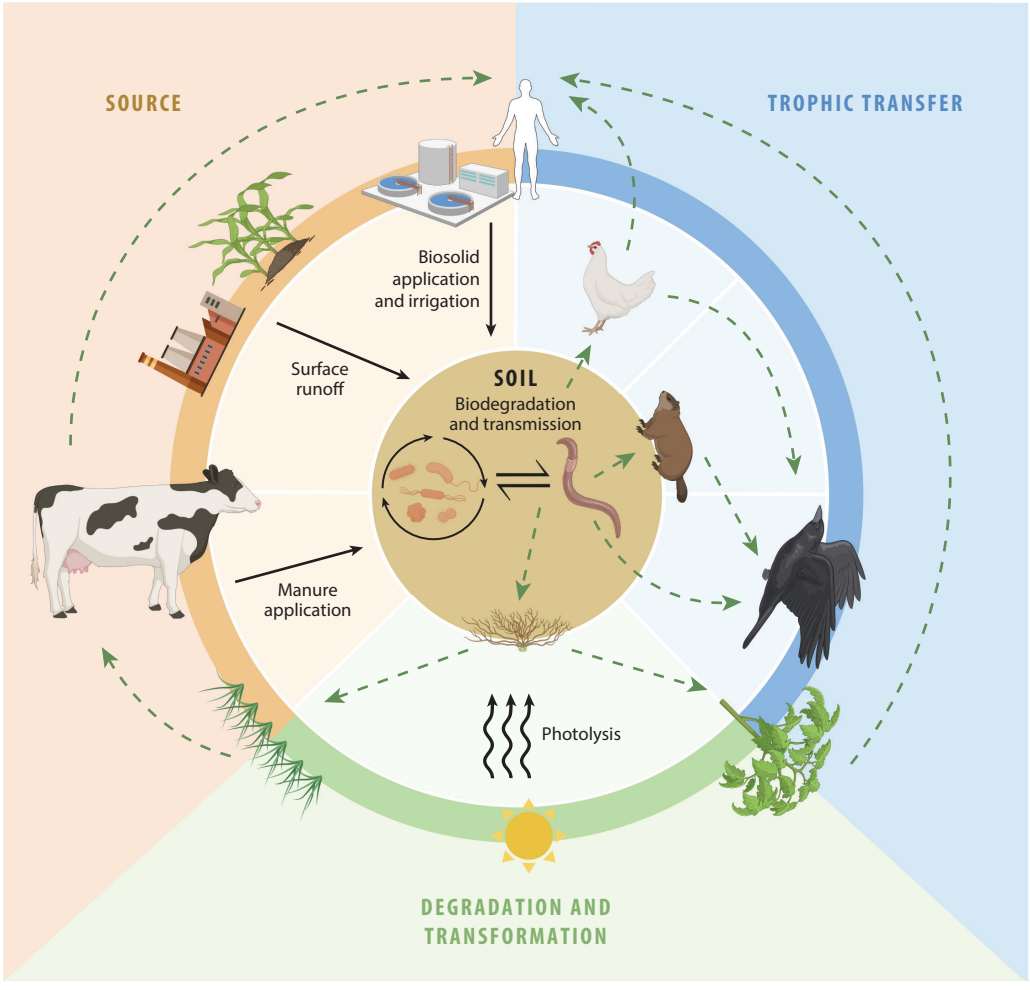

Figure 2

The potential sources, degradation, and transformation, as well as transfer paths, of pharmaceutical and personal care products in the terrestrial environment. The dashed green arrows represent possible trophic transfer paths via plants and metazoans. Figure adapted from images created with BioRender.com.

irrigated with wastewater (96, 129), highlighting potential risks to public health. Organic compounds with specific reactive structures and physicochemical properties, such as naproxen and lamotrigine, exhibit an enhanced mobility in soil, potentially contributing to further microbial utilization and plant uptake. These mobile pharmaceuticals may exert a significant impact on groundwater and soil health, even if they are rapidly transformed. The limited penetration of light through the soil matrix hampers the photodegradation of light-sensitive drugs, although some photodegradation can occur in biosolids prior to their release into the soil. At what point the rate of photodegradation (combined with soil properties) influences the transportation of pharmaceutical remains unknown, at least for most compounds.

By design, most pharmaceuticals are less stable than persistent organic pollutants, thus increasing the probability of the generation of metabolites. The degradation processes and emergence of pharmaceutical metabolites are driven by specific soil bacteria, but the current knowledge linking

pharmacology and soil microbiology is unfortunately still limited. Pharmaceuticals can also affect ecosystem health via their uptake by plants and animals and subsequent movement through food webs. Crops and other fresh products may therefore introduce pharmaceutically active compounds and their stable metabolites into animals and humans. In summary, this review highlights the urgent need to focus on the public health risks that can arise from the indirect and unintentional introduction of pharmaceuticals into soil, with a particular emphasis on antibiotics and antibiotic-resistant entities. Monitoring these antibiotic resistance genes in quality standards should guide future regulations governing reclaimed water use in agriculture and enhance the quality of human and environmental health.

DISCLOSURE STATEMENT

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