

Review

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How Pharmaceutical Residues Occur, Behave, and Affect the Soil Environment

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Posted Date: 9 July 2024

doi: 10.20944/preprints202407.0757.v1

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Review

How Pharmaceutical Residues Occur, Behave, and Affect the Soil Environment

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Abstract: Many pharmaceuticals (PhMs), compounds used to treat or prevent human and animal diseases, have been identified as pollutants of emerging concern (PECs) due to their wide distribution in the environment and their potential adverse effects on non-target organisms and humans. They are often found in significant concentrations in soils due to the continuous release of effluent and sludge from wastewater treatment plants (WWTPs), which is significantly faster than their removal rates. Although they are generally present at low environmental concentrations, conventional wastewater treatment processes cannot effectively remove pharmaceuticals from influent streams and biosolids. In addition, land application of animal manure can result in the pollution of soil, surface-, and groundwater with PhMs through surface runoff and leaching. Irrigation with treated wastewater and land application of biosolids are common agricultural practices in arid and semi-arid regions, resulting in the distribution of a wide range of PhMs in agricultural soils. The ability to accurately determine the fate of PhMs in soils is essential for rigorous risk assessment associated with wastewater reuse or biosolids return to the environment. The behavior and fate of PhMs in soils are determined by a number of processes, including adsorption/desorption (accumulation) to soil colloids, biotic (biodegradation) and abiotic (chemical and photochemical degradation) degradation, and transfer (movement) through the soil profile. In soil-plant systems, the amount of organic chemicals taken up by plant roots depends largely on the sorption/desorption of PhMs in soils. The extent of this process depends on several factors such as crop type, physicochemical properties of the compound, environmental properties and soil-plant characteristics. It is assumed that PhMs present in soil pore water are readily bioavailable for uptake by plants and that soil water acts as a carrier to move PhMs into plants. Determining microbial responses under different exposure conditions can help elucidate the impact of PhMs on soil microbial activity, community size and structure. For all of the above reasons, soil remediation is critical when soil pollutants pose a threat to the environment.

Keywords: emerging pollutants; pharmaceuticals; plant uptake; soil behavior; soil remediation

1. Introduction

Since the beginning of this century, a large body of qualitative research has been developed worldwide to investigate the occurrence and fate of emerging pollutants (EPs), also known as pollutants of emerging concern (PECs), in the environment as a result of point and diffuse pollution [1]. Recent studies have drawn attention to the presence in the environment of a wide variety of identified compounds of anthropogenic origin (including microorganisms) from domestic wastewater, industrial effluents, hospitals, livestock farming, and agricultural activities [2]. The occurrence of these compounds (mostly organic) and their adverse effects on aquatic and terrestrial ecosystems and human health is currently a matter of concern in the scientific community, as the potential ecotoxicological effects on non-target receptors due to their exposure remain unknown [3,4]. A review of the literature extracted from The Web of Science™ (WoS), managed by Clarivate Analytics (Philadelphia, PA, USA), using the following search terms “emerging pollutants” (title) OR

“emerging contaminants” (title) AND “environment” (topic) AND “2010-2024” (year published) reveals over 2,600 publications, with a clear exponential growth trend in the last decade.

In addition to the well-known environmental pollutants, more and more EPs are being identified thanks to the development of analytical techniques (mainly GC-MS² and LC-MS²) that allow the detection of very low concentrations (ng L⁻¹/ng kg⁻¹) in environmental matrices, although their toxicity, environmental occurrence and characteristics are still less known than those of conventional pollutants [5–11].

EPs are not necessarily new compounds. They are chemicals and/or micro-organisms that have often been present in the environment for a long time, but whose presence and importance is only now being understood. EPs can be defined as new chemicals, including their transformation intermediates, that have not been subject to regulatory evaluation and whose effects on the environment and human health are not well understood. Between 30,000 and 50,000 industrial chemicals have been found in everyday products, many of which are considered potential EPs due to their release into the environment, based on the number of substances listed under the European Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) established by the European Chemical Agency [12]. These include pesticides, pharmaceuticals, personal care products, illicit drugs, lifestyle compounds, industrial compounds and by-products, microplastics, flame retardants, nanomaterials, disinfection by-products, etc., and more recently, microorganisms such as the SARS-CoV-2 virus have been detected in wastewater worldwide in recent years [13–16].

Pharmaceuticals (PhMs) are products containing drugs in specific dosages that can be used for health care purposes. The population profile of most countries is aging, as the proportion of the world's population aged 65 and over is steadily increasing, which is a major driver of the PhMs market. The research, development, production, and distribution of medicines is the responsibility of the pharmaceutical industry. The market has experienced significant growth since the beginning of the century, with a linear increase ($R = 0.99$) and revenues of 1.61 trillion US dollars (USD) worldwide in 2023 and is expected to grow at a compound annual growth rate (CAGR) of 7.6% from 2023 to 2030 [17] (Figure 1).

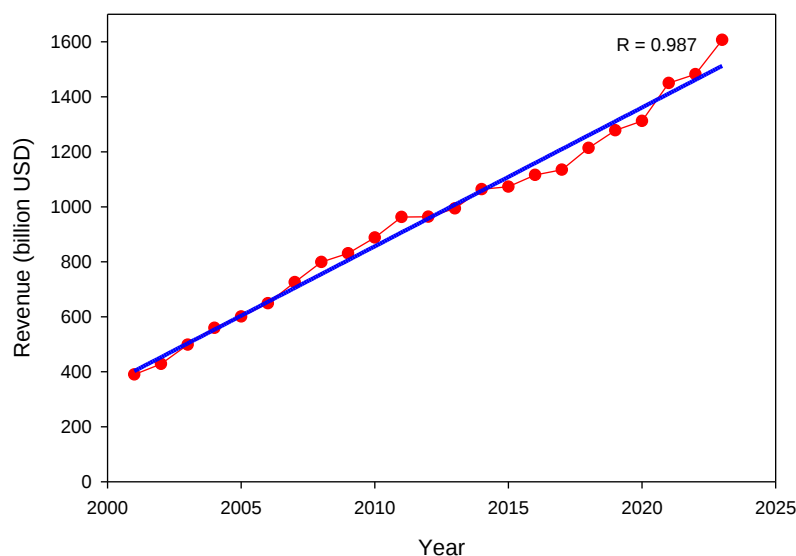


Figure 1. Worldwide pharmaceutical market sales (2001-2023).

By advancing science and developing research technologies, the pharmaceutical industry has achieved many benefits in protecting human and animal health and life. However, when talking about the achievements in the field of pharmacotherapy, one should also consider the numerous unresolved problems with residues of active pharmaceutical ingredients in the environment [18–22]. In particular, PhMs, compounds used to treat or prevent human and animal diseases, are often found in significant concentrations in soils due to the continuous release of effluent and sludge from

wastewater treatment plants (WWTPs), which is significantly faster than their removal rates [23–29]. Since the 1990s, a number of PhMs have been reported to have health effects on organisms such as fish, algae and others in the environment [30]. After ingestion by human and animals, some of them are excreted unaltered and can therefore reach WWTPs via the sewerage system [31,32]. In addition, most PhMs are metabolized in the human and animal body. The metabolites are mostly excreted and subsequently enter the environment directly or via WWTPs [33]. The levels of PhMs in the environment have only recently begun to be monitored and recognized as potentially harmful to ecosystems, and in recent years they have become a major public health concern as environmental pollutants. In this context, Directive 2013/39/EU [34] identify so-called priority substances, whose emissions must be reduced or phased out and also establish the need to create a monitoring list of EPs. Thus, through different Implementing Decisions (2015/495/EU, 2018/840 and 2020/1161) compounds such as some PhMs (diclofenac, macrolide antibiotics, sulfamethoxazole and venlafaxine) and other EPs were included because their occurrence, persistence and lack of regulation. All this with a view to achieving goals such as the Zero Pollution Ambition announced in the European Green Deal [35], which is linked to the Chemicals Strategy for Sustainability [36]. In the context of this initiative, PhMs are highlighted in the Strategic Approach on Pharmaceuticals in the Environment [37] and the Pharmaceuticals Strategy for Europe [38], both of which highlight the environmental and potential health impacts of pollution from pharmaceutical residues and list a number of actions to address these challenges included in six areas: i) Raise awareness and promote prudent use, ii) Improvement of training and environmental risk assessment, iii) Collection of monitoring information, iv) Promote greener pharmaceutical development, v) Reduction of manufacturing emissions, and vi) Reduce waste and improve wastewater management. More recently, in October 2022, the European Commission adopted a proposal to revise the list of priority substances in surface water, which includes a number of PhMs used as painkillers, anticonvulsants and antibiotics [39]. These proposals aim to counteract the negative impacts of PhMs on the environment and cover all phases of the lifecycle of PhMs, from design and production to use and disposal.

Therefore, further measures are needed to prevent pollution in the first place, as well as measures to clean up and remediate it, in order to improve its subsequent reuse while protecting the health of the population. In this sense, the contaminated wastewater (urban, agricultural and industrial) treated by conventional WWTPs is in some cases insufficient to reach the level of purity required by law for some of the most persistent pollutants [40]. This fact is evident from numerous monitoring studies conducted worldwide on WWTPs effluents, where a wide range of PhMs have been found [10,31,41–44]. Reclaimed water is increasingly being used to supplement water resources. However, it has a complex matrix that includes EPs that are introduced into the soil when this water is used for irrigation.

Water scarcity and the unequal geographical distribution of rainfall is an issue of concern in arid and semi-arid areas like Mediterranean basin, where water management strategies are advocating the re-use of treated wastewater effluents in agriculture because of climate change. Given the wide variety of EPs entering WWTPs, many substances end up in the receiving environment after with or without alteration. The use of wastewater and its discharge into waterways exposes the agro-environment (soil and crops) to PhMs, many of them still unknown and unassessed [22,24]. To avoid this concern, the EU has focused on this issue by revising the minimum requirements for water reuse in the context of integrated management under Regulation 2020/741/EU on minimum requirements for water reuse [45] to ensure that recycled water is safe for agricultural irrigation, to promote the circular economy, to support resilience to climate change by addressing water scarcity and related pressures on water resources. Thus, where necessary and appropriate, water quality requirements and monitoring will include, in addition to BOD₅, TSS, turbidity, *E. coli*, *Legionella* spp., intestinal nematodes and others, the control of PhMs and other EPs such as heavy metals, disinfection by-products, pesticides, microplastics, etc. to ensure the protection of the environment and human/animal health. Although conventional WWTPs act as a primary barricade against environmental pollution by EPs, they are not designed to remove them at low concentrations or are

ineffective in their removal [46]. Therefore, many countries around the world are investigating the upgrading of WWTPs with new (advanced) treatment technologies to achieve the removal of EPs and protect the environment [42,44,47–55]. As a result, the growing concern of public authorities about the presence of PhMs and other EPs in wastewater is leading to the development of new regulations that will undoubtedly have an impact on the design and operation of WWTPs in the coming years.

Although PhMs are generally present at low environmental concentrations, it is still unclear whether their levels in terrestrial and aquatic environment can cause undesirable effects in humans and wildlife. Hence, to better understand their impact on the environment and human health, information on their occurrence, behavior and fate in the environment must be studied in detail. Therefore, the occurrence, environmental fate and effects of PhMs on the soil are the focus of this review.

2. Methodology

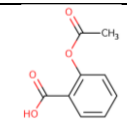
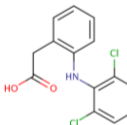
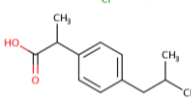
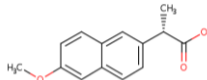
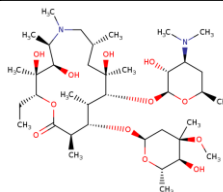
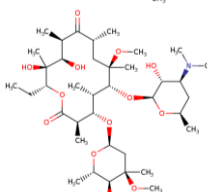
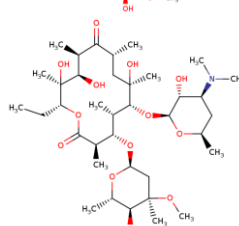
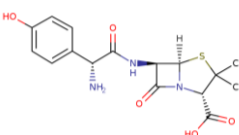
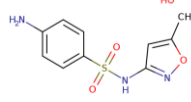
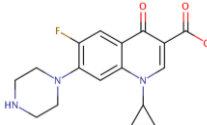
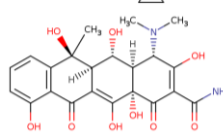
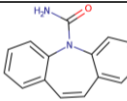
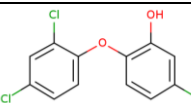
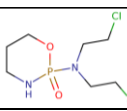
Data for this review were obtained from the Science Citation Index Expanded (SCIE) of the Web of Science Core Collection (WoSCC) database, the world's oldest bibliographic data source and the most comprehensive and widely used source for research evaluation and analysis [56]. Scientific literature published in the last 15 years was searched and analyzed during May 2024. The following questions were raised prior to starting the process and subsequently considered when reviewing the extracted information: i) What are the sources of PhMs in the environment? ii) How do PhMs occur in the soil environment and how do they behave? iii) How are PhMs affecting soil health? iv) How can PhMs-polluted soils be remediated? The analysis included records resulting from a systematic search for documents containing the following combined terms: "*pharmaceuticals*" (title) AND "*soil*" (title) AND "*2010-2024*" (year of publication). Our search identified 219 publications containing 5304 citing articles that were considered eligible for inclusion in this review. To minimize the risk of bias, extensive standardization was applied to this analysis. In addition, we also searched for other relevant studies that had been published by international organizations and specialized working groups.

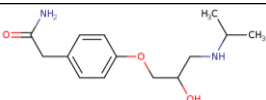
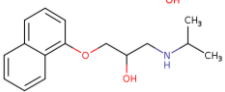
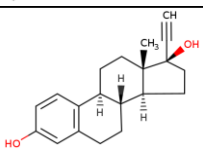
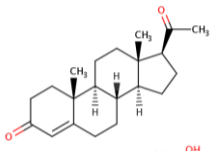
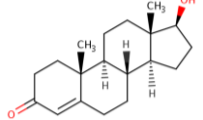
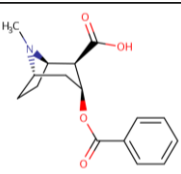
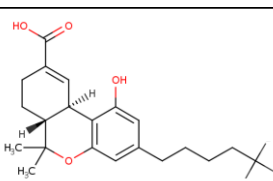
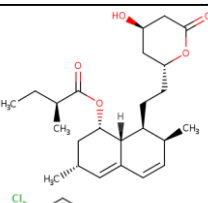
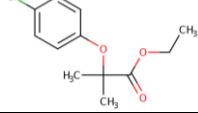
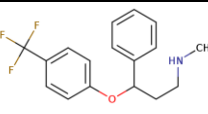
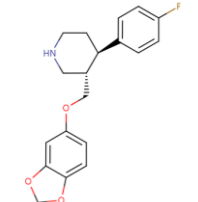
3. Sources of PhMs in the Environment

PhMs released into the environment can be divided into two broad groups, veterinary (VPhMs) and human (HPhMs). VPhMs are used worldwide to treat disease and protect animal health, with the type of compound used depending on the animal sector and specific region [57]. Common classes of veterinary medicines found in animal products in Europe include antimicrobials, anti-inflammatories, growth promoters, antiparasitics and insecticides, and tranquilizers [58,59]. Land application of animal manures can lead to VPhMs pollution of soil, surface- and groundwater via surface run-off and leaching [60–65]. On the other hand, large quantities of HPhMs are used and prescribed in human medicine worldwide. They represent a wide range of therapeutic classes. Data extracted from different European countries indicate that analgesics and anti-inflammatory drugs (acetaminophen, acetylsalicylic acid, ibuprofen, dicoflenac, etc.), antibiotics (macrolides, penicillins, quinolones, tetracyclines and others), antiepileptics (carbamazepine), β -blockers (atenolol, propranolol, etc.) hormones (progesterone, testosterone, 17 α -ethinylestradiol), lipid regulators (lovastatin, clofibrate, etc.), selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, paroxetine), illicit drugs (cocaine, cannabinoids, amphetamines, opioids, etc.) and others are the compounds sold in the highest quantities [18,59,66]. Table 1 shows the chemical structures and physicochemical properties of the major HPhMs used [67].

Table 1. Chemical structures and physicochemical properties of some of the main PhM compounds.

Therapeutic class	Compound	Structure	Log Kow	pKa	Solubility (H2O) (mg L ⁻¹)
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Analgesics and, anti-inflammatorys	Acetylsalicylic acid		1.2	3.5	4600
	Diclofenac		4.5	4.1	2.4
	Ibuprofen		4.0	4.9	21
	Naproxen		3.2	4.1	16
Antibiotics	Azithromycin ^{MC}		4.0	8.7	7.1
	Clarithromycin ^{MC}		3.2	9.0	0.3
	Erythromycin ^{MC}		3.1	8.9	1.4
	Amoxicillin ^{PN}		0.9	4.4	3430
	Sulfamethoxazole ^{SF}		0.9	3.8	610
	Ciprofloxacin ^{QN}		0.3	6.1	3x10 ⁴
	Oxytetracycline ^{TC}		-0.9	3.3	313
Antiepileptics	Carbamazepine		2.5	2.3	17.7
Antimicrobials	Triclosan		4.8	8.7	1.0
Antineoplastic agents	Cyclophosphamide		0.63	7.6	4.0x10 ⁴

β-blockers	Atenolol		0.16	9.4	1.3x10 ⁴
	Propanolol		3.5	9.4	23
Hormones	17α-ethinylestradiol		3.7	12.2	4.3x10 ⁻⁵
	Progesterone		3.9	9.8	8.8
	Testosterone		3.3	9.7	23
Illicit drugs	Benzoyllecgonine (cocaine metabolite)		1.6	4.4	3820
	Tetrahydrocannabinol (THC-COOH) (cannabinoid)		4.2	4.2	Very low
Lipid regulators	Lovastatin		4.3	-	2.1
	Clofibrate		3.6	-	Very low
SSRIs	Fluoxetine		4.0	-	3.5
	Paroxetine		3.9	-	8.5

MC: Macrolide; PN: Penicillin; QN: Quinolone; SF: Sulfonamide; TC: Tetracycline.

The main sources of both groups of compounds in the environment are shown in [Figure 2](#). A major route by which VPhMs enter the environment is through the excretion of urine and feces from medicated animals and the spreading of contaminated manure on agricultural land. Residues of VPhMs in soils, plants, and soil organisms can later enter the food chain [68]. Several comprehensive studies have investigated the environmental fate and effects of VPhMs, either from a regional or national context, or from a European or global perspective [69]. The results show that emissions of

VPhMs to the environment vary between livestock sectors due to differences in the use and excretion of VPhMs and manure production. The main conclusion of these studies is that information on veterinary medicines is available for the identification of environmental risks, but the quantitative knowledge on administered veterinary medicines is very limited and needs urgent attention. With regard to HPhMs, their occurrence in the environment is mainly due to the discharge of wastewater from manufacturing processes, the inappropriate disposal of unused or expired PhMs and accidental spills during production or distribution, the discharge of treated wastewater into the aquatic environment, the use of treated wastewater for irrigation of crops, and the use of sewage sludge as fertilizer (organic amendment) on agricultural fields [66]. Environmental pollution can also result from the disposal of incinerated pharmaceutical waste in landfills, although this is changing as a result of stricter regulations such as the EU Landfill Directive [70] and subsequent regulations [71]. A key objective of EU waste policy is to reduce the amount of waste going to landfill. The landfill rate has decreased (from 23% to 16% overall between 2010 and 2020 in the EU-27, even though the total amount of waste generated continues to increase. Furthermore, the amount of waste landfilled in 2020 is 27% lower than in the same period, equivalent to 106 kg of waste per EU citizen per year. For some waste streams, such as (mixed) household and similar waste, relatively good progress has been made in diverting waste from landfill. However, the amount of sorted residual waste going to landfill has doubled since 2010.

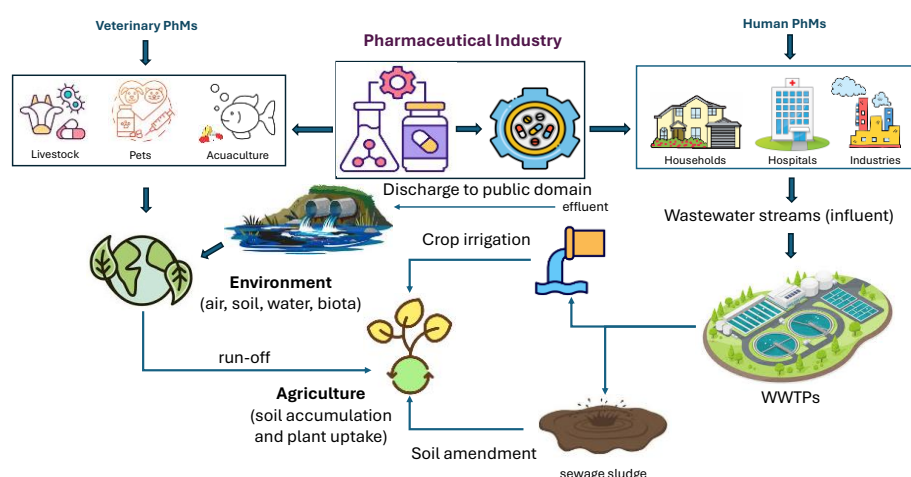


Figure 2. Main sources of occurrence of VPhMs and HPhMs in the environment.

Abdallat et al. [72] showed that in all farms using a drip irrigation system with different WWTP effluents, carbamazepine concentrations were higher in the top soil layers (0 to 20 cm) than in the root zone (20 to 40 cm). In plants, especially during the olive growing season, carbamazepine levels were detected only in olives and not in twigs and leaves, indicating a high rate of plant uptake. In addition, fruits, leaves and stems of plants left on the farm after harvest are usually consumed by cattle, which means that they enter the human food chain. Other results show the ubiquitous presence of several PhMs (mainly those that act on the metabolism and the nervous and cardiovascular systems) in the effluents of wastewater treatment plants used for irrigation, although the concentration pattern in irrigation water did not resemble the pattern of contents in soils and plants, since only paracetamol, nicotine, ibuprofen and carbamazepine were detected in maize grains at rather low concentrations, confirming the limited potential uptake of PhMs by maize [73]. Numerous studies have been conducted, especially at the laboratory scale, showing that the transfer of a pollutant from water and/or soil to different parts of the plant depends on several factors, such as the physicochemical properties of the soil (pH, clay and organic matter content), the plant species, and the properties of the pollutant (ionization, water solubility, etc.) itself [74,75]. Despite the importance of these findings, there is a need to study plant uptake of pollutants under real agricultural practices, where plants are under field water conditions and pollutants are present in the soil environment as multicomponent mixtures. Christiou et al. [24] indicated that the concentration of diclofenac,

sulfamethoxazole, and trimethoprim in soil and tomato fruit varied depending on the qualitative characteristics of the applied treated wastewater and the duration of irrigation. Total concentrations of PhMs detected by Biel-Maeso et al. [25] in surface soil samples after irrigation with wastewater effluent ranged from 2 to 15 ng g⁻¹, with analgesics and anti-inflammatories being predominant (maximum = 10 ng g⁻¹), followed by antibiotics and psychiatric drugs (maximum = 5.4 ng g⁻¹ and 3.8 ng g⁻¹, respectively). Both wastewater effluents and irrigated soils showed similar compositional patterns, with active ingredients such as hydrochlorothiazide and diclofenac being predominant. In addition, they were also detected in soil samples at a depth of 150 cm, suggesting that these compounds are leached in association with heavy rainfall episodes. Moreover, their occurrence in soils was also influenced by temperature, as maximum levels were measured in colder months (up to 14 ng g⁻¹), indicating higher persistence at lower temperatures. Another study shows that the highest amounts of PhMs discharged via secondary effluent are related to an antihypertensive drug and several beta-blockers and analgesics/anti-inflammatories, while the highest risk is posed by antibiotics and several psychiatric drugs and analgesics/anti-inflammatories [41]. These results are reported to assist scientists and administrators in planning measures to reduce the impact of treated urban wastewater discharges to surface waters and/or soils.

The European policy is directly towards the increase of agricultural reuse of sewage sludge (SS) on soil for the improvement of its fertility; however, the effects of long-term application on soil properties are still unknown. Cucina et al. [76] evaluated the agronomic and environmental effects on soil after 17 years of organic amendment addition with pharmaceutical SS derived from daptomycin production. They showed a positive agronomic potential, improving soil organic matter quality, increasing soil humified organic matter and increasing plant nutrients, although in long-term agricultural reuse, environmental risks were related to the increase of some heavy metals (Zn, Hg and Cu) and exchangeable Na. However, SS generated in WWTPs and managed for agriculture, poses the risk of spreading all the pollutants it contains [77]. The factor limiting the agricultural application of SS is the presence of sanitary pollution, where PhMs are an important concern that may affect the limitation of their use as fertilizers, resulting from the specificity of their activity and the potential possibilities of immunizing pathogenic microorganisms against the active substances contained in the SS. Mejías et al. [28] recently reviewed that antibiotics, antimicrobials, antidepressants and antidiabetics, and non-steroidal anti-inflammatory drugs were the most abundant PhMs found in sludge matrices. Overall, there is a decrease in their concentrations during sludge stabilization, especially during anaerobic digestion and composting. Their sorption to sludge is strongly correlated with the physicochemical properties, the sludge matrix, and the operational and environmental conditions. The total concentrations of 38 selected pharmaceuticals from 7 therapeutic classes (antibiotics, anticancer agents, analgesics, anti-inflammatories, beta-blockers, lipid regulators, and psychotropic drugs) monitored in the anaerobically treated sludge of the urban WWTP in Turkey ranged from 280 to 4898 µg kg⁻¹ of dry matter (dm), with clarithromycin and azithromycin being the most abundant compounds [78]. A study by Verlicchi and Zambello [79] provides a snapshot of the occurrence of selected compounds in primary, secondary, mixed, digested, conditioned, composted, and dried sludge from municipal wastewater treatment plants fed primarily with urban wastewater, as well as in sludge-amended soil. The study concludes that the most critical compounds found in sludge-amended soil were caffeine, ciprofloxacin, 17β-estradiol, ofloxacin, tetracycline, triclosan, and triclocarban. Some studies show that the concentration of PhMs in soil is strongly correlated with the maturity of the sludge used [26]. Martín et al. [80] evaluated the distribution and ecotoxicological risk of sixteen PhMs belonging to seven different therapeutic groups (two antibiotics, five anti-inflammatory drugs, one b-blocker, one antiepileptic drug, one nerve stimulant, two lipid regulators, and four estrogens) in SS from WWTPs. Only three of the 16 pharmaceuticals were never detected in the SS, while eleven of the investigated PhMs were still detected in the compost. The highest ecotoxicological risk, in digested sludge and compost, was due to the estrogenic compound 17β-estradiol. High concentrations of ciprofloxacin, norfloxacin, and ofloxacin were detected in SS [81]. Additionally, these antibiotics were detected after a longer time after the application of the sludge, which indicates the persistence of these compounds in the soil.

Meanwhile, in soil samples treated with composted sludge, the concentrations of this group of antibiotics were definitely lower [82]. Martín et al. [83] evaluated the contamination of PhMs in digested sludge and compost, with the highest levels found in digested sludge corresponding to caffeine (up to 115 ng g⁻¹), ibuprofen (45 ng g⁻¹) and carbamazepine (9.3 ng g⁻¹). The concentrations measured in compost were even lower than in digested sludge, and no compound was detected in sludge amended soils, concluding that this fact could be due to the dilution effect after sludge application to soil. Barreiro et al. [84] analyzed the presence of different antibiotics (amoxicillin, cefuroxime, ciprofloxacin, clarithromycin, levofloxacin, lincomycin, norfloxacin, sulfadiazine, and trimethoprim) in sludge from different WWTPs in Galicia (NW Spain). The results show that almost all sludge samples contained antibiotics, with ciprofloxacin and levofloxacin being the most abundant, reaching maximum values of 623 and 893 ng g⁻¹, respectively. The treatment with sewage sludge resulted in a significant reduction in the number and concentration of antibiotics. In 12% of the soil samples in which the sludge was applied, some antibiotics were detected, but they were always present in low concentrations. With regard to the crops, no antibiotics were detected in the roots, stalks, leaves and grains of maize, nor in the grapes sampled in the vineyards. Overall, the sludge treatments have a great influence on sludge pollution. Once applied onto the soil, the agronomic benefits will depend on the soil's properties as well as the sludge's characteristics. The risks concerning the ecotoxicity of PhMs, found in the sludge, are low although not insignificant [26].

4. Behavior and Fate of PhMs in the Soil Environment

PhMs can enter the soil environment from the pharmaceutical industry (point sources) or from the application of animal manure and sewage sludge as fertilizer or from irrigation with contaminated water (non-point sources) [85]. The occurrence of PhMs in the environment from veterinary and human consumption has been the subject of increased scientific attention in recent decades due to concerns about their combined environmental effects in aquatic and terrestrial environments and, to some extent, on human health. [86,87]. The ability to accurately determine the fate of PhMs in soil is essential for rigorous risk assessment associated with wastewater reuse or biosolids recycling to the environment. The natural affinity for one of the four environmental compartments (soil, water, air and biota) determines the environmental behavior and fate of PhMs (Figure 3).

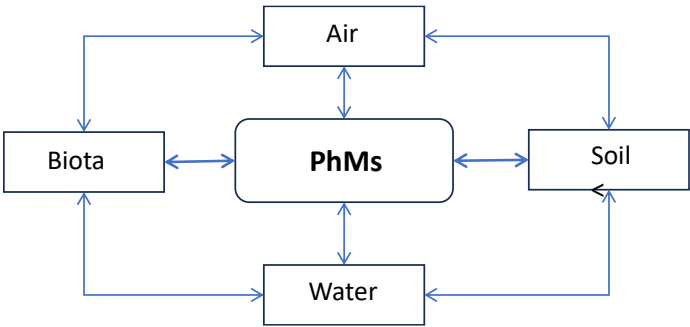


Figure 3. Environmental compartmentalization of PhMs.

The tendency of a compound to move from one phase to another is often referred to as compartmentalization. To understand the behavior of PhMs in the environment and their ultimate fate, it is necessary to know certain information about their identity and chemical composition, their physicochemical properties, and the environmental characteristics of the site where they have been released. Some of these physicochemical properties are summarized in Table 2.

Table 2. Environmental behavior of PhMs as a function of their physicochemical properties [88].

Parameter	Values	Comments
Water solubility (mg L ⁻¹)	< 50	Low
	50-500	Moderate

Parameter	Values	Comments
Hydrolysis (TD ₅₀ , días)	> 500	High
	< 30	Nonpersistent
	30-100	Moderately persistent
	100-365	Persistent
	> 365	Very persistent
Vapor pressure (P _v , mPa)	< 5	Low volatility
	5-10	Moderately volatile
	< 10	Highly volatile
Henry's Law Constant (H, Pa m ³ mol ⁻¹)	> 10 ²	Volatile
	10 ⁻¹ - 10 ²	Moderately volatile
	< 10 ⁻¹	Nonvolatile
Octanol-water partition coefficient (log K _{ow})	< 2.7	Low bioaccumulation
	2.7-3.0	Moderate bioaccumulation
	> 3	High bioaccumulation
Organic carbon partition coefficient (log K _{oc} , ml g ⁻¹)	< 1.2	Very mobile
	1.2-1.9	Mobile
	1.9-2.7	Moderately mobile
	2.7-3.6	Slightly mobile
	> 3.6	Nonmobile
Dissociation constant (pK _a)	pH < pK _a	Neutral state
	pH > pK _a	Negative charge
GUS Index	> 2.8	High leachability
	2.8-1.8	Transition state
	< 1.8	Low leachability

These parameters are well known and are used to predict the environmental fate of a given compound and to estimate its persistence, understood as "the tendency of a given PhM to retain its structural properties unchanged for a given period of time in the environment in which it is distributed and/or transported". Once incorporated into the soil, PhMs enter a dynamic ecosystem and begin to move within it, degrading "in situ", remaining in it with their original structure or being degraded to a greater or lesser extent over a variable period of time (Figure 4).

The concentration of PhMs may be virtually constant for a period of time, followed by a mono- or biphasic decrease in concentration. There are three phases in the disappearance of a PhM in soil: (i) the lag phase, which is a short period of time during which the ingredient is maintained at a certain concentration, (ii) the dissipation phase, which is relatively rapid in terms of disappearing from the soil, and (iii) the persistence phase, which is responsible for the persistence of the PhM and is expressed in units of time (hours, days, weeks, months and even years). Half-life (t_{1/2}), defined as "the time required for half the amount of PhM initially present or deposited in the soil to disappear", is the most commonly used term to express persistence. In some cases, it is more appropriate to use disappearance time expressed as DT₅₀, DT₇₅ and/or DT₉₀, which indicate "the time required for 50, 75 and/or 90% of the initial concentration of the PhM present or introduced in soil to disappear". According to Gavrilescu [89], a compound with a half-life (t_{1/2}) greater than 100 days is considered persistent, while non-persistent compounds have t_{1/2} < 30 days. Therefore, those with 30 > t_{1/2} < 100 days are classified as moderately persistent. Kodešová et al. [90] studied the persistence of different groups of PhMs such as antibiotics (trimethoprim, sulfamethoxazole, clindamycin, and clarithromycin), beta-blockers (atenolol and metoprolol), and psychotropics (carbamazepine) in 13 different soil types. Among them, carbamazepine was found to have the highest persistence in soil, followed by clarithromycin, trimethoprim, metoprolol, clindamycin, sulfamethoxazole and atenolol. The half-life, which is related to soil properties, reflects the sorption process of PhMs on soil particles and increases with the increase in soil sorption capacity.

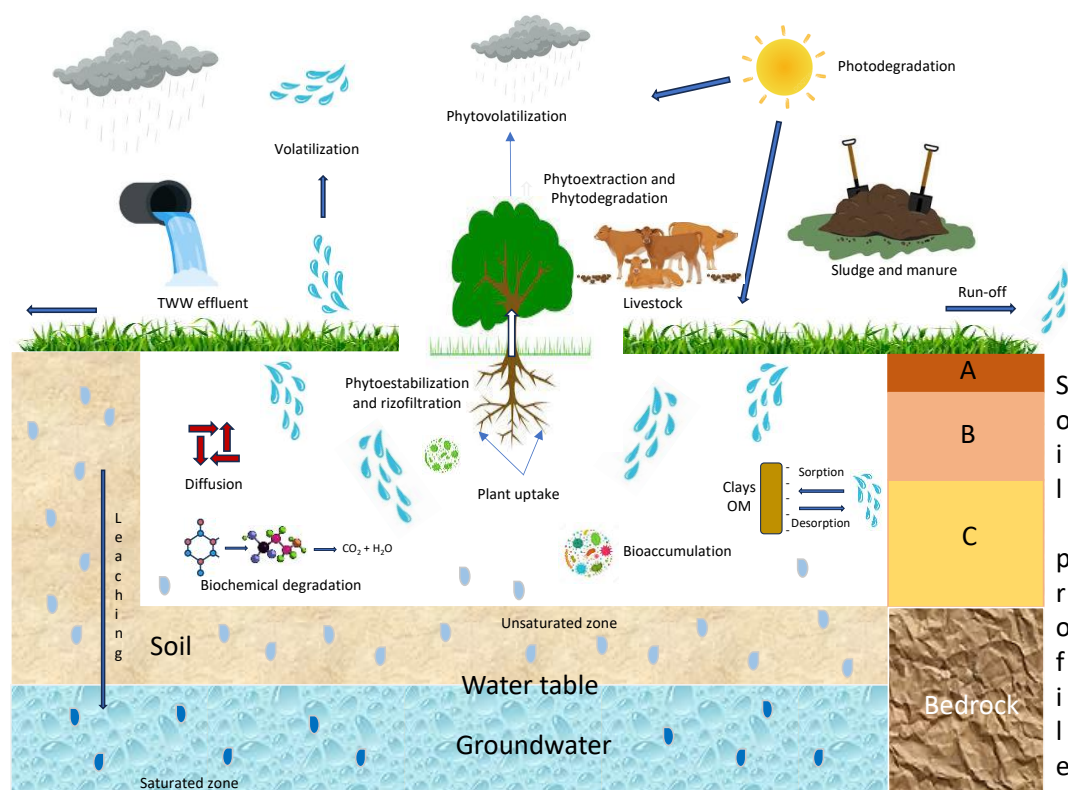


Figure 4. Schematic drawing of the behavior and fate of PhMs in the soil.

The behavior and fate of PhMs in soils are governed by a number of processes [91]. These include sorption (adsorption/desorption) to organic and inorganic colloids, biotic (biodegradation) and abiotic (chemical and photochemical degradation) degradation, and transfer (movement) through the soil profile (a vertical section showing its horizons, layers parallel to the surface, and the primary material and hence availability for plant uptake) [92,93]. Soil-pharmaceutical-plant interrelationships are quite complex (Figure 5). Colloidal adsorption-desorption and degradation dominate this dynamic process (inactivation, losses and transformations), which involves various physical, chemical and microbiological processes, all of which are interrelated and responsible for their behavior and ultimate fate [94]. It is possible to predict the behavior of PhMs in soil and their possible toxicological effects with remarkable reliability based on physicochemical properties, adsorption, mobility and degradation data obtained in the laboratory.

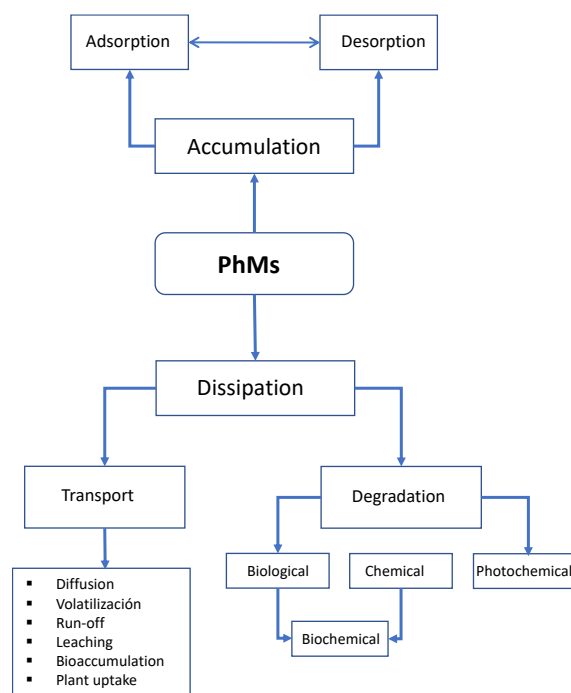


Figure 5. Processes involved in the fate of PhMs in the soil.

4.1. Adsorption-Desorption

Sorption is one of the key processes affecting the fate, mobility, migration and bioavailability of pharmaceuticals in the soil environment. Adsorption refers to the disappearance of solutes from a solution by adsorption onto a solid phase. In general, adsorption is defined as the enrichment of molecules, atoms, or ions near an interface. Adsorption occurs whenever a solid surface is exposed to a gas or liquid, and gas adsorption has become one of the most widely used methods for determining the surface area and pore size distribution of powders and porous materials [94]. The material in the adsorbed state is known as the adsorbate, while the adsorptive state is the same component in the liquid phase. The adsorption space is the space occupied by the adsorbate. PhMs (adsorbates) that can be retained in soil colloids (adsorbents) are subject to this concept. Due to the innumerable negative charges of both colloids on the natural pH of the soil, the colloidal fractions of the soil, both inorganic (clays) and organic (humus), play a fundamental role in this process.

Two types of forces are involved in the process: physical adsorption (physisorption), where van der Waals interactions are involved, and chemical adsorption (chemisorption), where the adsorbed molecules are bound by chemical bonds. Chemisorption is therefore irreversible. Physisorption is reversible, and a physically adsorbed gas can be desorbed from a solid by increasing the temperature and decreasing the pressure. Chemisorbed molecules are bound to reactive parts of the surface, and adsorption is necessarily confined to a monolayer, whereas physisorption generally occurs as a multilayer at high relative pressures. The distribution of a PhM between the water and soil compartments depends on the properties of the compound and the matrix and may also be influenced by external factors such as temperature and soil moisture. The relationship between the concentrations of a compound in the solid and liquid phases is known as the coefficient of distribution (K_d) and is directly proportional to the solubility of the PhM in water and inversely proportional to the organic matter and clay content of the soil (Eq. 1):

$$k_d = \frac{C_a}{C_e} \quad (1)$$

where C_a is the amount of PhM adsorbed per unit mass of adsorbent (M/M) and C_e is its concentration in solution (M/V).

Batch experiments are commonly used for direct measurement of K_d (ml g⁻¹) [96,97]. A mass (g) of soil is mixed with a volume (ml) of water or another medium, such as aqueous 0.1 M CaCl₂ (to minimize disturbance of the soil mineral balance). To give an initial concentration of the chemical in

the liquid phase, a mass (g) of a PhM is added to the slurry (or added to a phase before mixing). The slurry is then gently mixed to minimize disturbance to the soil structure. This is typically done for a period of between 2 and 48 hours (usually 24 hours). This is followed by an analysis of the equilibrium concentration C_e of the PhM in aqueous solution. High K_d values (> 100) indicate that the majority of PhMs are adsorbed on the soil surface at any given time and are therefore less likely to be mobile in soil, but it is not an indication of the strength (reversibility) of this sorption. K_d is often standardized to the organic content (OC) of the soil to give the organic carbon-water partitioning factor, K_{oc} (ml g^{-1}), which is typical of many of the current protocols (Eq. 2).

$$k_{oc} = \left(k_d / OC \right) \times 100 \quad (2)$$

where K_d is the coefficient of distribution and OC is the organic carbon content (%).

This approach was originally developed for hydrophobic compounds. However, it is not clear whether such normalization is appropriate for ionizable pesticides. Consideration of soil pH may be more relevant for such normalization, especially considering the potential effects of the pK_a of the PhM on its potential ionization and subsequent sorption. Karickhoff et al [98] showed that there is a linear correlation between partition coefficient and soil organic carbon content. The K_{oc} is linearly correlated with the octanol-water partition coefficient (K_{ow}), which is an indication of the degree of affinity of PhMs for water (low value) or soil (high value). If the adsorption process is very intense (chemisorption), the molecule will not be bioavailable. Thus, its biological activity will be reduced. In addition, it will not be biodegradable, which will increase its persistence in the soil. Finally, its mobility will be greatly reduced, so that the possibility of groundwater contamination will be minimal. However, the compound may desorb and return to the soil with the associated biocidal risk when soil conditions change (moisture, temperature, etc.). K_d values are often determined over a range of concentrations at constant temperature. The resulting plot, the relationship between the concentration of the adsorbed compound (C_a) and the equilibrium concentration of the compound (C_e) at constant temperature, is called an adsorption isotherm.

Sorption of PhMs by soil generally reduces their uptake by plants, especially for those chemicals with strong hydrophobicity or positive charge [75,99,100]. Lin and Gan [93] showed that the rate of degradation of PhMs is influenced by the presence of microorganisms and aerobic conditions in the soil, by the soil type and by the properties of the PhM itself, indicating that naproxen and trimethoprim showed moderate to strong sorption, while the sorption of diclofenac, ibuprofen and sulfamethoxazole was negligible in the soils studied, which could increase their mobility in soils and cause their leaching into groundwater. A higher persistence of ketoprofen in soils rich in OM may be attributed to a reduced availability of the compound due to increased adsorption in this soil type. The half-life of ketoprofen was longest for silt loam and shortest for loamy sand, clearly indicating the relationship between the sorption capacity of soils and the half-life of this compound [101]. The results of another study showed that levonorgestrel (a synthetic progesterone used as an active ingredient in hormonal contraception) can be highly absorbed in soil, mainly by binding to OC [102]. The adsorption of PhMs in soil depends both on their hydrophobic properties and electrostatic interactions with sediment particles and on the activity of microorganisms. The acidic compounds, including acetylsalicylic acid, ibuprofen, ketoprofen, naproxen and diclofenac, as well as indomethacin with pK_a values ranging from 4.9 to 4.1, similar to clofibric acid and bezafibrate (pK_a 3.6), exist in ionic forms at neutral pH and have a low tendency to adsorb to soils, although the adsorption of these compounds in soil increases at lower pH values. At neutral pH, negatively charged PhMs are mainly in the liquid phase [103]. Paz et al [104] studied the sorption of two highly persistent anticonvulsants, lamotrigine and carbamazepine, and two of their metabolites (EP-CBZ and DiOH-CBZ) by soils and found that it was mainly determined by the soil OM content. The sorption affinity of the compounds to soils followed the order lamotrigine > carbamazepine > EPCBZ > DiOH-CBZ. Sorption was reversible and no competition between sorbates in bi-solute systems was observed. The results of the lysimeter studies were consistent with the results of the batch experiments and showed accumulation of lamotrigine and carbamazepine in OM-enriched topsoil layers. Similar results were found by Thiele-Bruhn and Zhang [105] working with sulfadiazine, caffeine, and atenolol in an arable Cambisol topsoil after the addition of manure. According to

Kodešová et al [106], pedotransfer rules for predicting sorption coefficients of various PhMs include hydrolytic acidity (sulfamethoxazole), organic carbon content (trimethoprim and carbamazepine), base cation saturation (atenolol and metoprolol), exchangeable acidity and clay content (clindamycin), and soil active pH and clay content (clarithromycin). Pedotransfer rules, which predict Freundlich sorption coefficients, could be used to predict PhM mobility in soils with similar soil properties. Predicted sorption coefficients, together with PhM half-lives and other inputs (e.g. soil hydraulic, geological, hydrogeological, climatic), can be used to assess potential groundwater contamination.

Kočárek et al. [107] studied the sorption affinities of 4 PhMs (atenolol, trimethoprim, carbamazepine, and sulfamethoxazole) applied in solute mixtures to soils taken from different horizons of 3 soil types (Greyic Phaeozem on loess, Haplic Luvisol on loess, and Haplic Cambisol on gneiss). In the case of carbamazepine (neutral form) and sulfamethoxazole (partially negatively charged and neutral), the sorption affinity of the compounds decreased with soil depth (i.e. with soil OM content). On the other hand, in the case of atenolol (positively charged) and trimethoprim (partially positively charged and neutral), the sorption affinity of the compounds was not depth dependent. Batch sorption experiments of ketoprofen, atenolol, and carbamazepine on biochar-amended soils conducted by Wu and Bi [108] showed that the sorption affinity was in the order of cationic atenolol > neutral carbamazepine > anionic ketoprofen due to the electrostatic attraction of atenolol to amended soils. A thermodynamic study carried out to investigate the adsorption behavior of three ionizable compounds present in different forms: propranolol (cationic), sulfisoxazole (anionic) and sulfaguanidine (neutral) on soil under different temperature conditions shows that the sorption of Propranolol is exothermic, spontaneous and enthalpy driven, while the sorption of sulfaguanidine is endothermic, spontaneous and entropy driven and the sorption of sulfisoxazole is endothermic, spontaneous only above the temperature of 303.15 K and entropy driven [109]. The sorption-desorption behavior of four commonly consumed anti-inflammatory drugs (naproxen, ibuprofen, ketoprofen, and diclofenac) was investigated by Zhang et al. [110] in a loam-textured soil exposed to either a single compound or a mixture of the four compounds. The results show that the proportion adsorbed to the soil in the mixture-compound system ranged from 72% to 45% for diclofenac and ibuprofen, respectively, and differed slightly from the adsorption of the individual compounds.

Several models have been developed to estimate the sorption of organic chemicals, including ionizable compounds, in soil [111,112]. However, the applicability of these models to PhMs has not been extensively tested. The results show that sorption coefficients for PhMs in soil can vary by many orders of magnitude, e.g. $0.09 \text{ sulfameter} < K_d < 1277873 \text{ ciprofloxacin ml g}^{-1}$, and sorption coefficients for a single PhM can vary by up to three orders of magnitude between different soil types (e.g. K_d values for ciprofloxacin range from 726.8 to 1277873 ml g⁻¹). Li et al [113] generated a high-quality data set on the sorption of twenty-one pharmaceuticals in different soil types and used these data to evaluate existing models and to develop new improved models, finding K_d values ranging from 0.2 (antipyrine) to 1249 ml g⁻¹ (perphenazine). Principal component analysis (PCA) indicated that the sorption of the studied PhMs was driven by hydrophobic forces as well as electrostatic interactions and a number of soil parameters.

4.2. Degradation

Residues of PhMs found in soils can lead to significant bioaccumulation with adverse effects on soil organisms, crops, and even humans through dietary consumption [114]. Laboratory studies show that degradation rates of PhMs in soils vary widely, with half-lives ranging from days to years. Within the same therapeutic class, half-lives can still be significantly different. These differences are due to differences in soil properties (moisture content, organic carbon and clay content, pH, and soil bioactivity), soil temperature and physicochemical properties of the compound (degree of dissociation and lipophilicity). Adsorption and degradation are two major environmental pathways of PhMs in soil. Sorption of PhMs on soil colloids affects the mobility of PCs and even their degradation and bioavailability in the soil environment [5,94,115]. The soil type-dependent surface

chemistry leads to variations in the retention, distribution, transport, and transformation of PhMs in soil. The mixture of different classes usually exhibited enhanced sorption due to the cooperative multilayer sorption on soil constituents, and the mixture of the same class often resulted in a different adsorption capacity compared to the sorption of a single compound due to the competitive sorption. PhMs preferentially adsorb to a soil component or to a specific soil type, and exhibit soil type-dependent sorption affinity, mobility, and dissipation [116]. Therefore, the soil-dependent surface chemistry of the soil is critical for predicting the persistence and bioavailability of PhMs in soil. Monteiro et al. [117] investigated the effect of chemical mixture interactions on the degradation of three pharmaceuticals (naproxen, carbamazepine, and fluoxetine). They found that in single compound studies, naproxen degraded in a range of soils with half-lives ranging from 3.1 to 6.9 d, while carbamazepine and fluoxetine were more persistent. When degradation was evaluated using a mixture of the three study compounds and the sulfonamide antibiotic sulfamethazine, fluoxetine and carbamazepine degraded similarly to the single-compound studies, while naproxen degraded significantly slower in the mixture-spiked soils than in the single-compound studies. In a study conducted by Salvia et al. [118] that included 23 PhMs and two soils with different textures (silty clay loam and sandy loam), the majority of the compounds degraded relatively rapidly ($t_{1/2} < 20$ d), with the exception of roxithromycin ($t_{1/2} = 57\text{-}88$ d) and carbamazepine ($t_{1/2} = 170\text{-}330$ d).

Although there are many factors that influence the disappearance of PhMs in soil, most of the proposed models to study degradation are based on considering the concentration of PhMs as the only dependent variable. For the assessment of their persistence, knowledge of degradation kinetics is essential. The degradation of PhMs can be described by several models. Simple Single-First-Order (SFO) kinetics (monophasic model) remains the most common mathematical description of decay in the scientific literature. However, it is not always possible to describe degradation using SFO kinetics. When a rapid initial decline in PhM concentration is often followed by a slower decline, the pattern is usually referred to as a biphasic model, such as First Order Multi Compartment (FOMC), Double First Order in Parallel (DFOP), First Order Sequential Biphasic (FOSB), and Hoerl (H). Therefore, kinetic degradation experts from the European Commission funded FOCUS group (Forum for the Coordination of Pesticide Fate Models and Their Use) proposed alternative equations for the degradation of soil organic pollutants [119], as summarized in Table 3.

Table 3. Kinetic models for PhMs degradation.

Model	Equation	Parameters	Endpoints
SFO	$C_t = C_0 e^{-kt}$	2 (C_0, k)	$DT_x = \frac{\ln \left[\frac{100}{(100 - X)} \right]}{k}$
FOMC	$C_t = C_0 \left(1 + \frac{t}{\beta} \right)^{-\alpha}$	3 (C_0, α, β)	$DT_x = \beta \left(\frac{100}{(100 - X)} \right)^{\left(\frac{1}{\alpha} \right)} - 1$
DFOP	$C_t = C_1 e^{-k_1 t} + C_2 e^{-k_2 t}$	4 (C_1, C_2, k_1, k_2)	DT_x values can only be calculated via an iterative procedure
FOSB	$C_t = C_0 e^{-k_1 t}$ when $t \leq t_b$	4 (C_0, k_1, k_2, t_b)	$DT_x = \frac{\ln \frac{100}{100 - X}}{k_1}$ when $DT_x \leq t_b$
	$C_t = C_0 e^{-k_1 t_b} e^{-k_2 (t - t_b)}$ when $t > t_b$		$DT_x = t_b + \frac{\left(\frac{\ln 100}{100 - X} \right) - k_1 t_b}{k_2}$ when $DT_x > t_b$
H	$C_t = C_0 e^{-kt} t^a$	3 (C_0, k, a)	DT_x values can only be calculated via an iterative procedure

C_t = concentration at time t ; C_0 = concentration at $t=0$; k = rate constant; t = time since application; C_t = total amount of pollutant at time t ; C_1 = amount of pollutant in compartment 1 at time = 0; C_2 = amount of pollutant in compartment 2 at time = 0; k_1 = rate constant in compartment 1; k_2 = rate constant in compartment 2; α = shape parameter determined by coefficient of variation of k ; β = location parameter; t_b = breakpoint (time at which the rate constant changes); a = parameter that indicates the

deviation from the single-phase model (if $a \neq 0$, the kinetic behavior will be biphasic); DT = disappearance time.

Degradation, together with movement, is the process responsible for the disappearance of PhMs in soil. Three processes deserve special attention: i) photodecomposition (photochemical degradation), ii) chemical degradation and iii) biological degradation (biodegradation). To study degradation of chemicals in soils, different guidelines have been proposed by OECD [120] and US EPA [121].

4.2.1. Photochemical Degradation

Many micropollutants such as PhMs are degraded by ultraviolet light. Based on the interaction of the wavelengths of UV radiation with biological materials, three divisions have been identified: i) UVA (400 - 315 nm), also known as black light, ii) UVB (315 - 280 nm), responsible for the most well-known effects of radiation on organisms, and iii) UVC (280 - 100 nm), which does not reach the surface of the Earth. The process begins when the pollutant receives energy. This results in the excitation of electrons, which can break or form less stable bonds. The absorption of light by PhMs can cause bond breakage. This occurs as long as the energy of the absorbed photons is equal to or greater than the bond energy [122]. Photolysis can be direct, where the compound absorbs UV light within the solar spectrum (< 400 nm), or indirect, where the energy is absorbed by other compounds that subsequently transfer it to the PhM molecule or generate various reactive species. Direct irradiation promotes the PhMs to their excited singlet states, which can then transition to triplet states. As shown in Figure 6, these excited states can then undergo (i) homolysis, (ii) heterolysis, or (iii) photoionization, among other processes [123].

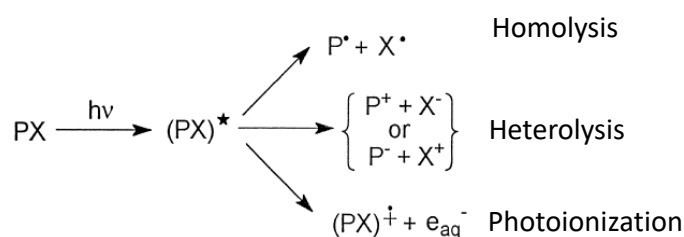


Figure 6. Possible direct photolysis chemical events.

Compounds that are photodegradable, water soluble, and nonvolatile are particularly susceptible to photodegradation on soil surfaces. These three properties are common to most antibiotics [124]. It has generally been assumed that light has little effect on the degradation of PhMs in soils, in contrast to what happens in aqueous solution [125]. Thus, soil samples spiked with 0.5 mg kg⁻¹ of two widely used veterinary fluoroquinolones (marbofloxacin and enrofloxacin) were exposed to solar light, which promoted extensive degradation (80%) of both compounds in 60-150 h, although two orders of magnitude slower than in aqueous solution [126]. In another study in which soil samples containing oxytetracycline, chlorotetracycline, sulfanilamide, sulfadimidine, sulfadiazine, sulfadimethoxine, sulfapyridine, fenbendazole, and p-aminobenzoic acid were irradiated with arc light or, in parallel, kept in the dark for 28 d, all antibiotics were directly photodegraded in water with first-order rate coefficients (k) ranging from 0.005 to 0.12 d⁻¹. However, for sulfonamides and fenbendazole, the average k in soil and sand was 0.01 d⁻¹, which is 2.4 times lower than in water [127]. Therefore, photochemistry could be considered as an important pathway for the removal of PhMs in soil, with the presence of photochemical catalysts, irradiation intensity and duration, soil pH and aeration, chemical structure and physical state of the PhM and the degree of adsorption on colloids as the main factors influencing the process.

4.2.2. Biochemical Degradation

In principle, a distinction can be made between chemical and biological degradation. However, in many cases they are closely related and it is not easy to establish the independence of the two processes. [Chemical degradation involves oxidation, hydrolysis, and other reactions that occur in the soil as a function of pH, temperature, and moisture, while biodegradation can be defined as "the process by which soil microorganisms metabolically or enzymatically transform or modify the structure of PhMs present in the soil" [128] (Figure 7). To study both types of degradation (chemical and biological) separately, it would be necessary to destroy the soil microorganisms by appropriate irradiation or sterilization techniques. This would also require modification of other catalytic systems that have a significant impact on degradation. For this reason, the two types of degradation are often combined and treated as biochemical degradation.

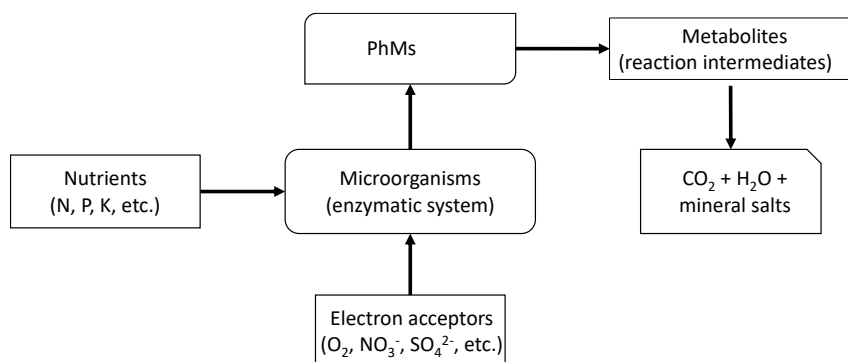


Figure 7. Diagram showing the biodegradation of PhMs in the soil.

In general, the biodegradability of a PhM in an aerobic environment decreases as the molecular weight and the number of carbon atoms and aromatic nuclei in the molecule increase [122]. The process of biological degradation is slowed by (i) a lack of essential nutrients for microorganisms (e.g., nitrogen and/or phosphorus); (ii) a lack of sufficient electron acceptors (usually oxygen); (iii) a lack of appropriate environmental conditions (pH, redox potential, humidity, temperature); (iv) a lack of microbial populations with sufficient enzymatic potential to degrade contaminants; and (v) the presence of toxic components in the contaminant mixture. While biodegradable PhMs are degraded by soil microorganisms within days or weeks, recalcitrant PhMs persist for long periods of time (years or even decades).

PhMs can be degraded by soil microorganisms (bacteria, fungi, algae, protozoa and viruses) by aerobic processes in which oxygen acts as an electron acceptor [129], or by anaerobic processes in which nitrates, sulfates and others act as electron acceptors [130]. Some results show that the biodegradation of some anti-inflammatory drugs (clofibric acid, gemfibrozil, ibuprofen, fenoprofen, ketoprofen, naproxen, diclofenac and indomethacin) was poorly decreased in anaerobic condition, except for naproxen [131]. The higher degradation rates under aerobic conditions suggest the possibility of enhanced degradation of PhMs by oxygenation. In general, lower average dissipation half-lives and variability for some PhMs (i.e., atenolol, clindamycin, metoprolol, trimethoprim, and sulfamethoxazole) were found in soils of higher quality with well-developed structure, high nutrient content, etc., and better microbial conditions (i.e., chernozems) than in soils of lower quality (cambisols) [90]. Non-ionic compounds such as carbamazepine, lamotrigine, caffeine, sildenafil, sulfapyridine, and metoprolol were recalcitrant and accumulated in soils irrigated with effluents from WWTPs containing these PhMs, whereas the weakly acidic PhMs exhibited rapid degradation rates in soils, probably related to their chemical structure. However, Carr et al. [132] demonstrated that the half-lives of different PhMs (estrone, 17 β -estradiol, estriol, estrogen, 17 α -ethinylestradiol, triclosan and ibuprofen) increased in water saturated conditions as compared to draining soil, with degradation in wet soils increasing after the third day when soils neared field capacity after draining, although Grossberger et al. [133] show that the physicochemical properties of PhMs have a major influence on biodegradation kinetics, while soil properties have a minor influence.

Due to the large number of PhMs with different properties currently in use, the number of metabolites or residual products generated by dealkylation, dehalogenation, hydrolysis, oxidation, etc. is very high [134]. These new structures can be completely degraded by mineralization to CO₂, H₂O and mineral salts. Alternatively, they can be incorporated into the humic substances of the soil by polymerization. This leads to the formation of other highly stable substances. These non-extractable and chemically unidentifiable fractions, which remain in the humic fractions of the soil after extraction with solvents of different polarities, are known as soil-bound residues.

4.3. Movement (Transport) of PhMs in the Soil

Several processes can transport PhMs in the soil environment [85]: (i) diffusion (movement through the soil from a site of higher concentration to a site of lower concentration), (ii) volatilization (conversion of solids or liquids into a gas that moves through pore space), (iii) erosion and runoff (movement of soil particles exposed to transport by water on a sloping surface, wind, or organisms), (iv) bioaccumulation and plant uptake (movement of PhMs into organisms and plants), and (v) leaching (the movement of pollutant in water through the soil, up, down and/or sideways).

4.3.1. Diffusion

According to Fick's law, which states that the net number of particles passing through a given area per unit of time is proportional to the concentration gradient with opposite sign, a PhM will move through the soil from an area of higher concentration to an area of lower concentration (Eq. 3):

$$J = -D \frac{\partial \phi}{\partial x} \quad (3)$$

where J is the diffusive flux (mol m⁻² s⁻¹), D is the diffusion coefficient (m² s⁻¹), ϕ is the pollutant concentration (mole m⁻³) and x is the position (m).

This is observed both in the gaseous phase of the soil as well as in the liquid or air phase between the solid particles. The diffusion coefficient, the solubility and the vapor pressure of the PhM and, in particular, the temperature, the humidity and the porosity of the soil and the degree of adsorption of the compound are the main factors influencing this process [135].

4.3.2. Volatilization

The volatilization of PhMs from the soil and their subsequent dispersion into the atmosphere could be a common pathway for the movement and disappearance of PhMs. However, some studies suggest that the removal of PhMs by volatilization could be neglected due to their low Henry Law constants [136]. Their potential volatility is closely related to their vapor pressure, but their effectiveness depends largely on soil temperature, colloidal composition, porosity, structure, water content, and pH, as well as PhM type, concentration, and degree of adsorption. High temperatures favor the process unless the soil dries quickly. The water content of the soil is also important, as PhMs will evaporate more quickly from wet soils than from drier soils. On the other hand, it should be noted that PhMs with a physical adsorption (weak) will volatilize faster than those with a strong adsorption (chemical). The reason for this is that they are more susceptible to exchange with water molecules.

4.3.3. Run-Off

There are two interdependent processes involved in runoff. The first is the disruption of soil aggregates and the movement of the resulting fragments. The second is that particles from the fracture are at the mercy of transport agents (water, wind, or living organisms) once the aggregate has been destroyed [137]. Runoff/erosion processes result in the transfer of soil from fields to adjacent land/water bodies. In contrast to channel runoff (or streamflow), surface runoff (also known as overland flow or terrestrial runoff) is the unconfined flow of water over the land surface. It occurs when an excess of rainwater, storm water, snowmelt, or other sources of water cannot infiltrate into the ground fast enough. This can occur when the soil is completely saturated with water (saturation-

excess overland flow), when rainfall occurs faster than the soil can absorb it, or when the soil is unsaturated but the rate of water delivery to the surface exceeds the rate of infiltration into the soil (infiltration-excess overland flow). These processes transport plant nutrients (nitrogen, phosphorus, etc.) and micropollutants such as pesticides, PhMs, etc. The main factors influencing runoff are: i) volume and intensity of rainfall events, ii) soil type and properties, iii) landscape factors (e.g. slope), iv) time since application of the PhM, v) physicochemical properties of the molecule in question and its degree of adsorption, and vi) soil and crop management practices and land use patterns.

4.3.4. Bioaccumulation

There are many organisms in agricultural soils that degrade or absorb certain PhMs during their life cycle, which may result in higher concentrations in their bodies than environmental levels [138]. To assess the likelihood of absorption and distribution of a PhM in a given organism, it is very useful to determine the partition coefficient (K_{ow}) between octanol and water (the equilibrium relationship between the molar concentrations of the substance dissolved in a two-phase system, octanol and water). These values, usually expressed as a decimal logarithm ($\log K_{ow}$), are constant for each PhM at a given temperature. A high coefficient indicates that the product is likely to accumulate in living organisms, and the nature of binding to biological receptors also plays a role. On the other hand, a low coefficient reduces the potential of bioaccumulation, that is, the net accumulation of PhM in an organism over time from both biotic (other organisms) and abiotic (soil, air and water) sources [139].

4.3.5. Plant Uptake

Numerous studies have shown that many crops grown in areas where PhMs are notoriously present as consequence of wastewater irrigation or addition of polluted biosolids can absorb some of these compounds from the soil in varying proportions [87,91,100,140–151]. The extent of the process depends on a number of factors such as the type of crop, the physicochemical properties of the compound (water solubility, vapor pressure, molecular weight, octanol-water partition coefficient), environmental characteristics (temperature, soil type, water content in soil, agricultural practices), and plant characteristics (root system, shape and size of leaves, and lipid content) [152].

The bioconcentration factor (BCF), which is typically calculated as the ratio of the drug concentration in the plant to that in the bulk soil, is commonly used to characterize the distribution of PhMs in soil-water-plant systems [153]. To better understand how soil PhMs enter plant cells, it is important to discuss the major pathways and processes involved in the uptake and translocation of these contaminants. Contaminants can be taken up by plants from the soil and its constituents through the root system. The movement of PhMs across a cell membrane is achieved by passive diffusion, which does not require the cell to expend energy, as opposed to active transport, which requires energy to move nutrients and contaminants across the cell membrane [154]. Water is believed to transport PhMs across the root cortex by symplastic (intracellular space) and apoplastic (extracellular space) pathways. In plant roots, the Casparian strip, composed mainly of hydrophobic suberin and lignin, acts as a water-impermeable barrier to prevent water and drugs from crossing the endodermis via the apoplastic pathway. Therefore, pharmaceuticals must re-enter the symplastic pathway to cross cell membranes and enter the xylem. The xylem is responsible for moving water and nutrients upward from the roots to the upper parts of the plant. PhMs can also enter plants from the atmosphere after volatilization from the soil, which is influenced by several factors such as temperature, plant species, contaminant concentration and the hydrophobicity of the chemical. This process occurs through stomata. Once the gas molecules enter the stomata, they can be transported by the phloem to other parts of the plant tissues, including the root system. Contaminants with high vapor pressure and high Henry's law constants, such as volatile organic compounds, affect the uptake of contaminants from the air due to their high gaseous concentrations. The major uptake pathways in plants are shown in [Figure 8](#).

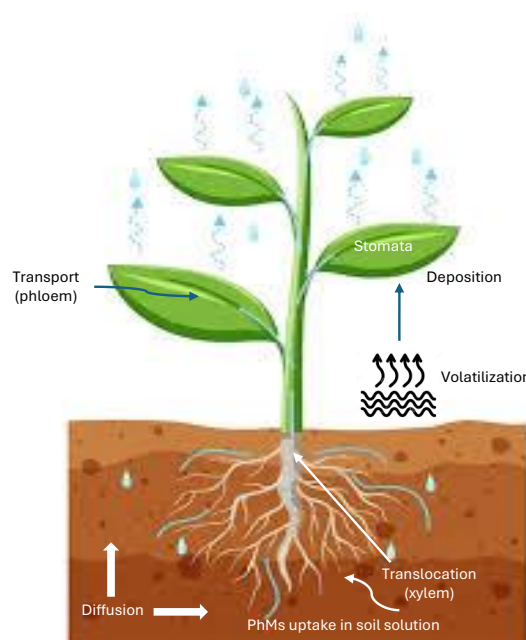


Figure 8. Scheme showing main plant uptake pathways.

One area where researchers have made great strides is in understanding the mechanisms that affect the uptake of PhMs by food crops. These include chemical-specific factors such as the $\log K_{ow}$, the charge of the chemical (positive, negative or neutral) and the half-life value. The type of plant species is also important in estimating the potential risk to human health. For many non-ionic organic compounds, accumulation in plants is positively related to their lipophilicity, as indicated by the linear relationship between BCFs and K_{ow} [155]. However, the uptake of ionic compounds by plants is determined by the combination of hydrophobicity, chemical speciation and the pH of the surrounding solution. Most PhMs are ionizable compounds and have low hydrophobicity ($\log K_{ow} < 2$). Therefore, the relationships developed for nonionic organic contaminants may not be applicable to the uptake of PhMs. For example, no apparent relationship was observed between $\log BCF$ and $\log K_{ow}$ for 20 pharmaceuticals (including acids, bases, and neutral compounds) in hydroponically grown lettuce, spinach, cucumber, and pepper [99]. However, strong correlations were observed when the data were restricted to neutral pharmaceuticals. Zhang et al. [156] found that uncharged compounds, such as caffeine, are readily taken up by aquatic plants, while negatively charged compounds, such as diclofenac, are not, due to the fact that plant cells have a negative electrical potential at the cell membrane, which leads to the repulsion of the negatively charged anions [157]. In addition to pollutant-specific pathways, contaminant uptake may vary by plant species due to root system, transpiration rate, leaf shape and size, and lipid content. For example, the uptake of contaminants from soil is likely to be higher in root vegetables (e.g. carrots) than in tree fruits (e.g. apples). This is because root crops are in close contact with the soil, whereas tree fruits are not. However, the uptake of contaminants directly from the air is expected to be higher for tree fruits than for root crops [152].

A major consequence of soil pollution with PhMs is that residues of these compounds may enter the food chain after uptake by plants and pose potential risks to human and animal health through dietary consumption. Concerns regarding the presence of PhMs in food crops have been increased following the evidence that plants are able to take up and accumulate these contaminants, not only in roots but in edible parts of the plant [158]. Although the measured concentrations found in food crops have been generally low, a little is known about the long-term effects of these compounds to human health. Paltiel et al. [159] found that carbamazepine and its metabolites were detected in human urine after consumption of fresh produce irrigated with treated wastewater. Several studies have estimated the potential human health risk associated with the consumption of plants contaminated with PhMs. Wu et al [99] used data from the leafy vegetables lettuce and spinach to

estimate an individual's annual exposure. Annual exposures ranged from 0.08 to 150 μg for lettuce and 0.04 to 350 μg for spinach. Wu et al. [160] also calculated the annual exposure to seven PhMs from the consumption of mature crops irrigated with PhM-enriched reclaimed water and found the exposure value to be 3.7 μg per capita. This exposure value is much smaller than that found in a single medical dose, which is typically ranging from 20-200 mg [161]. Another study concluded that the concentrations of most PhMs in the edible parts of plants pose a de minimis risk to humans [162]. Other studies have reported similar results [163].

4.3.6. Leaching

Transport processes can determine the fate of PhMs and the risks associated with their exposure in the environment. Under certain conditions, some PhMs can migrate through the soil profile by leaching [164–174]. Soil leaching of PhMs is a common process. It occurs through the action of rainwater or irrigation. It is essential that the product has sufficient water solubility for this process to occur. The transport of PhMs in soils is mainly by matrix flow. However, in many cases the macropores of the soil act as a preferential pathway, resulting in rapid movement of contaminants towards the unsaturated zone. In many European countries where a high percentage of drinking water is obtained from underground sources, the leaching process is of critical importance.

In the leaching process, the physicochemical properties of the contaminants as well as the characteristics of the soil (texture, clay content, organic matter and permeability) play a predominant role [175]. Among these factors, however, the K_{oc} content is the most important because it largely determines the adsorption of chemical contaminants and, consequently, their mobility [176]. K_{oc} is commonly used as a measure of the potential mobility of pesticides and PhMs in soil. The PhM may be in solution, suspended in water or simply emulsified. The extent of the process depends on the nature of the product used and, more importantly, on the colloidal composition of the soil and its adsorption potential, which can be partially quantified by laboratory experiments using soil columns with the compound of interest or in the field using lysimeters. The relative mobility (leaching distance) is inversely proportional to the K_d in the soil. Several guidelines have been proposed by OECD [177] and US EPA [178] to study the movement of chemicals in soils. Several models to assess the mobility of micropollutants through the soil have been proposed in recent decades. Most of the indices published to assess leaching potential are based on adsorption and degradation as the main factors. However, there are others that include soil and environmental parameters [176].

As mentioned above, many authors have noted that the adsorption-desorption process is primarily responsible for regulating the rate and extent of PhM leaching. Thus, a compound should not be affected by other processes if it is adsorbed to the clay-humic complex. Therefore, a good strategy to reduce leaching is to increase the organic matter content of the soil through various agronomic practices, such as the addition of fresh or composted biosolids or the addition of plant biomass, as this will increase the adsorption of non-ionic compounds [179]. It should also be noted that the addition of organic residues to agricultural soils is a common "ecological practice" in many European countries to increase soil fertility and consequently productivity. The main effect of adding organic matter (OM) to soils is to reduce the mobility of contaminants. However, this reduction is not only due to the additional presence of OM, but also to structural changes in soil porosity as a result of the increase in OC. Quin et al [169] investigate a surface pore-integrated mechanism that allows soil organic matter (SOM) to influence the retention and transport of two PhMs (ibuprofen and carbamazepine). The results show that SOM could significantly influence the environmental behavior of PPCPs via two mechanisms: surface coating and pore filling. Surface coating with molecular SOM decreases the sorption of dissociated PhMs (ibuprofen) but increases the sorption of non-dissociated (carbamazepine), while pore-filling with colloidal SOM improves the retention of both compounds by providing nano-/micropores that limit diffusion. The higher retention and lower mobility of these compounds in soil microaggregates than in bulk soil suggests that SOM content and SOM-altered soil pore structure may have a coupled effect on their retention. In addition, it should be noted that dissolved organic matter (DOM) can affect the adsorption and movement of PhMs in soil, as there may be competition between them and DOM for adsorption sites, and there may also be PhM-DOM

interactions that favor leaching. However, the addition of OM to soil usually implies an increase in microbial activity, which increases the biodegradation of PhMs, although in some cases microorganisms may prefer to use OM as a source of carbon and energy rather than micropollutants [180].

After irrigation of soil columns with contaminated wastewater for the equivalent of one crop cycle, between 0% and 7% of the total added amounts of ibuprofen, naproxen, and diclofenac were recovered from the soil profiles, while carbamazepine was more persistent (55%-107%). Levels in leachates suggested that movement through the soil was possible for all analytes, particularly in profiles with low organic matter and clay content [164]. Bondarenko et al, [166] irrigated mature turfgrass plots with unspiked tertiary treated wastewater for over 6 months and collected leachates at the 90 cm depth on a weekly basis. Trimethoprim and primidone were commonly detected in leachates, whereas sulfamethoxazole, meprobamate, and carbamazepine were less commonly detected (<50%). When detected, the total mean leachate concentration was 10 ng L⁻¹ for trimethoprim, 7 ng L⁻¹ for primidone, and 3 to 12 ng L⁻¹ for carbamazepine, sulfamethoxazole, and meprobamate. Column leaching experiments showed that application of biosolids generally increased the retardation of PCs, whereas treated wastewater increased the mobility of weakly acidic PCs in biosolid-amended soils [167]. Pan and Chu [170] indicated that long periods of rainfall promoted downward leaching of tetracycline, sulfamethazine, norfloxacin, erythromycin, and chloramphenicol in soils, with higher leachability in sandy soils than in clay or loamy soils. Compared to vadose zone (an active zone where lithosphere, hydrosphere, and biosphere interact) soils irrigated with groundwater, wastewater-irrigated vadose zone soils had significantly higher PhMs detection frequencies and contamination levels, suggesting the important role of irrigation water sources on PhMs accumulation and transport in the vadose zone [171]. Hill et al [172] demonstrated the presence of flunixin, 17 α -hydroxyprogesterone, triclosan, and sulfadimethoxine in leachates using undisturbed soil columns. Other studies show a high to moderate mobility of tramadol and carbamazepine as well as two transformation products, O-desmethyltramadol and 10,11-dihydro-10-hydroxycarbamazepine, in sandy soils [173].

5. Impact of PhMs on the Soil Health

Soil health can be defined as the continued capacity of soil to function as a vital living ecosystem that sustains plants, animals, and humans. Soil does all this by performing five essential functions: i) regulating water, ii) sustaining plant and animal life, iii) filtering and buffering potential pollutants, iv) Cycling nutrients, and v) providing physical stability and support. Healthy soils are essential for achieving climate neutrality, a clean and circular economy and stopping desertification and land degradation. They are also essential to reverse biodiversity loss, provide healthy food and safeguard human health. The EU soil strategy for 2030 provides the framework and concrete steps towards protecting and restoring soils and ensuring that they are used sustainably. As part of this, a new Soil Monitoring Directive has been proposed to ensure a level playing field and a high level of environmental and health protection [181]. This proposal aims to address key soil threats in the EU, such as erosion, floods and landslides, loss of soil organic matter, salinization, pollution, compaction, sealing, as well as loss of soil biodiversity.

The ideas that prevailed until the 1960s about the Earth's ability to purify itself by diluting pollutants in the soil, air and water can no longer be accepted. We now know that nature has certain mechanisms for retaining and concentrating pollutants, which in certain cases can cause not only significant changes in the ecological balance, but also undesirable toxicological effects on the life forms they affect. Because a variety of biological and geochemical processes occur in soils with a high degree of spatial and temporal heterogeneity, there are three types of indicators to quantify soil quality [182]: chemical, physical and biological. Thus, different authors agree that biochemical and biological properties are the most appropriate to estimate soil quality due to their high sensitivity to changes that occur in soil nutrients such as N, P, C and S [183]. Enzymatic activities provide information on the microbiological state of the soil and its physicochemical properties and quickly reflect changes in soil quality. Therefore, evaluation of microbial responses to PhMs in agricultural

soils is essential to improve our fundamental understanding of the fate of micropollutants and their potential impact on the environment and human health.

Different studies on microbial response to PhMs in soil have mainly focused on the impact of antibiotics on microbial activity and communities, exposure to a single compound, exposure to high concentrations, exposure during a short-term incubation period (< 21 days), and/or a single soil type [184–190]. Most recent studies have highlighted that PhMs affect the soil microbial community by both stimulating and inhibiting microbial respiration and biomass, indicating diverse microbial responses to exposure to pharmaceuticals in soil [191]. Frková et al. [192] focused on the immediate (1 d), short-term (13 d) and long-term (61 d) effects of six PhMs (clindamycin, sulfamethoxazole, carbamazepine, citalopram, fexofenadine and irbesartan) on microbial communities in seven soils with different physicochemical properties. Basal respiration was used as an indicator of microbial activity, while phospholipid fatty acids were used to determine microbial biomass and community structure. The authors identified four microbial responses to PhMs: stimulated, inhibited, stressed, and dormant, which were highly significant in the short term. The stimulatory effect was most pronounced for sulfamethoxazole. It was accompanied by shifts in microbial community structure toward fungi and G- bacteria. The inhibitory effect, with minor changes in the microbial community structure compared to the unsupplemented control, was mainly observed for citalopram, irbesartan and the pharmaceutical mixture in Cambisol Dystric. The stress effect was detected for all PhMs in Arenosol and Cambisol Haplic, while the dormancy effect was mainly observed in Chernozem Siltic for most of the PhMs. Microbial responses were highly dependent on soil type, specific PhM and time, highlighting the importance of considering these parameters, including the resilience of soil microbial communities to micropollutants, within long-term agricultural soil management. Thus, considering the resilience of soil microbial communities to PhMs in long-term agricultural soil management, determining microbial responses under different exposure conditions may help elucidate the impact of PhMs on microbial activity, community size, and structure in diverse soils.

6. Remediation of PhMs-Polluted Soils

Remediation is a term generally used to describe the cleanup or restoration of a polluted environment. It means taking action to prevent the spread of pollution and further degradation of the environment to a level that allows for future use, revitalization, and reclamation. Therefore, the goal of remediation is to reduce the concentration of pollutants in the environment (air, water, soil) to an acceptable level or to eliminate them completely [193]. The procedures and methods of ecological soil management, commonly called soil ecosystem management or soil conservation, are aimed at the maintenance or improvement of soil fertility, health and general quality. There are three areas of equity that should be considered in ecological soil management, including i) environmental equity, ii) scientific equity, and iii) socioeconomic equity.

Restoration of degraded soils is one of the greatest strategies that can be used to improve soil quality and support sustainable agriculture while contributing to long-term environmental conservation [194]. Thus, the goal of ecological management in soil science is to maintain sustainability, which refers to the conservation, preservation, and improvement of soil quality and production while reducing environmental degradation to maintain long-term health and productivity. The process of minimizing, cleaning up, or restoring soils that have been damaged by stressors such as pollution, invasive species, or other types of soil degradation mechanisms is referred to as soil restoration [195].

Sustainable soil remediation has been defined by the International Organization for Standardization (ISO) working group as an approach that minimizes the overall negative environmental, social, and economic impacts of remediation activities while eliminating and/or controlling unacceptable risks in a safe and timely manner [196]. The ISO paper concludes that the need for remediation is identified through risk assessment and that the process of selecting the remediation strategy involves determining the feasible plan that would provide the best overall environmental, social, and economic benefits from the remediation effort [197].

Soil remediation is a critical process aimed at returning contaminated soil to a clean and healthy state. It involves various techniques and strategies to mitigate the presence of PhMs and other harmful pollutants to ensure the protection of human health and the environment. Soil remediation is critical when soil contaminants pose a threat to the environment. They can leach into groundwater and surface water, affecting the entire ecosystem. Contaminated soil is a major challenge to agricultural productivity. By remediating contaminated farmland, we can ensure the production of safe and healthy food, protect crop yields and support sustainable agricultural practices. In addition, by remediating contaminated soil, we can prevent the further spread of contaminants and protect sensitive habitats, flora and fauna.

Traditional methods of soil pollution management have relied on the isolation of affected areas and the use of containment barriers to prevent potential leaks [198]. While these methods were effective in preventing the spread of toxic substances in the soil, they were a temporary solution because they did not address the source of the contamination. Since the beginning of this century, new technologies have been developed for the decontamination and reuse of contaminated soils, called remediation techniques, which include a series of operations that modify the structure of contaminants through chemical, physical, or biological actions in order to reduce the toxicity, mobility, or volume of the contaminated material. It should be noted that the selection of the appropriate remediation technique, as well as the design and strategy of the process, determine the success of a decontamination process. However, in order to make this selection, certain factors must be taken into account. Each situation is different and must be studied in detail. Below are the main criteria that have an impact on the choice of remediation technique:

- Environmental characteristics. Topography, demography, hydrology and ecology of the contaminated area.
- Type of contaminant, concentration and toxicity. The type of pollutant (organic or inorganic) and its physicochemical characteristics provide us with the necessary information on the behavior of the pollutant in the soil and its greater or lesser persistence and hazardousness.
- Physicochemical properties and type of soil to be treated. Texture, structure, porosity, permeability, heterogeneity, pH, temperature, humidity and organic matter content are the parameters that determine the choice of one technique or another.
- Cost of the technique. The inherent uniqueness of each pollution event makes it difficult to rigorously compare the costs of different remediation techniques. The data on which we can rely are based on a treatment applied under specific conditions, and it can be very difficult to extrapolate to other conditions with a different contaminant, at a different concentration, and with a different type of soil. In addition, these costs can be expressed in different parameters/units (volume of soil treated, reduction of pollutant concentration, reduction of pollutant mobility, mass of pollutant removed or area treated), which increases this difficulty. In general, we can say that thermal techniques are the most expensive and biological techniques are the most economical.

Remediation techniques can be classified based on three criteria: i) The remediation strategy, ii) The place where the remediation process is carried out, and iii) The nature of the treatment (Figure 9).

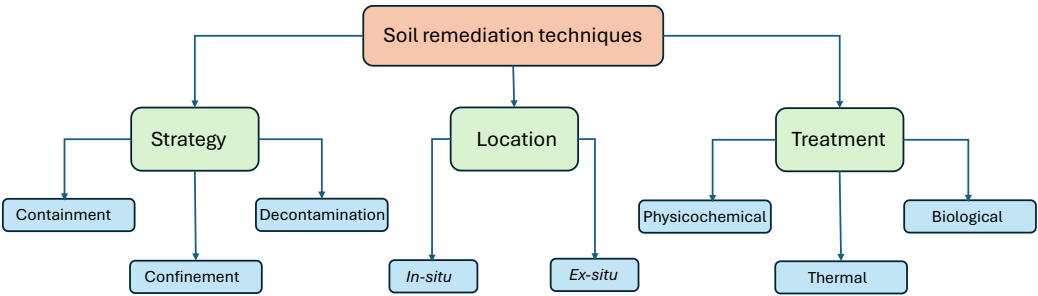


Figure 9. Soil remediation techniques depending on the strategy to be used, the location of the process, and the type of treatment.

Depending on the strategy to be used, we can distinguish three basic methodologies that can be used, individually or together, to remediate contaminated soils:

- Immobilization or isolation of contaminants.
- Separation or extraction of contaminants.
- Destruction or transformation of pollutants.

Depending on the place where the treatment is performed, two types of techniques can be differentiated:

- *In-situ*: When the treatment is carried out directly on the contaminated area, without the need to excavate the site. These are more economical techniques because the soil does not have to be excavated or transported. They have the disadvantage of requiring longer treatment times, the heterogeneous distribution of contaminants in the soil and the difficulty of verifying the effectiveness of the processes.
- *Ex-situ*: When a process (dredging, excavation, etc.) is necessary to remove (move/transport) the contaminated area before its treatment, which can take place on site or in a different place (off-site). Among the advantages of these techniques, we can mention shorter treatment times and greater uniformity in the soils to be treated, as they can be homogenized periodically. In contrast, they need some equipment to excavate the soil, which makes the process more expensive. In addition, there are risks associated with handling the material and possible exposure to the contaminant.

Finally, depending on the type of treatment, three methods can be used:

- Bioremediation, which is a natural and environmentally friendly approach that uses microorganisms or plants to break down or neutralize contaminants in the soil. Microorganisms, such as bacteria and fungi, are able to metabolize contaminants and convert them into less harmful substances. Plants, in a process known as phytoremediation, can absorb and accumulate contaminants. For organic contaminants, including petroleum hydrocarbons, solvents, pesticides, and pharmaceuticals, bioremediation is effective.
- Chemical remediation, which involves the use of chemicals or chemical processes to treat soil contamination. The chemical composition of contaminants is altered to make them less toxic or immobile using techniques such as oxidation and reduction reactions. Soil washing, soil vapor extraction, and chemical oxidation are common chemical remediation methods. A wide range of persistent organic pollutants are amenable to these methods.
- Physical remediation techniques that focus on the physical removal or isolation of contaminated soil from the surrounding environment. A common approach to physical remediation, particularly for localized contamination, is to excavate and remove contaminated soil. Soil capping is another method in which the contaminated soil is covered with a barrier to prevent further contamination of the soil. Physical remediation is often used for soils that have been contaminated with hazardous materials, such as asbestos or radioactive materials.

Therefore, the problem of soil decontamination can be treated from two fundamental perspectives: i) Techniques for isolating contamination, and ii) Decontamination techniques. The dilemma that arises in the face of contaminated soil is to recover it or destroy it. In recent years, special attention has been paid to recovery techniques that make it possible to reuse them as opposed to traditional isolation techniques [193,199,200]. The main techniques to be used are summarized in [Table 4](#).

Table 4. Summary of the main techniques to be used in soil decontamination.

Treatment		Technique	Application
Removal	Physicochemical	Aeration	<i>In situ</i>
		Whasing	<i>Ex situ</i>
		Dragging	<i>In situ</i>
		Adsorption	<i>In situ</i>
		(Photo)chemical oxidation	<i>In situ</i>
		Electrokinetic treatment	<i>In situ</i>
	Biological	Bio-augmentation and bio-stimulation	<i>In situ</i>
		Biopiles	<i>Ex situ</i>
		Composting	<i>Ex situ</i>

		Phytoremediation	<i>In situ</i>
		Landfarming	<i>Ex situ</i>
		Bioventing	<i>In situ</i>
		Natural attenuation	<i>In situ</i>
		Enzymatic degradation	<i>In situ</i>
		Biosorption	<i>In situ</i>
	Thermal	Incineration	<i>Ex situ</i>
		Thermal desorption	<i>Ex situ</i>
		Plasma	<i>In situ</i>
	Solar	Solarization	<i>In situ</i>
		Biosolarization	<i>In situ</i>
	<i>Containment and confinement</i>	Barriers	<i>In situ</i>
		Deep sealing	<i>In situ</i>
		Solidifying injection	<i>In situ</i>
		Vitrification	<i>In situ</i>

7. Conclusions

Among the major types of EPs, PhMs are one of the groups of greatest interest due to their widespread use worldwide and their environmental impact. The PhM market has experienced significant growth since the beginning of the century and is expected to grow at a CAGR of 7.6% from 2023 to 2030. The pharmaceutical industry has made many contributions to the protection of human and animal health and life through the advancement of science and the development of research technologies. However, when we talk about the achievements in the field of pharmacotherapy, we should also take into account the many unresolved problems related to the residues of active pharmaceutical ingredients in the environment.

PhMs are often found in significant concentrations in soils. This is due to the continuous release of effluent and sludge from wastewater treatment plants, which is significantly faster than their removal rates. In addition, the land application of animal manure can lead to the contamination of soil, surface- and groundwater with PhMs through surface runoff and leaching. Reclaimed water is increasingly being used to supplement water resources in arid and semiarid zones. However, it is a complex matrix that includes PhM residues among other EPs that are introduced into the soil when this water is used for irrigation. In addition, the use of sewage sludge as an organic amendment in soils can contribute pollutants to the soil. European policy is directly directed towards increasing the use of treated wastewater for crop irrigation and the agricultural reuse of sewage sludge on soil to improve its fertility, although the effects of long-term application on soil properties are still unknown. Although PhMs are generally present at low environmental concentrations, it is still unclear whether their levels in terrestrial and aquatic environments can cause adverse effects in humans and wildlife.

The behavior and fate of PhMs in soils is governed by several processes, with adsorption determining how they degrade and move. In this regard, the colloidal components of the soil, both inorganic (clays) and organic (humus), play a fundamental role. Sorption of PhMs by soil generally reduces their uptake by plants, especially for those chemicals with strong hydrophobicity or positive charge. However, numerous studies have shown that many crops grown in areas where PhMs are notoriously present can absorb some of these compounds from the soil in varying proportions. The extent of the process depends on a number of factors such as the type of crop, the physicochemical properties of the compound (water solubility, vapor pressure, molecular weight, octanol-water partition coefficient), environmental characteristics (temperature, soil type, water content in soil, agricultural practices), and plant characteristics (root system, shape and size of leaves, and lipid content). A major consequence of soil pollution with PhMs is that residues of these compounds may enter the food chain after uptake by plants and pose potential risks to human and animal health through dietary consumption.

In addition, recent studies have shown that PhMs affect soil health by altering the soil microbial community through both stimulation and inhibition of microbial respiration and biomass, indicating diverse microbial responses to PhM exposure in soil. In view of the above, further measures are needed to prevent soil pollution by PhMs in the first place, as well as measures to clean up and

remediate such pollution in order to improve its subsequent reuse while protecting the health of the population.

Author Contributions: Conceptualization, S.N.; methodology, G.P-L., and S.N.; validation, S.N.; formal analysis, G.P-L., and S.N.; writing—original draft preparation, G.P-L., and S.N.; writing—review and editing, G.P-L., and S.N.; supervision, S.N.; project administration, S.N.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest

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