Impact of PhACs on Soil Microorganisms

Sara Gallego and Fabrice Martin-Laurent

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Abstract The use of reclaimed water in crop irrigation helps to mitigate water shortage. The fertilization of arable soils with sewage sludge, biosolids, or livestock manure reduces extensive application of synthetic fertilizers. However, both practices lead to the introduction of pharmaceutical active compounds (PhACs) in arable soil, known to host a wide range of living organisms, including microorganisms which are supporting numerous ecosystem services. In soils, the fate of PhACs is governed by different abiotic and biotic processes. Among them, soil sorption and microbial transformation are the most important ones and determine the fate, occurrence, and dispersion of PhACs into the different compartments of the environment. The presence of PhACs in soils can compromise the abundance, diversity, and activity of the soil microbial community which is one of the key players in a range of soil ecosystem services. This chapter reviews the current knowledge of the effects

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of PhACs, commonly found in wastewater effluents and derived organic fertilizers, on the soil microbial community.

Keywords Ecosystem services, Microbial activities, Microbial ecotoxicology, Microbial function, Pharmaceuticals

1 Ways of Entrance of PhACs in Arable Soils

Every year, million tons of pharmaceutical active compounds (PhACs) are consumed worldwide for prophylaxis and curative treatments in human and veterinary medicines [1, 2]. Following their ingestion, formulated PhACs enter the body where they are partially assimilated by the organism and, thereafter, largely excreted through feces and urine [3, 4]. On the one hand, excreted residues of PhACs used in human medicine are collected in domestic and hospital sewage disposal systems to reach wastewater treatment plants [5, 6]. Direct dumping of unused or expired medication [7, 8] and illegal drugs [9] can also contribute to wastewater contamination. Since PhACs are relatively stable, conventional wastewater treatment plans have proven to be moderately effective at removing them [10]. As a result, complex mixtures of PhACs and their main metabolites are frequently found in treated wastewater effluents discharged directly in the river and/or in sewage sludge applied to arable soil as organic fertilizers [11, 12]. On the other hand, excreted veterinary PhACs accumulate in livestock manure [13–16] in concentrations that can be severalfold greater than in sewage sludge [17].

In arid or semiarid regions, such as the Mediterranean rim, where rainfalls are uneven and water resources limited, the use of treated wastewater in crop irrigation and groundwater recharge constitutes a promising alternative to release green water pressure on water cycle. Irrigation of crop with wastewater provides not only water but also nutrients to plant [18–20]. This agricultural practice may thereby reduce the application of agrochemical fertilizers, improve plant growth, and limit the wastewater discharged in rivers, thereby decreasing the PhACs pressure on surface water resources especially during the low-water period. Similarly, organic amendment of arable soils with livestock manure and/or sewage sludge/biosolid is also known to be beneficial for mineral fertilization of soil (especially nitrogen) and plant nutrition: it contributes to the maximization of crop yields [21, 22]. However, both practices lead to the release of numerous micro-pollutants including PhACs into arable soils with unknown consequences on both their abiotic and biotic components [23–28]. Although introduced PhACs concentrations are quite low, their repeated input in soil may lead to their accumulation, cause toxic effects to in soil living organisms, and transfer to surrounding aquatic compartments [29, 30].

In addition to diffuse contamination sources in arable soils, improper disposal of drugs or pharmaceutical waste products and accidental spills from pharmaceutical manufacturing plants and hospitals constitute important point sources of contamination. PhACs residues from these polluted sites [31–34] can contaminate water resources (runoff, surface water; leaching, groundwater), which can be used for crop irrigation, and indirectly contribute to both soil pollution and crop contamination.

2 Processes Involved in the Fate of PhACs in Arable Soils

As described above PhACs reach the environment via different entry routes. They reach soil via organic amendment (sewage sludge and farmyard manure) and crop irrigation (wastewater) and water resources via discharge of treated wastewater from wastewater plants in rivers and runoff and leaching from amended arable field. Once they enter the environment, the principal processes governing their fate are found at different degrees in both terrestrial and aquatic compartments. PhACs present in solid and liquid phases interact with both abiotic and biotic compartments of the environment.

In soils, PhACs are subject to several abiotic (sorption, photolysis, chemical transformation) and biotic (bioaccumulation and biotransformation) processes, which determine their ultimate distribution into the different environmental compartments [30, 35]. The rate and degree of each of those processes are determined by PhACs physicochemical characteristics as well as pedoclimatic conditions including temperature, humidity, and soil physiochemical characteristics [36–38].

Among the different mechanisms involved in the environmental fate of PhACs, sorption to soil components is by far one of the most important. It implies their close interactions with organic matter and mineral constituents of soils, involving ion exchange, surface adsorption to mineral constituents, hydrogen bonding, and formation of complexes with ions such as Ca^{2+}, Mg^{2+}, Fe^{+3}, or Al^{3+} [30]. Examples of PhACs with a strong tendency to bind to soil particles are found among those that are poorly soluble such as the analgesic paracetamol, [39], the biocides triclosan and triclocarban, and some antibiotics such as tetracyclines, macrolides, sulfamethazine [40, 41], and quinolones, which form stable complexes through cation bridging to clay minerals. As a result, PhACs remain adsorbed in soils for a long period of time although lowly bioavailable to in soil living organisms [41–51].

On the contrary, the analgesics and anti-inflammatory compounds diclofenac, ibuprofen, and naproxen, the β-blocker propranolol, and some antibiotics such as sulfamethoxazole are less adsorbed to soils [38, 52–54] from where they can runoff to surface waters or leach to groundwater after a heavy rainfall event [25, 54–58]. This was also observed for carbamazepine, meprobamate, trimethoprim, and primidone applied to soil via crop irrigation with spiked wastewater, thereby confirming their low sorption to soil components and their relatively high mobility in soil [56, 59–64]. In addition, PhACs present in the soluble fraction are not only ready to leach to groundwater but also available for plant uptake [24, 65–70], macro- and mesofauna bioaccumulation [71–73], and/or microbiota uptake and further transformation [74].

Additionally, PhACs in soil can be transformed by biotic or abiotic reactions, leading to transformation products that can be more stable, more toxic, and persistent than their parent compounds [75, 76]. Among abiotic processes, photodegradation [77] and hydrolysis [78] are known to transform PhACs in aquatic media. The anti-inflammatory drugs diclofenac, naproxen, ibuprofen, and the diuretic agent amiloride were found to be transformed to hydroxyl metabolites, presenting higher toxicity, after a photocatalytic treatment [79–84]. Additionally, studies from Yamamoto et al. [85] reported a slow rate in sunlight photodegradation of acetaminophen, mefenamic acid, as well as ibuprofen and carbamazepine. In soils, photodegradation was observed for sulfonamides and tetracycline antibiotics which spread on the soil surface and pig slurry following first and biphasic kinetics, respectively [86].

Biotic transformation of PhACs is mainly achieved by microorganisms, which have developed during their long-lasting evolution an impressive enzymatic array able not only to detoxify their environment but also to get access to nutrients for their growth. PhACs biodegradation is achieved by two types of microbial guilds catalyzing two types of transformation: one the one hand, co-metabolic transformation is catalyzed by non-specific enzymes (such as P450 monooxygenase also involved in the biodegradation of other xenobiotics such as pesticides) [74, 87–96]. On the other hand, metabolic transformation is catalyzed by specific enzymes leading to partial or full mineralization of PhACs that are used as nutrients and energy sources for the growth of the degrading microbial guild [87, 90, 97–112]. From this point of view, transformation of PhACs by fungi and bacteria is a key process for their dissipation in the environment [113–116]. Since PhACs are designed to remain active after ingestion, most of them are relatively recalcitrant to biodegradation. However, it was shown that chronic or punctual exposure of soil microbial communities to PhACs can enhance their degrading capacities toward them [109, 117]. Biodegradation of PhACs in soils has been reported for naproxen [38, 74, 118]; ibuprofen [38, 114, 119, 120]; diclofenac [74, 114, 121–123]; paracetamol [39]; carbamazepine [62]; antibiotics such as sulfamethazine [109] and sulfadiazine [124]; triclosan [51, 125–133]; antifungals such as fluconazole, clotrimazole, and miconazole [25, 131, 134–136]; and caffeine [113].

3 Impact of PhACs on in Soil Living Microorganisms

Residues of human and veterinary PhACs enter terrestrial environments as complex liquid or solid biomixtures applied to crop as organic fertilizer or for watering. Like other active ingredients used for plant protection (pesticides), PhACs are relatively recalcitrant to biodegradation, active at rather low concentrations, and target key enzymes involved in essential biological functions that are widespread in the tree of life. During the last decades, the presence of pharmaceutical residues in the aquatic environment has raised special attention, and numerous studies have reported their effects on the aquatic living organisms and supported ecosystem services [137–140]. However, little is known regarding the effect of antibiotics and other PhACs on soil ecosystem services supported by microbial guilds. Soil microorganisms play a pivotal role in multiple ecosystem services. They contribute to soil health, mediate in biogeochemical cycles, and regulate climate change among other processes. Thus, the exposure of soil microorganisms to PhACs can influence their functioning with direct consequences on soil ecosystems. On the one hand, PhACs such as antibiotics and antifungals can inhibit specific microbial guilds and supported functions and thereby compromise the survival and growth of certain microbial guilds. On the other hand, some microorganisms can either develop mechanisms of defense against toxic PhACs (development of antimicrobial resistance, for instance) or use them as nutrient source (biodegradation) for their growth leading to the emergence of specific bacteria. It is noteworthy that some of the PhACs, such as the antibiotics, are particularly of concern because, when they are released in the environment, they exert a selection pressure favorable to the development and dissemination of antimicrobial resistance that can impair human and animal health [141].

Here we report some studies regarding the characterization of the ecotoxicological effects of some PhACs on soil microbial communities. The compounds were selected based on their ubiquitous detection in different environmental matrices and relevance.

3.1 Non-steroidal Anti-inflammatory Drugs (NSAID): Naproxen, Ibuprofen, and Diclofenac

Non-steroidal anti-inflammatory drugs (NSAID) are medicines used to relieve pain, decrease fever, and reduce inflammation. These compounds inhibit the cyclooxygenase (COX) enzyme, required to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins, preventing the platelet adhesion, vasodilation, and increasing body temperature [142]. Among the different types, naproxen, ibuprofen, and diclofenac are the most frequently detected NSAIDs in wastewater effluents [143–148].

3.1.1 Naproxen

Naproxen is an acidic compound frequently found in wastewater effluents and receiving waters [143, 147, 149, 150]. It was found to be rapidly biodegraded in liquid microcosms containing either natural microbial communities from river water [151, 152] or bacteria, fungi, and algae [90, 91, 153–157]. To date, only three studies have addressed the dissipation of naproxen on agricultural soils, and little information is available regarding its ecotoxicological effects on microorganisms [158]. On soil microcosms carried out with three different agricultural soils (sandy loam, loam and silt) never exposed to this NSAID, Topp et al. showed a rapid mineralization of naproxen after application of liquid municipal biosolids [118]. Naproxen was also shown to be degraded in two soils collected from arid regions under aerobic conditions while it was more persistent under anaerobic conditions, suggesting that in terrestrial ecosystems its biodegradation is catalyzed by microorganisms under aerobic conditions. The differences in naproxen half-lives were attributed to specific soil types and microbial characteristics [38]. Studies from Grossberger et al. [74] on agricultural soils irrigated with reclaimed water showed a rapid dissipation of naproxen. Kinetics of dissipation were not enhanced in soils previously exposed to this NSAID, suggesting that in this experiment the naproxen was co-metabolically degraded.

Based on these studies, naproxen seems to be rapidly dissipated in soils where under aerobic conditions it does not remain for long period of time. However, as recurrent contaminant of reclaimed water that is repetitively applied in large volumes to irrigate various crops, it may persist long enough to impact in soil living microorganisms. Indeed, naproxen was found to irreversibly inhibit nitrite production in the ammonia oxidizing bacterium *Nitrosomonas europeae* following the loss of its membrane integrity, which can potentially compromise nitrogen removal in wastewater treatment plants [159]. Naproxen was also shown to change the abundance and the enzymatic activities of soil microorganisms inducing disturbances in soil functions [160].

3.1.2 Ibuprofen

Ibuprofen is a nonprescription drug widely used for the treatment of pain, fever, and rheumatic disorders. Ibuprofen is a chiral compound that contains two enantiomers, the S-enantiomer (pharmacologically active) and the R-enantiomer (inactive) [161–163]. During human metabolisms, R-ibuprofen undergoes chiral inversion, resulting in S-ibuprofen, which is excreted in urine [164, 165]. This pharmacokinetics transformation to S-enantiomer is consistent with the observation of a selective enrichment of S-ibuprofen not only in wastewater influents [166, 167] and effluents [168] but also in surface water [166, 169]. R-enantiomer biodegradation was reported in aquatic systems [169, 170]. However, the depletion of S-enantiomer was shown in wastewater effluents [167] and lake water microcosm spiked with ibuprofen [166] suggesting that ibuprofen enantiomerization may also happen after its release in in the environment.

The ability of both microbial communities [90] and pure microbial strain to degrade ibuprofen has been widely reported [171]. The bacterium *Nocardia.* sp. transforms ibuprofen to ibuprofenol and subsequently to the corresponding acetate derivative [172]. *Sphingomonas* sp. uses ibuprofen as a sole carbon and energy source via deoxygenation of the ring followed by meta-cleavage and catechol formation catalyzed by enzymes encoded by *ipfABDEF* genes [107, 108, 171]. *Bacillus thuringiensis* and *Serratia marcescens* degrade ibuprofen more efficiently in the presence of other carbons sources suggesting co-metabolic transformation [91, 92, 95]. Ibuprofen was also found to be degraded by white-rot fungi [153, 173] that yielded a number of transformation products more toxic than the parent compound.

Ibuprofen degradation was negligible in anaerobic and sterile soil [174] and water-saturated soil [119], further indicating that it is degraded by microorganisms and principally under aerobic conditions.

Ibuprofen has been found in different terrestrial ecosystems [175, 176] at different concentrations ranging between 0.2 and 610 μg/kg. In soils ibuprofen is rapidly degraded under aerobic conditions with half-lives values between 30 to 34.3 days, 10 to 15 days, and 1 to 6 days, respectively [38, 114, 119]. Similar maximum mineralizable amounts of ibuprofen were shown in both aqueous and soil microcosms but with about 3.5 times lower mineralization rate in soil systems [120].

To our best knowledge, the effect of ibuprofen on microorganisms has only been studied in liquid cultures and aquatic populations, and not yet on soil microorganisms. Ibuprofen has antifungal activity against dermatophytes [177] and inhibits the growth of some Gram-positive species [178, 179]. Ibuprofen caused the decrease in the biomass of riverine biofilms and inhibited the growth of *Cyanobacteria* and of alpha, beta-proteobacteria, cytophaga-flavobacteria, and SRB385 populations [180]. Additionally, ibuprofen was also shown to significantly modify the growth of the microbial community of a river sediment incubated at different temperatures and light exposure [181]. Pollution-induced community tolerance (PICT) analysis performed on fluvial biofilms exposed to wastewater effluents showed that at the highest concentrations of ibuprofen and diclofenac, they acquired a tolerance to these components accompanied by an alteration of the algal composition and metabolic profile of microbial organisms [182]. Recently, a mixture of ibuprofen, naproxen, and diclofenac was shown to change the composition of the microbial community (increase in *Actinobacteria* and *Bacteroidetes* and a decrease of *Micropruina* and *Nakamurella*) but not the total nitrogen removal in batch reactors [183]. Although the environmental risk assessment concluded that ibuprofen represents a risk for the aquatic environment [184], it was not included in the list of priority substances under the Water Frame Directive due to a lack of sufficient evidence for its environmental toxicity [185].

3.1.3 Diclofenac

Diclofenac, the most used NSAID in the world, is poorly removed in conventional sewage treatment plants [186–188]. Hence, diclofenac residues are frequently detected in the environment [53, 175, 189–192]. As a consequence, it is considered as a contaminant of emerging concern, and it was added to environmental quality standards (EQS) with a threshold value of 0.1 μg/L (European Community document (COM(2011)876)). More recently, diclofenac was included in the list of priority substances (PSs) of the Directive 2013/39/EU and Watch List of Decision 2015/495/EU [193–195].

Diclofenac is a polar pharmaceutical compound poorly adsorbed to soil components and therefore easily transferable to surrounding environmental compartments via leachates and runoff [38]. In agricultural soils, under aerobic conditions, diclofenac is readily biodegradable [74, 114, 121–123] within 10 days, whereas it persists in sterile soils, indicating that soil microorganisms are responsible for its rapid dissipation. This was confirmed by the isolation and characterization of several fungal [156, 196–200] and bacterial strains able to degrade diclofenac as sole carbon source [87, 97, 201] or through cometabolism [87, 93, 94, 196, 202–205].

Ecotoxicity of diclofenac on Gram-positive [206, 207] and Gram-negative bacteria [208, 209] was reported because of the inhibition of DNA synthesis [210] or of the impairment of membrane activity [211, 212]. To date, only two studies have assessed the effects of diclofenac on soil microorganisms [123, 160]. Experiments performed by Cycon et al. [160] with different endpoints including substrate-induced respiration, soil enzyme activities, and enumeration of culturable bacteria and fungi showed that diclofenac exposure led to an increase in the number of culturable bacteria and fungi. At the highest dose (10 mg/kg), diclofenac increased soil respiration as well as the activity of some soil enzymes (acid and alkaline phosphatase, urease). On the contrary, it inhibited the activity of soil dehydrogenases, while it does not affect enzymatic activities (nitrification and ammonification) of N cycle. Experiments performed by Thelusmond et al. [213] by means of Illumina sequencing, STAMP and PiCRUST in agricultural soils observed an increase in *Proteobacteria*, *Gemmatimonadetes*, and *Actinobacteria* and identified four metabolic pathways positively impacted (propanoate, lysine, fatty acid, and benzoate metabolism) during diclofenac biodegradation.

3.2 Other Analgesics and Antipyretics: Paracetamol or Acetaminophen

Paracetamol or acetaminophen is one of the most widely used over-the-counter analgesic and antipyretic drug. The mechanism of action is complex and includes the inhibition of the cyclooxygenase isozyme COX-3 involved in the synthesis of prostaglandins and the activation of metabolites influencing cannabinoid receptors [214, 215]. As result of its popular use, paracetamol has been frequently found in wastewater treatment plants and in various environmental matrices all over the world [147, 175, 216–227].

Paracetamol is transformed by both fungal [228, 229] and bacterial cultures [96, 98, 99, 111, 230, 231]. In bacteria, two different biodegradation pathways via hydroquinone [101, 111] or pyrocatechol [232] have been characterized [233]. To date, only one study has addressed the fate of paracetamol in soil [39] showing that 17% of initial dose applied was mineralized in 120 days, while 73.4–93.3% was recovered as non-extractable residues. Additionally, eight different transformation products were identified, and new biodegradation pathways for paracetamol degradation in soil were proposed. In this study, paracetamol dissipation was mainly explained by the rapid formation of bound residues preventing the dispersion of paracetamol by leaching and/or runoff but accumulating in soil where it may represent a risk for in soil living organisms.

Although numerous studies have shown toxic effects of paracetamol on aquatic organisms [234–236], little information is available regarding its ecotoxicity toward microorganisms. Paracetamol has antibacterial properties on isolated Gram-positive strains [179]. In combination with doxycycline, it was found to inhibit the activity of nitrifying, denitrifying, and anaerobic ammonium oxidation (anammox) bacteria involved in N cycle from different batch reactors [237]. The microbial toxicity of paracetamol was assessed using the MARA (microbial assay for risk assessment), the Microtox, and the Ames microplate assay [96]. Gram-negative bacilli and Serratia were the most sensitive bacteria, while the most resistant were *Enterococcus* and yeast *Pichia anomala*. According to MARA performed with 11 different strains, the mean value of microbial toxic concentration (MTC equivalent of EC50) was 3,435.00 $\pm$ 129.90 mg/L, and the EC50 estimated values using Microtox with *Aliivibrio fischeri* were 7,923 mg/L and 9,487 mg/L after 5 and 15 min of paracetamol exposure, respectively. Ames assay concluded that paracetamol was non-mutagenic, according to the EPA standards [96].

3.3 Antidepressants: Fluoxetine (Prozac) and Citalopram Hydrobromide (Celexa)

Antidepressants are medications that can help ease symptoms of depression, anxiety, and affective disorders. Among them, selective serotonin reuptake inhibitors (SSRI) are the most commonly prescribed. They increase the levels of serotonin in the brain and block the reabsorption of serotonin into neurons. Examples of SSRI antidepressants are citalopram and fluoxetine, commonly marketed with diverse trade names such as Prozac and Celexa, respectively.

Citalopram is a chiral compound sold as a racemic mixture, but only the S-enantiomer (sold as Escitalopram) has the desired antidepressant effect. Similarly, fluoxetine is commercialized as a racemic mixture, with the S-enantiomer approximately 1.5 more potent than the R-enantiomer. In the human body, fluoxetine is metabolized to norfluoxetine. Several studies have found citalopram, fluoxetine, and its major metabolite norfluoxetine in different environmental matrices [222, 238–242]. Under laboratory conditions, citalopram and fluoxetine are relatively recalcitrant to hydrolysis, photolysis, and microbial degradation [243, 244]. Nonetheless, the biodegradation of fluoxetine by a single bacterium (preferably the R-enantiomer) [105] or microbial consortium has been reported [245, 246]. Fluoxetine biodegradation applied at 1 μg/L was reported in estuarine and coastal seawaters with half-lives ranging from 6 to 10 days [247]. Similarly, in activated sludge the biodegradation of citalopram was reported with 60% and 40% elimination rates under aerobic and anoxic conditions, respectively [248, 249]. In activated sludge [250], similar elimination rates (70%) of citalopram were observed under aerobic conditions, and this biotic transformation led to the formation of 14 different transformation products.

The ecotoxicity of fluoxetine and citalopram on aquatic organisms has been widely documented [251–253]. They affect the behavior, reproduction, development, and survival of aquatic invertebrates and vertebrates [254, 255]. On microbes, psychotropic drugs such as fluoxetine have been found to inhibit microbial activity [256]. In this regard, fluoxetine has significant antibacterial effect and potential antibiotic modulating activity against multiresistant bacteria [257]. Fluoxetine reduced the richness and increased the beta diversity of gut microbiota [258].

3.4 Antiepileptics: Carbamazepine

Carbamazepine is a relatively lipophilic antiepileptic drug used to control and prevent seizures [259, 260]. Due to its scarce removal in wastewater treatment plants [186, 188, 261–263], carbamazepine is frequently found in municipal effluents [63, 188, 260]. For this reason, it has been proposed as an anthropogenic marker of sewage contamination in aquatic environments [264–266]. Carbamazepine is also frequently detected in arable soils irrigated with wastewater, amended with biosolids or in soils where reclaimed water is used to recharge groundwater [239, 240, 267].

In soils carbamazepine was barely degraded (1.2% of mineralization after 120 days of incubation) and transformed to a range of transformation products not adsorbed to soil components (4.2% recoveries as non-extractable residues of initially applied carbamazepine) [62]. The persistence and accumulation of carbamazepine in soils have been reported by many authors [123, 268]. However, some fungi [153, 269–273], bacteria [102, 274, 275], or the combination of both [276] is able to degrade carbamazepine [277]. In this context, a recent study performed in four agricultural soils identified by means of shotgun sequencing the most abundant phytolypes (*Rhodococcus*, *Streptomyces*, and *Pseudomonas*) and associated functional genes [130]. The uptake and metabolism of carbamazepine by endophytic bacteria were studied by Sauvêtre et al. who reported a number of degrading endophytic isolates and identified several degradation products [278, 279].

The ecotoxicological effect of carbamazepine was studied on riverine biofilm communities where it was found to reduce the bacterial biomass and the abundance of gamma-proteobacteria, suppress the *Cyanobacteria*, and increase in algal biomass and abundance of beta-proteobacteria [180]. In soils, the ecotoxicological effects of carbamazepine on soil microorganism have been recently reported indicating an enrichment of *Sphingomonadaceae*, *Xanthomonadaceae*, and *Rhodobacteraceae* [213] and an increase in *Proteobacteria* and *Verrucomicrobia* possibly due to the emergence of carbamazepine degraders [123, 213]. In addition, the abundance of *Flavobacterium*, three genus incertae sedis and *Bacteroidetes* decreased [213] revealing the toxicity of carbamazepine toward these microorganisms.

It is noteworthy that carbamazepine applied at environmental concentrations can induce horizontal transfer of plasmids carrying antibiotic resistance among the bacteria community [280]. Given the co-occurrence of PhACs in environments, these findings pointed out the potential threat of carbamazepine in the environmental spread of antimicrobial resistance.

3.5 Antibiotics

Antibiotics are natural or synthetic substances that kill (bactericidal) or inhibit the growth (bacteriostatic) of bacteria [281]. They are commonly used in human and veterinary medicines [282] as well as in agriculture [283–285] and aquaculture [286, 287] to prevent or treat infections, as growth promoters [288, 289] and sometimes as food preservatives [290]. There are about 250 different antibiotics which can be classified on the basis of their mechanisms in four different groups [281] such as those that inhibit the:

– Synthesis of the cell wall (beta-lactam and glycopeptides)
– Biosynthesis of proteins (aminoglycosides, tetracyclines, chloramphenicol, macrolides, oxazolidinones)
– DNA replication (quinolones)
– Metabolism of folic acid (sulfonamides and trimethoprim)

As a result of their extensive use and their recalcitrance to degradation, antibiotics are frequently found in various matrices such as wastewater [291–297], biosolids [240, 298–301], sewage sludge [302–308], and farmyard manure [309–320]. Applications of these matrices to arable soils to water crop or as organic amendment can lead to the dispersion of antibiotic residues in both terrestrial and aquatic ecosystems [321, 322]. Indeed, antibiotics can runoff or leach from the soil polluting surface water and groundwater, respectively [25, 323, 324]. The ubiquitous detection of antibiotic residues in environmental matrices is cause for a great concern since even at rather low concentration they exert a selection pressure favorable to the emergence and further dispersion of antimicrobial resistances among environmental microbial communities [325–330].

In addition, antibiotic residues may also inhibit specific microbial guilds or functions and therefore disrupt critical processes for ecosystem functioning. Indeed, they have been shown to affect degrading microorganisms, thereby impairing the removal of organic matter and chemicals in sewage treatment plants [331–334]. In addition, antibiotic residues contaminating wastewater or biosolids/manure that are applied on arable soils can inhibit microbial populations involved in carbon and nitrogen geochemical cycling [335, 336], climate regulation [337], and degradation of xenobiotics and therefore may alter soil fertility and ecosystem health [338–343] .

In soils, antibiotics are subjected to microbial transformation with variable degrading rates depending on their molecular structure and physicochemical properties [48, 344]. Amoxicillin (beta-lactam) and chlortetracycline are easily degradable [345, 346], while ciprofloxacine, norfloxacine (fluoroquinolones), azithromycin (macrolides), and doxycycline (tetracyclines) are more recalcitrant to biodegradation remaining for a long period of time in soils [131]. Interestingly, in several studies performed on a long-term field experiment where various antibiotics were repeatedly applied, evidenced for enhanced dissipation of an impressive range of antibiotics (sulfamethazine, tylosin, chlortetracyclin, erythromycin, clarithromycin, and azithromycin) in exposed field plots as compared to control field plots [109, 117]. The number of studies reporting the degradation of different antibiotics in soils is important [124, 340]. Differences observed between studies for a given antibiotic are most likely due to variations in soil type, antibiotic concentrations, and environmental conditions.

Numerous bacterial strains able to degrade antibiotics have been isolated from various matrices including patient, animal, sediment, sludge, manure, and soil. For soils it includes strains belonging to the genera *Microbacterium* sp. (sulfamethazine, sulfadiazine, and sulfamethoxazole) [109, 347, 348], *Bacillus* sp. (penicillin) [110], *Escherichia* sp. (sulfonamides including sulfamethazine and sulfamethoxazole) [349], *Stenotrophomonas* sp., (tetracycline) [350], *Ochrobactrum* sp. (sulfamethoxazole and erythromycin) [351, 352], *Labrys* sp. (fluoroquinolones and sulfamethoxazole) [88, 351], and *Gordonia* sp. (sulfamethoxazole) [351]; the orders *Burkholderiales*, *Caulobacterales*, *Xanthomonadales*, *Pseudomonadales*, *Enterobacteriales*, and *Rhizobiales*; and the phyla *Bacteroidetes* (penicillin and neomycin) [112]. In this regard, bioaugmentation of sulfonamide-spiked soil microcosms with *Microbacterium* sp.C448 [109] was shown to reduce the persistence of antibiotic residues in soils and all associated side effects [353, 354].

3.6 Antiseptics and Disinfectants

Antiseptics and disinfectants, sometimes called biocides, are chemicals commonly used in a variety of medical and domestic settings to prevent or kill the growth of microorganisms. In general, biocides are less specific than antibiotics as their action mode has a broad spectrum of activity, generally not fully understood [355]. Among widely used biocides, triclosan has raised special concern due to its weak demonstrated benefit [356] and potential toxic effects on human health [357, 358]. At low concentrations, triclosan is a bacteriostatic, while at high concentrations, it is bactericidal agent effective against many types of Gram-positive and negative non-sporulating bacteria, some fungi, and certain parasites [359–363]. Although the use of triclosan was restricted in certain types of products [364–366], it is still found in many care products such as toothpaste, mouthwash, hand sanitizer, and surgical soaps. Due to its widespread use and incomplete removal from wastewater treatment plants [367–369], triclosan is frequently detected in several environmental matrices such as soil and surface waters [222, 370–373]. Triclosan was found to bioaccumulate in aquatic species, algae, snails, and earthworms [71, 373–375] in which it caused toxic effects [376–383]. Similarly, plants such as pumpkin, zucchini, onion, and tomato have been shown to bioaccumulate triclosan in the edible parts, thereby leading to the contamination of the food chain [384–386].

Although triclosan is an antimicrobial agent, some fungi [387, 388] and bacteria are able to degrade it co-metabolically or metabolically using it as sole carbon source for their growth [89, 100, 104, 106, 389–393]. In addition, repeated exposure to sublethal concentrations of triclosan may result in the development of resistant colonies [394, 395]. The mechanisms of triclosan microbial resistance share some similarities with those involved in antibiotic resistance [396, 397]. Several studies have demonstrated the development of cross-resistance between triclosan and antibiotics [398–400]. Therefore, triclosan like other biocides is suspected to take part to the selection pressure favorable to the emergence, spread, and maintenance of antibiotic resistances among environmental microbial communities [395, 401–404].

In soils, triclosan was reported to degrade to variable extent, with various half-lives depending on soil properties and conditions of incubation [51, 115, 125–132]. Regarding its ecotoxicological impact on soil microorganisms, triclosan was found to transiently inhibit microbial respiration, reduce microbial biomass [126], and sulfatase activity [405]. These effects were positively related to the dose of triclosan applied to the soil and inversely correlated with soil organic matter and clay content, suggesting that soil characteristics control its bioavailability and induced toxicity. Triclosan was also found to reduce the relative abundance of both Gram-positive and negative bacteria and fungi [406]. Recently, studies performed in four agricultural soils using shotgun sequencing observed an increase in *Pseudomonas*, *Sphingomonas*, *Methylobacillus*, and *Stenotrophomonas* and identified the most abundant functional genes associated with triclosan biodegradation [130].

3.7 Antifungals

Antifungals comprise a large and diverse group of drugs used to treat fungal diseases in humans, animals and plants. Based on their action mode, antifungals can be divided in three different classes: azoles, which inhibit the synthesis of ergosterol; polyenes, which physicochemically interact with fungal membrane sterols; and 5-fluorocytosine, which inhibits macromolecular synthesis [407]. Among the different azoles, of particular interest is the case of the triazoles, which constitute a synthetic group of heterocyclic compounds containing a five-membered ring of two carbon atoms and three nitrogen atoms commonly used for the control of fungal diseases in humans, animals, and plants. They include drugs such as fluconazole, clotrimazole, and miconazole and plant protection products such as tebuconazole and epoxiconazole. By inhibiting the activity of lanosterol 14α-demethylase (DMI), a member of the cytochrome P450 catalytic activity, triazoles alter the bioconversion of lanosterol to ergosterol, a fundamental component of the fungal cytoplasmic membrane, preventing fungal growth [407, 408]. Therefore, triazoles are fungistatic and not fungicidal, but although misleading, the term fungicide is commonly used in agriculture for this type of pesticide.

Due to their efficacy and broad spectrum of activity, triazoles are among the most common systemic fungicides used in the control of plant diseases [409]. Contrary to other available antimycotics, they are applied not only to prevent but also to treat plant fungal diseases. Triazoles have also been shown to promote the growth of plant leading to increase in the crop yield [410, 411].

In the medical field, synthetic antifungal agents are widely used for the treatment and prophylaxis of many mycoses [412]. As a consequence of their common use, substantial amounts of azoles reach the wastewater treatment plants [413–416]. There, as observed for many other PhACs, due to their intrinsic stability, triazoles can remain stable and active with only slight changes in their chemical structure. Studies investigating the occurrence of azole fungicides in wastewater are limited [413, 414, 417–419]. However, a number of studies have identified wastewater effluents as triazole pollution point source of surface waters and agricultural soil [134, 420–425].

The dissipation of triazole plant protection fungicides in soils has been widely documented. Pesticides such as tebuconazole [426–433], epoxiconazole [434, 435], propiconazole [436–438] and cyproconazole [439] have been shown to be relatively persistent in soil. In soil tebuconazole was shown to be transformed in 34 different transformation products [440]. To date *Burkholderia* sp. and *Pseudomonas aeruginosa* are the only two soil bacterial isolates known to degrade the fungicide propiconazole [441, 442].

Similarly, antifungal medicines are highly resistant to microbial degradation. Experiments performed in soil microcosms showed that fluconazole and clotrimazole were scarcely degraded, with half-lives in the range of 73 to 85 days for fluconazole and of 29 to 126 days or of 36.2 to 130.8 days for clotrimazole [135, 136]. In field conditions, a higher persistence was found in biosolid amended soils for the azole biocides climbazole, clotrimazole, and miconazole [25, 131, 134], with differences in dissipation half-lives attributed to soil types and biosolid application rates. To date, only one study has reported the ability of one edible fungal specie to degrade bifonazole and clotrimazole [443].

As observed with antibiotics, the intensive and repeated use of triazoles has led to the emergence of fungal resistances. Among the different mechanisms of resistance involved, the overexpression of the CYP51 gene that codes for the lanosterol 14α-demethylase, due to mutations (insertions or duplications) in the promoter region, and the increase in molecular efflux by ABC (ATP-binding cassette) transporters caused by the overexpression of genes coding for membrane transport have been mainly observed [407, 444–446]. Clinical isolates with observed resistance to triazoles include the species of *Aspergillus*, *Candida*, *Fusarium*, *Zygomycetes*, *Trichosporon*, *Penicillium*, *Bipolaris*, and *Scedosporium*, among others [447–452]. The majority of cases of azole-resistant diseases are due to resistant *Aspergillus fumigatus* which causes a variety of diseases in humans and animals ranging from allergic, chronic, and acute invasive diseases, the latter posing a significant threat to immunocompromised patients [453]. The surge of resistant fungi of human pathogens in the medical field has been related to the exposure to fungicides used in agroecosystems [454–456]. The important use of triazoles in agriculture may indeed exert a selective pressure favoring the survival of certain human pathogenic fungi, increasing the risks and chances for humans to encounter such resisting microbes.

Pathogenic fungi that have their natural habitat in the environment are the fungi *Coccidioides*, *Histoplasma*, *Aspergillus*, *Colletotrichum*, and *Cryptococcus* [457–461].

While a number of studies have evaluated the ecotoxicological impact of triazole fungicides [462] (propiconazole [463, 464], tetraconazole [465], tebuconazole [429, 466–473]) on soil microorganisms, the effects of antifungal medicines on soil microorganisms have been scarcely documented [474]. Climbazole, an antidandruff and antimycotic agent, was shown to be toxic to algae, aquatic lentils (Lemna), and terrestrial plants and exhibited low toxicity toward the soil bacterium *Arthrobacter globiformis* with an EC_{50} of 456 mg/kg soil for inhibition of dehydrogenase activity [474].

4 Perspectives

Although PhACs are found as contaminants in almost all environmental matrices, including soils, their environmental fate and ecotoxicological impact on in soil living organisms and supported ecosystem services remain poorly described and scarcely understood. This evident lack of information is most likely due to the absence of regulatory requirements to monitor soil quality in the absence of a soil protection directive that was proposed almost 20 years ago to the European Commission, but that is still not adopted [475]. In addition, the current regulation to release on the market PhACs does not consider enough their possible effect on the environmental compartment, in particular on soil.

Most of the studies are laboratory experiments that consider contaminant one by one spiked at high concentration in microcosms. Only a few of them are done at field or environmental scale with complex mixture of contaminants but with the problem of the reference (normal operating range) to interpret the variations observed. Although it is the rule at the environmental scale, no studies consider the effect of complex mixtures of PhACs to soil [476]. Until now, there are no consensus to assess the fate and the ecotoxicological effects of PhACs on soil microorganisms and supported ecosystem services.

Given the fact that human and animal health are unambiguously link to environmental health under the concept of “One health,” it could be concluded that there is an urgent need to unify current regulations on the release on the market of PhACs, biocides, and plant protection products in close connection with the regulations to protect the environment such as the water framework directive, air quality framework directive, and national directives on soil protection (pending the publication of the soil protection directive). This unification has to be done under a holistic policy embracing both a priori and a posteriori environmental risk evaluation assessment by targeting specific protection goals, including microbial communities that support soil ecosystem services.

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