The Transportation, Transformation and (Bio)accumulation of Pharmaceuticals in the Terrestrial Ecosystem

Chubin Zhang[1], Leon Barron[1,2] and Stephen Sturzenbaum[1*]

[1] Department of Analytical, Environmental & Forensic Sciences, School of Population Health & Environmental Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK; [2]Present address: School of Public Health, Environmental Research Group, Imperial College London, London UK; *tel: +44 (0)2078 48 4406;

email: stephen.sturzenbaum@kcl.ac.uk

Abstract: Soil dwelling organisms, plants and many primary consumers in food webs face the challenge of exposure to contaminants of emerging concern (CECs) present in terrestrial systems, including thousands of substances derived from pharmaceutical and personal care products (PPCPs). The recent increase in the consumption of modern human or veterinary drugs has resulted in a surge of anthropogenic pharmaceuticals, frequently introduced into terrestrial environments via untreated/treated wastewater. Pharmaceuticals display diverse degradation and accumulation behaviours in receiving bodies, however their impact on soils has, at large, been overlooked. Details about adsorption, absorption, degradation and uptake behaviours, as well as the fate and actual environmental impact of pharmaceuticals are a prerequisite before the traditional transportation prediction models originally designed for the aquatic environment can be extrapolated to terrestrial systems. Without this knowledge, our ability for informed risk assessments and the resultant implementation of contamination management strategies of soils will remain limited. This review discusses the current knowledgebase pertaining the introduction of pharmaceuticals to soils via wastewater irrigation or the application of biosolids. The focus on the transportation, transformation and accumulation of pharmaceuticals through the food chain highlights the urgent need to strengthen our capabilities concerning their detection and characterization in the terrestrial ecosystem.

Key words: PPCPs; metabolism; wastewater irrigation, biosolids, soil, food-chain

1. Introduction

Pollutants are present in the atmosphere, aquatic as well as terrestrial environments. The origin and distribution of these contaminants is driven by natural and man-made forces, thus organisms and ecosystems are exposed, on a daily basis, to a diverse and dynamically changing burden of contaminants. Pollutants undergo transportation and transformation pathways and modelling these processes has proved very challenging. The majority of research concerning the transport, transformation and fate of chemical pollutants has been conducted on the aquatic environment which is in stark contrast to the inhomogeneous terrestrial compartments, such as soil. Aside from priority pollutants listed by the US EPA or under the EU Water Framework Directive, several contaminants of emerging concern are currently being evaluated for potential future regulation, these include pharmaceuticals and personal care products (PPCPs). Certain compounds and their metabolites within treated wastewater can impact aquatic organisms and the general water body health, a notion which first emerged at the beginning of the 21st century and a succession of comprehensive reports have since been published. In contrast, the field data and analytical capacities regarding their transport, transformation and fate in soils as well as their potential to transfer within food webs is limited.

Soil is a prominent exposure route of toxic pollutants (Ljung et al., 2006), thus underlining the need to understand the chemical behaviour of the natural and anthropogenic compounds that reside in terrestrial environments. This knowledge will aid in defining priority pollutants for evidence based assessment of environmental risk. Besides direct dumping, pollutants can reach surface soil through three major paths: suspended particles deposition from the atmosphere, deposition of contaminated sediments or via the circulation of groundwater. Public concern and research efforts have traditionally focused on (heavy) metals and polycyclic aromatic hydrocarbons (PAHs), two disparate groups of pollutants that are ubiquitous in soils. The

source and fate identification of those contaminants, however, can be challenging due to their geographical redistribution by stormwater runoff and the circulation of groundwater. In addition, active pharmaceutical ingredients (API) can be observed in terrestrial systems that are characterized by elevated human activities, mainly due to the application of treated water and/or sewage sludge. A considerable number of studies have revealed the presence of pharmaceutically active compounds in commercial croplands and other agricultural soils, indicating that although the top four most frequently detected pharmaceuticals in the soil samples are reported to be analgesics and anti-inflammatories (especially, non-steroid anti-inflammatories drugs, NSAIDs), antibiotics and psychiatric drugs, the realistic abundance of a certain drug varies, spatially and temporally. For instance, Kinney et al. (Kinney et al. , 2006) reported erythromycin, carbamazepine, fluoxetine, and diphenhydramine as the most commonly detected pharmaceuticals in several sites in the USA during the summer of 2013, while triclocarban, 4-nonylphenol, salicylic acid and oxytetracycline were detected in most research sites across mainland China in 2008 (Chen et al., 2011). The same authors (Chen et al., 2011) warned of the potential high risk triclocarban can pose to soil organisms, especially earthworms (the LC50 value for *Eisenia fetida* was 40 mg/kg soil and the predicted no observed effect concentration (NOEC) was reported to be only 40 μg/kg). The exposure of humans via plant-derived food and daily meat consumption was predicted to be generally negligible and the risks to human health low (Boxall et al., 2006), however, chronic effects should be taken into consideration as some commercial croplands have a long history of irrigation or amendment by wastewater treatment products with limited regulation. Although encountered concentrations are frequently relatively low, they may result in dire consequences for human health due to their potential to accumulate in plants and soil invertebrates, highlighting the urgency of understanding the movements of these contaminants. In the following sections, major sources and (predicted) chemical behaviours of abundant pharmaceuticals will be

discussed to reveal the current status and (lack of) understanding regarding the potential transport and accumulation through food webs of newly emerging terrestrial contaminants.

2. Major paths of pharmaceuticals entering the soil environment

Water research has evolved from classical environmental contaminants studies on stable and acute highly toxic pollutants, such as pesticides, heavy metals and persistent organic pollutants (POPs), and now include domestic uses of pharmaceuticals and personal care products (PPCPs) (Ternes et al., 2004). Medicines typically constitute a multitude of different substances resulting in a combination of intact and metabolized molecules. Consequently, active pharmaceutical compounds enter the wastewater and in doing so reach natural receptors. A comprehensive 2-year study investigated 77 PPCPs from 49 German wastewater treatment plants (WWTPs) and over 46 compounds could be detected in their outflows at ppb level (Ternes, 1998). A similar detection rate of organic compounds in wastewater outflows was reported in the United States in 1999/2000 (Kolpin et al., 2002). Subsequent monitoring studies have since been conducted across the globe focusing on diverse target chemicals, but typically only a small subset of the PPCPs predicted to enter the environment were studied (Wang & Wang, 2016; Kosma et al., 2014). With the development of synthetic chemistry and pharmaceutical products we started to introduce new compounds into the environment via various production and consumption activities, and it is widely accepted that municipal wastewater serves as the main exposure route (Ternes et al., 2004). The Chemical Investigation Program 3 (CIP3) project, performed by the UK Water Industries to assess pharmaceuticals in different stages of wastewater treatment, warned that approximately 13% of WWTPs in the UK (roughly 900 WWTPs) might exceed predicted no effect downstream riverine concentrations (Comber et al., 2018).

Most wastewater treatment plants (WWTPs) were not designed to completely remove all pharmaceuticals, in fact most treatment plants predate the development of many modern human

or veterinary drugs, which are frequently defined as contaminants of emerging concern (CECs). Designed specifically for the removal of biological oxygen demand (BOD) in the 1950s, WWTPs have been modified in a step-by-step manner in response to the tightening of effluent discharge standards (Ternes et al., 2004). Unused pharmaceuticals are also frequently disposed via domestic wastewater to prevent, for example, access to children or limit illicit use; sewage systems therefore also encounter the parent molecule of pharmaceuticals that have not undergone the designated biochemical reactions in human/animal bodies prior to its arrival at WWTPs. Human-derived pharmaceuticals are typically re-introduced into the environment via two paths, either due to the discharge of treated effluent from WWTPs or by means of sewage sludge disposal (Kinney et al., 2006). According to the UK Water Services Regulation Authority (Ofwat, 2016), the ultimate destination of the majority of wastewater sludge is farmland where sludge is applied as biosolids for the purpose of increasing local soil nutrient and to boost agricultural yields. Wastewater recycling is a global phenomenon, and despite the abundance of rules which govern this practice (many of which originate from the last century) they have not been updated to take into account the infinite number of newly emerging pollutants. There are notably no routine tests that are applied to wastewater products prior to their deposition onto agricultural land. A legal platform concerning contaminants in biosolids pretreatment is all but absent and therefore has the potential to affect terrestrial health and food chains. For instance, biodegradation in the secondary stage of sewage treatment in WWTPs largely eliminates organic compounds. However, the removal efficiencies of pharmaceuticals varies based on the specific drug properties. Hydrophilic compounds are removed effectively by activated sewage bacteria in WWTPs as they bind weakly to organic matter. The degradation pathway and efficiency are not only dependent on the physical, chemical and biological characteristics of the pharmaceuticals, but also the design of WWTPs (e.g. the coexistence of different biodegradation pathways might promote or inhibit the elimination

process). A further removal mechanism is by sorption to microorganisms or extracellular polymeric substances (EPS), occurring mainly by hydrophobic interactions of the aliphatic and aromatic groups and electrostatic interactions of positively charged groups. Sorbed organic compounds can be removed by sedimentation as primary/secondary sludge which is then introduced to the environment via the application of digested sludge for soil amendment. The surface of most microorganisms is negatively charged when the environmental pH value exceeds the bacterial isoelectric point (typically pH 3-4). The gel-like matrix of EPSs is also made up of negatively charged deprotonated carboxylic moieties, suggesting that the elimination of acidic pharmaceuticals is less effective than their neutral and positively charges counterparts. Acidic pharmaceuticals might therefore readily enter the environment via WWTPs effluents. The use of recycled water for irrigation is a global practice: in California and Australia 37% of the recycled water is used for agricultural purposes (Olivieri et al., 2014), and over 70 % of the wastewater generated in Europe is recycled (Sato et al., 2013). The reuse of untreated wastewater is typically underestimated. Thebo et al. (2017) developed the first spatially-explicit assessment of this phenomenon who observed that 65% (35.9 Mha) of downstream irrigated croplands were located in catchment areas with high levels of dependence on urban wastewater flows. Many countries, in particular within Asia, apply raw wastewater irrigation (Figure 1).

It should be noted that domestic wastewater represents only one source of environmental active pharmaceutical compounds, others include water-based sources (e.g., hospital discharges, industrial effluent, and surface runoff) and solid-waste-based sources (e.g., landfill leachates). The introduction of PPCPs from these sources could, as with issues surrounding the treatment of domestic sewage, be due to the design of water treatment plants. It is conceivable that pharmaceutical-derived active ingredients, intermediate products, antibiotics and other veterinary drugs from farm/agricultural land runoffs, even atmospheric deposition by airborne

compounds can enter soil systems via the incomplete processing of WWTPs. Although the presence of most pharmaceuticals in WWTPs has been reported to be relatively low, individual molecules and/or a complex mixture of potential drugs has the potential to exert inhibitory effects on activated sludge bacteria which are typically responsible for the secondary treatment process, namely the degradation of organic matter (Yang et al., 2017). This would increase the risk of reduced elimination rates of pharmaceuticals in the effluents and other by-products, which, in turn, would introduce pharmaceuticals into terrestrial environments.

A further source of exposure is due to the disposal of expired or surplus PPCPs in landfills (Yu et al., 2020). The number of unused and/or expired drugs has increased over recent decades, however due to the absence of comprehensive recycling strategies they can enter municipal sewage systems and landfills (Bound & Voulvoulis, 2005; Musson & Townsend, 2009; Song et al., 2016). The most abundant PPCPs in landfill leachates and surrounding environments are insect repellents, anti-inflammatories, stimulants, anticonvulsants and antibiotics (Yu et al., 2020) The highest reported diethyltoluamide concentration exceeded 52,800 μg/L in landfill leachates, dropping to only 0.06-1000 μg/L in adjacent groundwater, suggesting that a portion of diethyltoluamide might be absorbed or degraded in the soil systems. A similar discrepancy between leachate and groundwater has been reported with other pharmaceuticals detected in landfill leachates. The underlying reasons resulting in the observed differences are not fully understood and efforts on eliminating pharmaceuticals from modern municipal solid waste landfills are still under development. A further leaching risk originates from the many historic landfills that were closed/abandoned before the late 1990s as these are rarely monitored and often lack sufficient impervious barriers.

3. The transport of pharmaceuticals in soil

The detection of pharmaceuticals in soils and biosolids has prompted concern due to their potential to be bioactive and/or potent at low doses. Certain drugs cause microbial resistance

(e.g. antibiotics), exhibit acute toxicity (e.g. diclofenac), and result in endocrine disruption (e.g. 17β-estradiol) (Thebo et al., 2017; Thelusmond et al., 2016; Gao et al., 2012). Non-steroidal anti-inflammatory drugs (NSAID), antibiotics, cardiovascular pharmaceuticals (β-blockers/diuretics), psychostimulants, anti-hypertensive, estrogens and other hormones, and antiepileptic drugs are the major pharmaceuticals introduced to the soil environment (Li, 2014), with antibiotics (trimethoprim, sulfadiazine, and triclosan), NASID (ibuprofen and diclofenac) and antiepileptic (carbamazepine) being the most common drugs detected in the soil (Table 1). Further attention was devoted to those drugs entering agricultural areas via the application of wastewater and biosolids because of the risk of their impact on the food chain. Paltiel et al. (2016), for example, reported that carbamazepine and its metabolites were detected in human urine following the consumption of fresh produce which was irrigated with treated wastewater. The movement of pharmaceuticals in soil, including transportation, transformation, degradation and uptake by plants and soil organisms is affected by the physicochemical properties and initial concentrations of compounds as well as the soil characteristics. The physicochemical properties of pharmaceutical compounds, such as polarity, octanol-water partition coefficient (log K_{ow}), and solid-water distribution coefficient (log K_d), influence the movement within the soil matrix. Ionization, cation-bridging and retention in stagnant pore water were also considered as potential reasons for various pollutant behaviours in soil environments (Carter et al., 2014). The presence of positive structures, e.g. triazine rings and amino groups, increase the sorption (both adsorption and absorption) affinity of lamotrigine, when compared to carbamazepine, resulting in the enhanced ability of the molecules to form hydrogen bonds with functional groups on soil surfaces, and in particularly polar soil organic matter (Paz et al., 2016). Higher mobilities in soil can contribute to further microbial utilisation and plant uptake. However, those mobilities have been reported to be highly dependent on soil quality (Wu et al., 2015a). The presence of soil organic matter and dissolved organic matter in

interstitial water or pore water can either enhance or inhibit pharmaceuticals movement, a concept which will be discussed in the next paragraph.

Certain pharmaceuticals display different sorption behaviours within various soil types where organic content and base cation saturation (e.g. metoprolol and atenolol) are expected to be the major drivers of the movement in soil (Borgman & Chefetz, 2013), via binding through hydrogen bonding and/or anion exchange. The same authors demonstrated that the increased retardation of drugs in soil columns was observed in soil with higher organic content, especially those amended with biosolids. This behaviour can be explained by the specific interactions between sorbate molecules and functional groups of soil organic matter, which are dominant at low sorbate concentrations (Delle Site, 2001). Normally, soil particles have sufficient capacity to allow the sorption of most compounds at their environmental concentrations, however different compounds compete for sorption sites, thus resulting in competitive effects of co-introduced pollutants (Paz et al., 2016). In contrast, sorption and desorption research on selected NASIDs suggested that naproxen and ibuprofen both exhibited significant differences between single-drug and mixture designs, presenting multilayer bonding effects and complexation with cations in the soil, possibly affecting the behaviour of drugs (Zhang et al., 2017). The ion and hydrophobic interactions observed in NASIDs illustrate how soil properties modulate drug sorption and retention when emerging pollutants are mixed, thereby highlighting the need for further studies to investigate behaviours of mixtures with diverse soil types. However, Koba et al. (2016) who applied a matrix effect evaluation experiment with thirteen different soil types, argued that adsorption of their studied compounds, i.e. atenolol, metoprolol, and carbamazepine, was not overly depended on the type of matrix. To what extent soil properties affect pharmaceuticals movement, namely adsorption and absorption, remains to be determined. A previous report concluded that wastewater irrigated soil suffered from higher mobilities of weakly acidic drugs due to the change in pH after irrigation, while the

application of biosolids to arable land increased the content of soil organic matter and therefore supported the retention of pharmaceuticals (Borgman & Chefetz, 2013). Similar enhanced mobilities have also been reported by Haham et al. (2012) who argued that the complexation of compounds with dissolved organic matter in wastewater was a key factor while Barron et al. (Barron et al., 2009) hypothesised that the hydrophobic interactions might not explain the drug movement within the complex matrix of soils and biosolids. The same authors suggested that artificial neural networks should be employed to model the behaviour of pharmaceuticals in soil matrices and define correlations between multiple chemical- and/or biological-transformation pathways. Higher mobilities increase the possibility of pharmaceuticals entering the groundwater, which in turn can impact the environment further.

Degradation, especially photodegradation and biodegradation, can render a drug to become either less harmful to soil systems or give rise to a new environmental health threat by generating new, more toxic, metabolites. Others have concluded that photodegradation of target pollutants in surface water is elevated in wastewater (Durán-Álvarez et al., 2015) . A major driver of photodegradation in wastewater prior to irrigation is the geographic location. The higher the latitude of the target area, the higher the photodegradation rate. Further factors are the suspended solids and turbidity which can hamper the photolysis of the organic compounds since both the dissolved and the particulate organic matter reflect the incident photons, hence impede direct photolysis. Limited information about photodegradation of pharmaceuticals is available and previous research has only focused on few frequently detected drugs (i.e. carbamazepine, triclosan and naproxen) and antibiotics (Borgman & Chefetz, 2013; Delle Site, 2001). The photodegradation rates of target pollutants in soil were significantly lower than those observed in water samples (see Table 2) which might be explained by the low penetration of light through the solid matrix (photolysis occurs only in the top 0.5 mm layer). In addition, the high content of carbonates in soil (accumulation by wastewater irrigation and

247 soil respiration) may cause a decrease in the photolysis rate of pollutants, even within the photic
248 zone of soil (Mountacer et al., 2014). Soil structure, moisture and quality/quantity of organic
249 compounds of soil have the potential to influence the extent of photolysis of the dissolved
250 organic matter, which can contribute to the generation of free radicals (either oxygen-based
251 radicals or excited dissolved organic matter molecules, •DOM). Produced in the surface layer
252 of the soil, these radicals might then interact with emerging contaminants, leading to further
253 degradation. It is reasonable to hypothesise that triplet state organic matter can be transported
254 by water and migrate to lower soil horizons following irrigation (Frank et al., 2002).
255 Many recent pharmaceutical drugs were designed to resist common biotransformation
256 processes with the view to protract the persistence of drugs. However, this stability may exert
257 harmful and long-term toxicological effects to the environment. Although biodegradation by
258 bacteria has been recognised as an important removal mechanism of xenobiotics in soils, the
259 specific bacteria and pathways involved in those pharmaceuticals biodegradation in the
260 terrestrial system are generally unknown (Thelusmond et al., 2016). Similar to
261 photodegradation, the mechanisms underlying biodegradation of certain drugs have not been
262 fully studied and most reports have focused on the aquatic environment and specific
263 microorganisms or catalysts. Recent reports have linked bacteria to pharmaceutical degradation
264 processes in biofilms inoculated with activated sludge (Kim et al., 2017; Bessa et al., 2017).
265 For example, in liquid media, *Enterobacter hormaechei* D15 (from activated sludge),
266 *Enterobacter cloacae* (from household compost) and *Brevibacterium sp*. D4 (from activated
267 sludge) have all been linked to the transformation of diclofenac, while *Pseudomonas*
268 *fluorescens* MC46 and *Ochrobactrum sp*. MC22 were able to transform triclosan (TCC)
269 (Thebo et al., 2017; Durán-Álvarez et al., 2015; Zhou et al., 2013). Previous publications have
270 identified bacterial isolates that may contribute to the biotransformation of carbamazepine
271 (CBZ) and triclosan (TCC) in the laboratory, but it is still unknown if these microorganisms

are capable of degrading these chemicals in agricultural soils when pharmaceuticals are present at environmental concentrations (most at ppb levels). Transformation of pharmaceuticals by different degradation processes may therefore result in multiple metabolites and degradation products in the soil (Challis et al., 2013; López-Peñalver et al., 2010; Mountacer et al., 2014). The impact of these secondary compounds on the environment requires further studies.

Carbamazepine, widely prescribed as an effective analgesic, non-narcotic, and anticonvulsant drug, is the most studied emerging pharmaceutical in the terrestrial system due to its low removal efficiency in wastewater treatment plants, and in some cases, even a negative removal efficiency with no seasonal concentration variation (Koba et al., 2016). Recognized as a representative indicator for pharmaceuticals (Mompelat et al., 2009) and considered a representative anthropogenic marker for environmental quality in wastewater (Hai et al., 2018), carbamazepine might therefore also be a good indicator for the presence of pharmaceuticals in soil. Li et al. (2013) demonstrated that, in soil, CBZ was transformed into various intermediates, including 10,11-dihydro-10-hydroxycarbamazepine (DHC), carbamazepine-10,11-epoxide (EPC), acridone-N-carbaldehyde, 4-aldehyde-9-acridone, and acridine (Figure 2). The increase in molecular weight (compared to the original pollutant, CBZ) can be explained by the oxygen insertion into the most reactive site which is the olefinic double bond on the central heterocyclic ring. Hydroxylation on the active site then form the hydroxyl derivatives (10,11-dihydro-10,11-trans-dihydroxycarbamazepine, i.e. DHC and 10,11-epoxycarbamazepine, i.e. EPC). These epoxidation metabolites support the assumption that the terrestrial biodegradation process is due to the activities of these enzymes. Similar epoxides have been observed during polycyclic aromatic hydrocarbon (PAH) metabolism as the products of CYP450 oxidation. The other three intermediates are the result of further ring contraction and conversion, due to the unstable structure of epoxides. It should be noted that free EPC in patient serum directly correlates with acute side effects, suggesting that the toxic biological activity to organisms and the acridine,

297 one of the final metabolites in this pathway, inhibits DNA repair and cell growth (Frank et al.,
298 2002; Kim et al., 2017). EPC's lower hydrophobicity (compared to CBZ) results in weaker
299 sorption and higher mobility in the terrestrial environment, making it more likely to travel to
300 deeper soil layers and pose a threat to the whole soil system and even groundwater. Other
301 studies observed additional intermediates (Thebo et al., 2017; Li, 2014; Franklin et al., 2018).
302 Experiments with bacteria proposed several potential pathways with enzymes, e.g. *Aspergillus*
303 *niger* (Gauthier et al., 2010), *Rhizobium radiobacter* and *Diaphorobacter nitroreducens*
304 (Sauvêtre et al., 2018), and *Phragmites australis* (Sauvêtre et al., 2018). Endophytic bacteria
305 (*Rhizobium radiobacter* and *Diaphorobacter nitroreducens*) were shown to transform CBZ
306 into EPC, DHC, and acridine, while *Phragmites australis* generated the intermediates cis-
307 10,11-dihydroxy-10,11-dihydrocarbamazepine and cis-2,3-dihydroxy-2,3-
308 dihydrocarbamazepine. Additional products from the *Phragmites australis* mediated pathway
309 and degradation mechanisms from *Aspergillus niger* are still unknown. These findings
310 highlight the importance of elucidating the potential degradation pathways of pharmaceuticals
311 in terrestrial compartments as their metabolites might benefit from higher mobility and toxicity
312 than the parent compound.

313 4. The potential transfer of pharmaceuticals through food chains

314 Ethical, scientific and practical drawbacks can limit the use of direct approaches to study the
315 risk of exposure to organisms. In aquatic environments, mechanistic bioaccumulation models
316 for piscivorous food chains are widely used to assess the environmental/biological hazards of
317 commercial chemicals, including metals, pesticides and other persistent organic pollutants
318 (POPs) (Armitage & Gobas, 2007). Since the concept of environmental pollution has now been
319 extended to include pharmaceuticals, the occurrence and trophic transfer of drugs (e.g.
320 carbamazepine and roxithromycin) have been established in aquatic food webs (Salgado et al.,
321 2013; Li et al., 2013).

For terrestrial environments, most attention regarding the accumulation of pollution in food webs has been devoted to plant communities. Traditional uptake experiments are typically performed under hydroponic conditions where the bioconcentration factor (BCF) is employed to evaluate the bioaccumulation potential of drugs and predict plant uptake mechanisms. Pharmaceuticals desorbed in pore water normally increase the availability for plant uptake (Paz et al., 2016), which suggests that hydroponic experiments can act as a rapid screen to determine priority drugs with high plant uptake potential. However, it is challenging to predict plant uptake of pharmaceuticals in real environments from hydroponic research results since the process of pharmaceuticals in the soil is more complex and highly dependent on soil properties. The differences between BCFs obtained from hydroponic and soil studies indicate that the bioavailability of certain drugs is reduced in soil. Carbamazepine is a commonly detected pharmaceutical in terrestrial systems and has one of the highest potentials to transfer from soil to plant tissues. Triclosan and triclocarban were found to be taken up by roots and then translocated to leaves and even fruits (Wu et al., 2012). One of the vital factors in the root uptake are the drug properties. Uptake of neutral pharmaceuticals, following a positive linear relationship with hydrophobicity, is primarily affected by the chemical hydrophobicity (Wu et al., 2013). For ionic medical drugs, ion trap and electrical attraction are the main factors driving the uptake and the slow membrane-crossing rate for ions, and might explain their lower uptake ability when compared to neutral drugs. Whilst the mechanisms for acidic/basic pharmaceuticals are still unknown, most reports focus on ion trap, electrical attraction and repulsion (Sauvêtre et al., 2018; Armitage & Gobas, 2007). For plants grown in commercial land, the potential human exposure to drugs via the daily consumption of root and leaf vegetables is estimated at 0.01-0.21% and 0.09-3.81% of the acceptable daily intake (ADI) for a single compound, respectively (Carter et al., 2014). Exceptions are triclosan, lamotrigine and the metabolites of carbamazepine which have the potential to reach or even surpass the

threshold of toxicological concern (TTC) (Malchi et al., 2014). Our limited knowledgebase concerning the human health risks that are derived from the plant-human food chain restricts our ability to predict the impact of the indirect ingestion of pharmaceuticals.

Indeed, the availability of data on bioconcentration and hazards linked to the uptake of pollutants are, at large, unaccounted for in small mammals, birds, and even humans. Although most drugs have rapid transformation and removal rates, the continuous influx of pharmaceuticals into the terrestrial system through human activities may well exceed the removal efficiency and pose pseudo-persistent threats on soil health. Ding et al. (2015) identified, through a lab-based experiment, the possibility of trophic transfer, namely the antibiotic roxithromycin passed through the aquatic food chain and differences in tissue accumulation were measured in the secondary consumers. This secondary poisoning via the food chain might also apply to the terrestrial food web, affecting predators sharing similar diets of terrestrial organisms. In recent years, regulatory agencies in Europe have relied primarily on the aquatic models to assess the bioaccumulation of chemicals which might provide misleading information about the movement of contaminants due to differences in the biomagnification of certain drugs in aquatic and terrestrial systems (Fremlin et al., 2020). In these protocols, bioaccumulation factors (BAF) or bioconcentration factors (BCF) are employed to evaluate potential risks, however both factors are only relevant to water-respiring organisms and the BCF excludes diet as an exposure path. Thus, explicit and accurate estimating models are required for studying the accumulation behaviours of contaminants of emerging concerns (CEC) in terrestrial invertebrates and organisms higher up in food chains. The biomagnification and trophic magnification factors (BMF or TMF) partly address this shortfall, as they take dietary exposure into account and are adaptable for both air-respiring and water-respiring systems (Borgå et al., 2012). Fremlin et al. (2020) assessed trophic magnification of legacy persistent organic pollutants (POPs) in an urban food web with over 13 species,

including the Himalaya blackberry (the primary producer), earthworms (the detritivores), beetles (the primary consumers), sparrows (the secondary consumers), and the copper's hawk (the apex predator). Their reports emphasized that terrestrial food webs can suffer from higher biomagnification of certain organic compounds than aquatic environments, which might be due to the greater ability to absorb/digest their diet. This result highlights the importance of developing specific models and standards for terrestrial systems. Having said that, the determination of TMFs is impractical when focusing on lower levels of the food chain, due to their trophic position and the presence of trace concentration of certain drugs (Conder et al., 2012). In addition, previous studies only involved simple models to generate trophic magnification factors (Armitage & Gobas, 2007). Consequently, relevant field studies and data collection are a critical requirement as they would assist in the development of biomagnification models and provide empirical data on CECs for further studies.

Earthworms, classified as primary consumers, participate in various food chains and therefore connect the soil media with higher trophic levels. Previous research suggested that some mammalian predators consume earthworms, ranging from moles and shrews to badgers and foxes (Dodgen et al., 2013; Malchi et al., 2014). Earthworms are a major dietary component of some small carnivorous mammals (Hamers et al., 2006), for example, they contribute 29% of the diet of the common shrew (*Sorex araneus*) and the share of earthworms in the diet of moles varies from 38–95% (Nesterkova et al., 2014). Although the consumption of earthworms was slightly less than one third in the daily diet, research concluded that shrews are prone to suffer from serious effects when feeding on contaminated earthworms, thereby emphasizing the potential side-effects from bioaccumulation through food chains (Hamers et al., 2006). European moles are stenophagous mammals, earthworms constitute over 90% of their diet, and are likely to suffer from a direct transfer of pollutants via the food chain. However, due to its strong musky smell, the mole contributes only 0.05–4.5% of the diet in owls, kestrels and

buzzards (Nesterkova et al., 2014), suggesting that the mole occupies the last position in this terrestrial food chain. Earthworms are mobile macroinvertebrates, a primary consumer in terrestrial food webs and contribute to at least two major food webs, with the apex predator being either small mammals or birds. Related species share diverse but similar dietary compositions, and this complicates the detection and movement of trace pharmaceuticals across the food chain. The major challenge for future studies will be the accurate detection of drug concentrations in the blood and the correlation to the exposure via food versus the environment.

5. Discussion

The source, transportation，transformation, and fate of pharmaceuticals in soil environments and ecosystems is reliant on complex individual, binary or even multiple factors. Given that the majority of PPCPs are introduced via the application of recycled wastewater, highlights the need to pinpoint the sources of terrestrial pharmaceuticals, as this would aid contamination monitoring designs and environmental risk assessment studies (Mompelat et al., 2009). The ability to effectively monitor soil quality, implement management regulations and preserve soil functions is reliant on (i) the documentation of historic environmental exposure (spatially and temporally), (ii) an understanding of the mechanisms which drive the environmental behaviour of pharmaceuticals, and (iii) the availability of a priority list of pharmaceuticals which impact the terrestrial (eco)system.

The majority of anthropogenic pharmaceuticals reach soil systems via three pathways, namely wastewater reuse applications, surface runoffs and landfill leaching. Pharmaceuticals introduced into terrestrial environments via wastewater irrigation is of particular concern as they pass through miscellaneous transportation and transformation processes (see Figure 3). The magnitude and specificities of transformation is dependent on their physicochemical

property and initial concentration, but also the soil properties, such as organic content and pH. Organic compounds with specific positive structures (e.g. triazine rings) and physicochemical properties display higher mobilities in soil and have the potential to contribute to further microbial utilisation and plant uptake, examples are naproxen and lamotrigine (Malchi et al., 2014; Paz et al., 2016). These pharmaceuticals, although characterised by high biodegradation rates, may still have an impact on the groundwater and soil health due to their mobility. Another important drug transformation mechanism is chemical and/or biological degradation. Low penetration of light through the soil matrix limits the photodegradation of light sensitive drugs. However, the photodegradation can already take place in the biosolid prior to the release of drugs into the soil. Biodegradation by bacteria has been reported to be an important removal mechanism of xenobiotics in the terrestrial environment. Most medical compounds are less stable than traditional persistent organic pollutants and due to this there is an increased risk of secondary pollution caused by their metabolites. Offering a hotbed for bacteria activities, individual pharmaceuticals may go through diverse biodegradation pathways, thus producing numerous intermediate metabolites and mixes of transforming products (Li, 2014). These by-products can be more toxic than parent molecules and exert heavy burdens on soil and organism health. The degradation and elimination processes of parent molecules results in by-products entering soil systems, however their behaviours and fates are, at large, not accounted for. More systematic investigations on monitoring these compounds and understanding their threats to the ecosystem and human health is therefore of paramount importance.

Previous reports have detected pharmaceutically active compounds and their metabolites in the excreta of individuals who consumed plant products which were irrigated with wastewater, thereby highlighting a potential risk to public health. Carbamazepine, for example, was shown to be relatively evenly distributed throughout the plant while triclocarban was found to be accumulated in leaves and fruits (Wu et al., 2012). Research regarding the terrestrial food chain

446 is rather limited, especially concerning small mammals (Dodgen et al., 2013; Malchi et al.,
447 2014; Fremlin et al., 2020). There is a need for well-defined bioaccumulation factors for soil-
448 dwelling organisms, as this will allow a more explicit and accurate estimation of contaminants
449 of emerging concerns (CEC) in terrestrial invertebrates and organisms higher up in the
450 respective food chains. The large home range of higher-level consumers (resulting in off-site
451 transport) and of the mixing of aquatic and terrestrial diets further complicate the assessment
452 of pharmaceutical exposure in terrestrial food webs.
453

454 ## 6. Conclusion

455 This review presents current studies on potential sources, transportation and transformation of
456 pharmaceuticals in the terrestrial system. Regarding the first point, it should be noted that most
457 studied focus on the parent compound only and neglect possible by-products of
458 pharmaceuticals. The degradation processes and the emergence of pharmaceutical metabolites
459 depends on the presence and composition of bacteria in the soil, but our knowledgebase that
460 allows the linkage between pharmacology and soil microbiology remains rather poor. Further
461 research is called for to determine to what extent soil properties influence the transportation
462 and the rate of photodegradation of pharmaceuticals. The presence of pharmaceuticals can also
463 impact ecosystem health due to their uptake by plants and animals and movement through food
464 webs. It has been suggested that crops and other fresh products can introduce pharmaceutically
465 active compounds as well as metabolites to humans. Taken together, this review highlights the
466 pressing need to focus on public health risks posed by the indirect and unintentional
467 introduction of pharmaceuticals to soil. A fuller understanding on how pharmaceuticals transfer
468 and transform in the terrestrial system will guide future research to assess the environmental
469 and human risk posed by those chemicals and their metabolites.

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Declaration of interest

The authors declare no competing interest.

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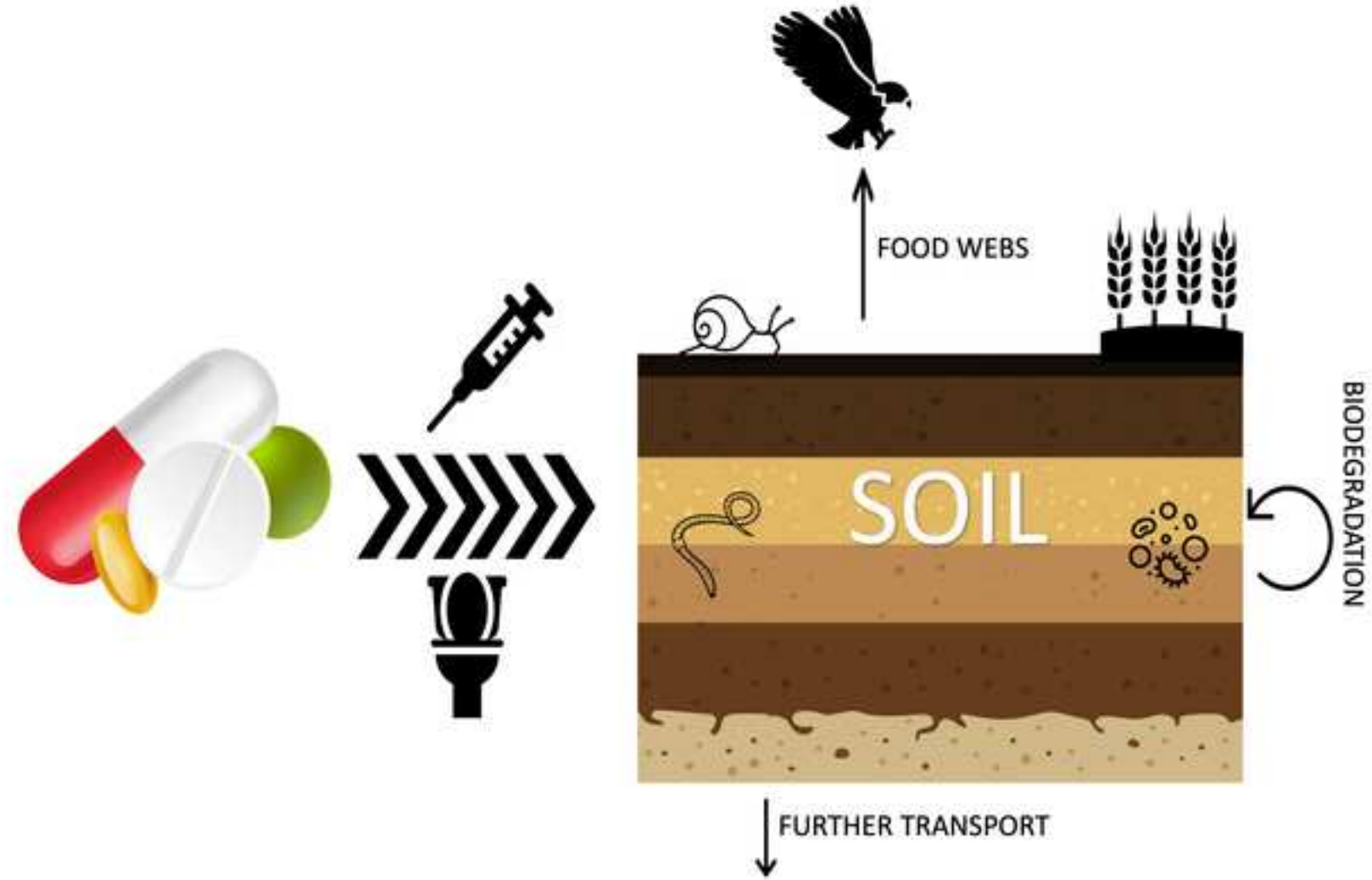
Graphical Abstract



Highlights

- Some soils receive wastewater/biosolids from wastewater treatment plants.
- This practice can result in the accumulation of pharmaceutical in soils.
- How this affects terrestrial organisms and food-web is largely unknown.
- The knowledgebase needs to be expanded to assist terrestrial risk assessments.

Table 1. Reported concentrations and locations of frequently detected PPCPs in soil systems.

PPCP	Type	Concentration Range (µg/kg dry soil)	Location	Ref.
Carbamazepine	Antiepileptic	0.19-0.55	Colorado, USA	Kinney et al., 2006
		5.89-7.07	Tula Valley, Mexico	Durán-Alvarez et al., 2009
Ibuprofen	NSAID	0.21 -0.29	Tula Valley, Mexico	Durán-Alvarez et al., 2009
Naproxen	NSAID	0.54 -0.56	Tula Valley, Mexico	Durán-Alvarez et al., 2009
Diclofenac	NSAID	101–257	Dosaco Chowk, Pakistan	Ashfaq et al., 2017
Trimethoprim	Antibiotic	0.12-0.26	Pennsylvania, USA	Franklin et al., 2018
Sulfadiazine	Antibiotic	100–1000	Various locations, China	Hu et al., 2019
Triclosan	Antibiotic	774–949	Bedfordshire, UK	Butler et al., 2011
Di(2-ethylhexyl) phthalate (DEHP)	Personal care products	733-907	Tula Valley, Mexico	Durán-Alvarez et al., 2009

Table 2. Photolysis kinetic constants for selected pharmaceuticals in water and the soil matrix. The kinetic constants for soil were derived from typical agricultural topsoil in Central Europe (Thiele-Bruhn & Peters, 2007) or the Tula Valley, Central Mexico (Durán-Álvarez et al., 2015). To assess the rate of photodegradation in water bodies, kinetic constants were obtained from different aqueous solution (Haham et al., 2012; Barron et al., 2009; Thiele-Bruhn & Peters, 2007) or surface water (Durán-Álvarez et al., 2015).

Compounds	Photolysis rate constant (k, 1/h)	
	in soil	in water
Naproxen	3.60×10^{-3}	4.10×10^{-2}
Carbamazepine	4.00×10^{-4}	6.90×10^{-3}
Triclosan	4.70×10^{-3}	0.13
Chlortetracycline	5.96×10^{-2}	2.88
Oxytetracycline	-	2.58
Sulfapyridine	8.33×10^{-4}	0.72
p-aminobenzoic acid	8.33×10^{-4}	4.53×10^{-3}

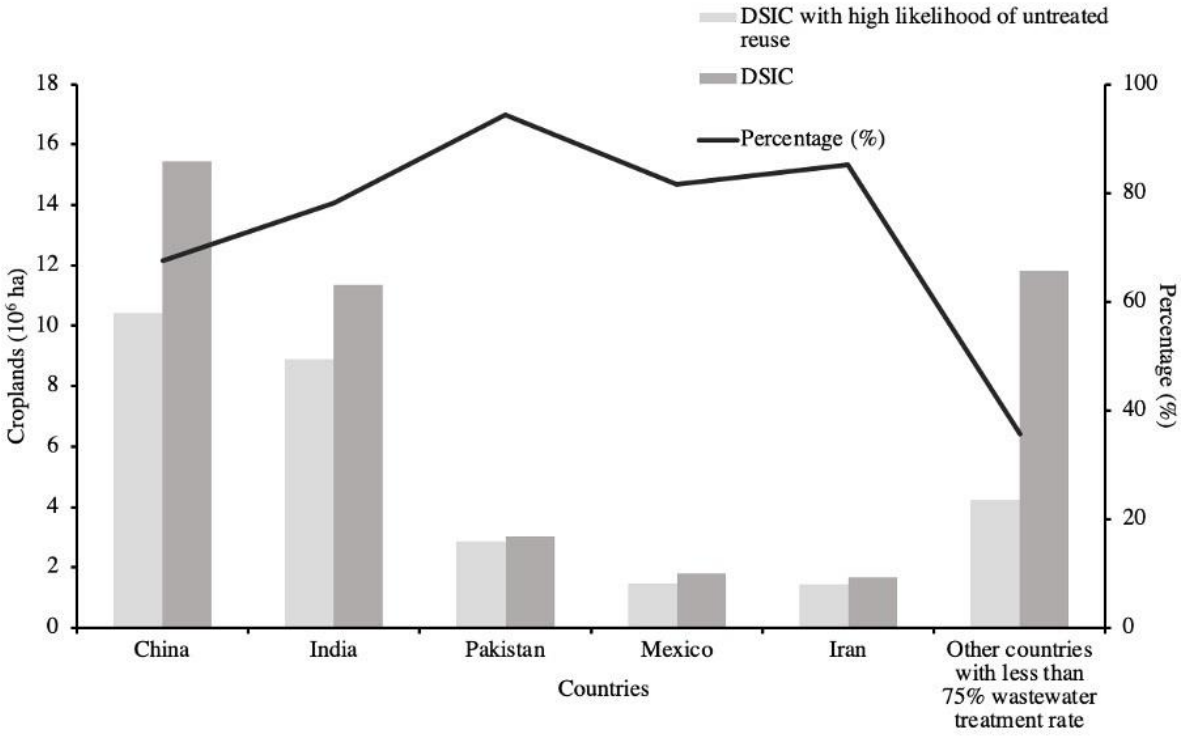


Figure 1. A selection of countries characterized by a high likelihood of applying untreated water to downstream irrigated croplands (DSIC). The DSIC with high likelihood of untreated reuse was defined as the croplands area located in the downstream catchments with high wastewater return ratio (>20%) and insufficient wastewater treatment rate (<75%). Data from Thebo et al. (Thebo et al., 2017).

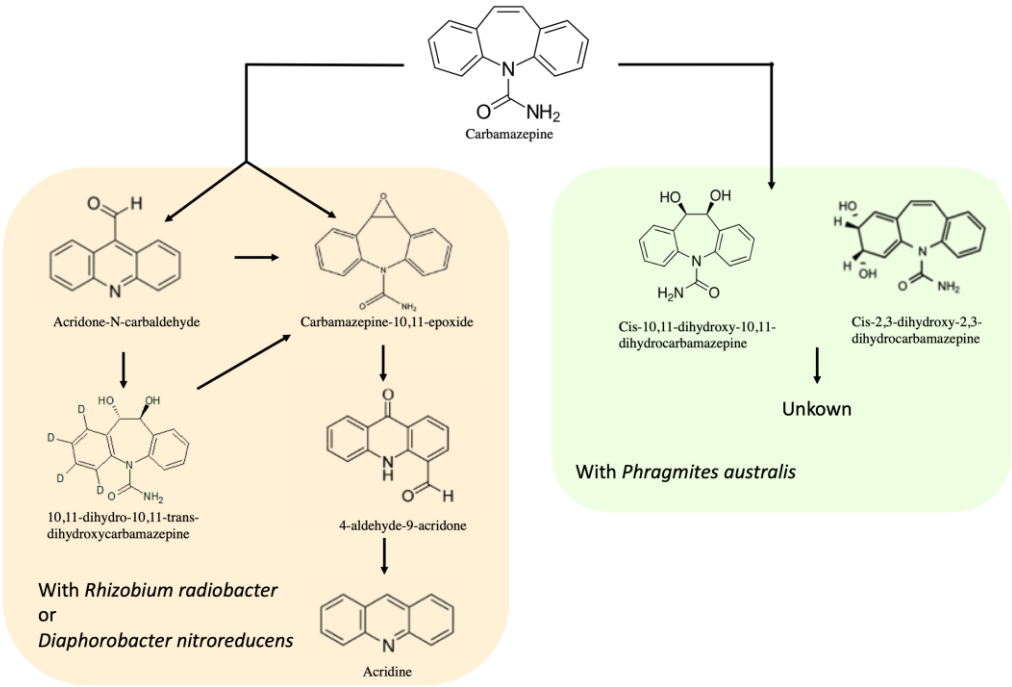


Figure 2. The terrestrial biodegradation process of carbamazepine (CBZ) with different bacteria. Adapted from Gauthier et al.(2010) and Sauvetre et al.(2018).

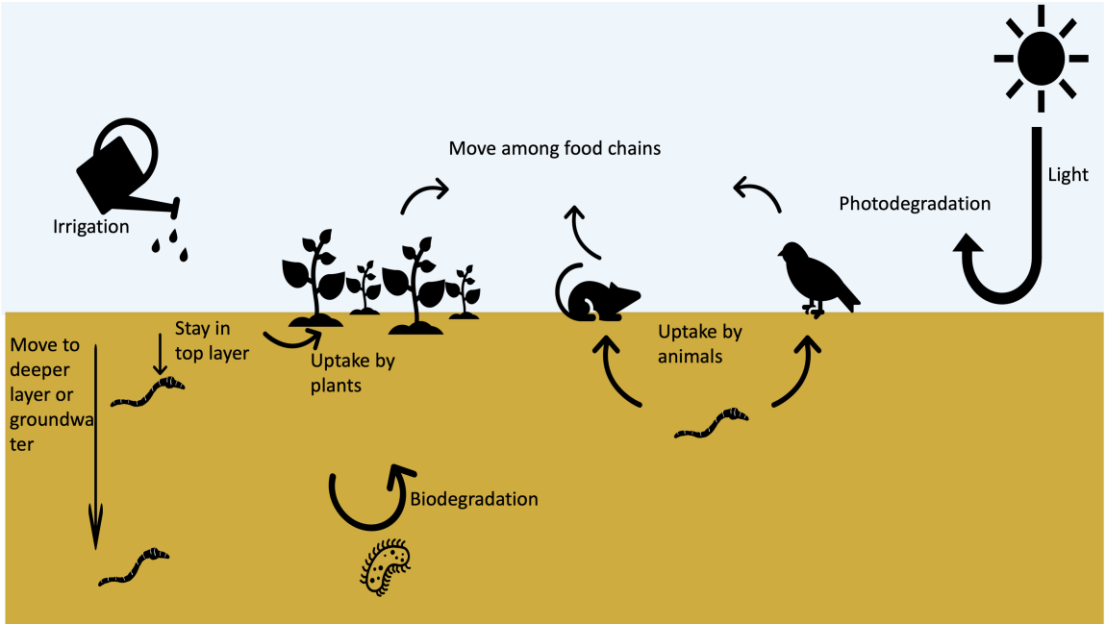


Figure 3. The potential movement of PPCPs after being introducing into croplands.