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Psychoactive substances in soils, plants, freshwater and fish: A mini review

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Abstract: This review focuses on the behaviour of four psychoactive compounds (carbamazepine, tramadol, sertraline and citalopram) in the environment. The review presents how they may directly affect freshwater systems, soils and living organisms and to which extent. The transformation of these very stable compounds in soils were controlled by oxidation, demethylation, decarboxylation and hydroxylation. Sorption to organic matter and clay particles controlled their mobility. Despite their expected sorption in soils, sediments and sludge, all compounds can be taken up by plants and by fish. In plants, all compounds and several of their metabolites were found in the leaves, indicating the mobility and transformation of the compounds within the plant systems. Factors that control the compounds mobility in plants were found to be the pH of soils and the xylem flow. As for fish, many of the compounds were found in the brain and muscles of fish, some of which, depending on the species, affected the behaviour of the fish. The implications of these compounds so widely present in the environment indicate the need for certain measures to be put into place to prevent these compounds from continuously entering plant and animal systems.

Keywords: dissipation; fish intake; metabolites; pharmaceuticals; plant uptake; sorption

The definition of a psychoactive substance is ‘a chemical that in small amounts influences the functioning of the human brain in such a way to have effects on the psyche or mind’ (Presti 2002). Such drugs influence the mood, feelings, behaviour, awareness and thoughts a person may have. These substances can also be a part of everyday life in the form of caffeine, nicotine, alcohol, and some pain medications (Jin et al. 2022). Other examples of psychoactive substances are central nervous system depressants and stimulants. Over the past several years, the use of psychoactive substances has increased at an alarming rate (UNODC 2017). This has led to the presence of these substances in wastewater, surface waters and soils as either parent compounds or their metabolites, caused by misuse and improper disposal techniques (Yang et al. 2017; Grabicová et al. 2020; Riva et al. 2020). Wastewaters from music festivals

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and hospitals are also a significant source of psychoactive substances (Mackulʼak et al. 2019a, b, 2021).

These contaminants are then usually not sufficiently removed from the treated wastewater in the wastewater treatment plants (WWTPs) and are then discharged to water receivers. The presence and particularly concentration of pharmaceuticals in aquatic environments depends on various factors including efficiency of WWTPs (Komesli et al. 2015) as well as dilution factor in a recipient (Grabicová et al. 2020). Generally, they reach the concentrations from ng/L to µg/L, and are considered as pseudo-persistent due to their continuous release (Baker & Kasprzyk-Hordern 2013). Their impact on aquatic wildlife is considered to be wide, covering various aspects from altered physiology (Carney Almroth et al. 2015) or gene expression (Gröner et al. 2017) to behaviour (Brodin et al. 2013). These changes are subsequently transferred from impacted individual to the population- and community-level dynamics (Saaristo et al. 2018), providing another model of unexpected evolutionary selection pressure for species living in urban environments (Johnson & Munshi-South 2017).

In addition, these compounds can enter the soil environment if reclaimed wastewater is used for irrigation and then contaminate agricultural crops (Figure 1) (e.g., Ben Mordechay et al. 2021, 2022a, b; Carter et al. 2019; Helmecke et al. 2020; Picó et al. 2020a, b).

Moreover, the management of sewage sludge is a huge issue in many parts of the world, with the production of sludge steadily increasing with better treatment systems in place for wastewater. This increase in sludge productions has raised questions on its use and disposal; in many European countries such as Denmark, France and Spain, approximately half or more of the sludge production is used in agriculture (Lamastra et al. 2018). This provides another clear pathway for pharmaceuticals to enter soils, leach into water sources and accumulate in crops (Ben Mordechay et al. 2018; Kodešová et al. 2019b). The stability of these pharmaceutical compounds in these environments raises many questions. Grabic et al. (2022) studied the desorption of various pharmaceuticals from different stabilized sludge types across different pH values. Their results found that there were lower desorbed fractions within aerobically stabilized sludges compared to anaerobically stabilized ones. The study showed the implications of pH on compound desorption from sludge and that if, for example, samples were treated at elevated pH values, there could be increased desorption from the sludge and with adverse effects on other environmental sectors after sludge application. This agrees with studies by Kim et al. (2010) and Mancuso et al. (2019) that confirmed the disintegration of sludge in alkaline conditions. This indicates that technologies that use higher pH conditions can lead to the formation of sludges with lower concentrations of pharmaceutical compounds.

This review focuses on four psychoactive substances (carbamazepine (CBZ), tramadol (TMD), sertraline (STL) and citalopram (CTP)) and their metabolites (Table 1). Because of their extensive use they frequently occur in treated wastewater and sludge from WWTP and subsequently in soils, plants, freshwater and freshwater fish. Carbamazepine is a medication used to treat/control certain types of seizures brought about from epilepsy. Tramadol is an opiate analgesic that is used to treat severe pain. Sertraline and citalopram are selective reuptake inhibiters used to treat depression and, in some cases, panic attacks. These substances were chosen to understand the differences between their behaviours due to differences in their properties, e.g. charge, lipophilicity (log Kow (n-octanol-water partition coefficient)), molecular weight (MW), dissociation constant (pKa) and H-bond acceptors (shown in Table 2). All compounds are very stable in the environment. Thus, they can affect various components of the environment in the long term. Two compounds are strongly sorbed onto soils and sediments, and two of them have much lower affinity to these sorbents. Therefore, different

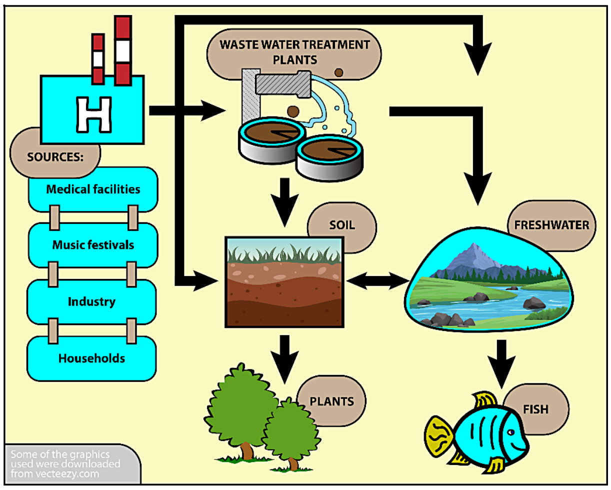

Figure 1. An example of the pathway for pharmaceutical compounds entering soil and water systems

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Table 1. Psychoactive substances and their metabolites

Substance	Metabolites
Carbamazepine (CBZ)	carbamazepine 10,11-epoxide (EPC) oxcarbamazepine (OXC) trans-10,11–dihydro-10,11-dihydroxy carbamazepine (RTC) 10,11-dihydrocarbamazepine (DHC)
Sertraline (STL)	N-desmethylsertraline (DSTL) hydroxylated sertraline (HSTL)
Citalopram (CTP)	N-desmethylcitalopram (DCTP)
Tramadol (TMD)	O-desmethyltramadol (DTMD)

mobility and accessibility to living organisms such as plant and fish is expected. The review looks at the concentrations, mobility, behaviour, and fate of the compounds within the different studied environmental sectors and through the environmental chain. The paper delves into the type of experimental set up (mostly laboratory) and how this can help understand their implications in the 'real world'.

PSYCHOACTIVE SUBSTANCES IN SOIL

Pharmaceutical mobility, potential availability and degradation is highly dependent on soil constituents and the presence of microorganisms capable of degrading pharmaceutical compounds (e.g., Schaffer & Licha 2015; Wu et al. 2015; Kodešová et al. 2015, 2016, 2020, 2023; Klement et al. 2018; Fér et al. 2018; Schmidtová et al. 2020; Frková et al. 2020). Within soil solutions, pharmaceutical substances can occur in various forms (non-ionic, anionic, cationic, zwitter-ionic) and the forms and fractions of each form is dependent on the soil solution pH and pKa value of the compound (Schaffer & Licha 2015). The differences in the chemical structures of individual pharmaceutical compounds cause them to behave differently in different soils, also depending on the soil properties (Kodešová et al. 2015, 2020, 2023; Klement et al. 2018; Carter et al. 2020; Li et al. 2020, 2021; Schmidtová et al. 2020). Due to these different chemical structures, there are different sorption affinities attributed to different sorption mechanisms of the compounds. Non-ionic molecule sorption is controlled by the hydrophobic partitioning to organic matter and by H-bonding with hydroxyl groups. Therefore, sorption coefficients describing equilibrium between compound concentration in soil solution and concentration of compound sorbed onto soil particles usually correlate with the organic matter content. Cationic molecule sorption is mainly controlled by the attraction to negative charges of the solid surfaces such as clay minerals and organic matter (Kodešová et al. 2015, 2023; Fér et al. 2018; Klement et al. 2018; Schmidtová et al. 2020). Thus, sorption coefficients usually correlate with the cation exchange capacity. Sorption of anionic molecules, that can be reduced due to their repulsion from the predominantly negatively charged surface of soil constituents, is driven by similar mechanisms as non-ionic molecules, and also by a cation bridging or under specific conditions by the ionic bonding on the positively charged soil constituents (characterized by anion exchange capacity). Moreover, the different compounds themselves can either compete with one another or cooperate with each other, therefore influencing their sorption abilities (Kočárek et al. 2016; Fér et al. 2018; Schmidtová

Table 2. Characteristics of each pharmaceutical compound

Substance	Charge	Lipophilicity (log Kow)	Molecular weight (g/mol)	pKa		H-bond donors, acceptors
				pKa_1 (basic)	pKa_2 (acidic)	
CBZ	neutral	2.25	236.27	1.0	13.9	1, 1
TMD	cation	2.4	263.38	9.23	13.8	1, 3
STL	cation	5.1	306.23	9.85	–	1, 1
CTP	cation	3.5	324.39	9.78	–	0, 3

CBZ – carbamazepine; TMD – tramadol; STL – sertraline; CTP – citalopram; sources: http://www.drugbank.ca et al. 2020). As a result, sorption can either decrease or increase.

The transformation of pharmaceuticals in soils is determined by reactions such as oxidation, demethylation, decarboxylation and hydroxylation (Rubasinghege et al. 2018). Many compounds degraded in soils with the help of microorganisms (De Groot et al. 2002; Xu et al. 2009; Biel-Maeso et al. 2019). In such cases, the dissipation rates rely on favourable conditions for microbial activity in the specific soil. Microbial composition is crucial for degradation of compounds in soils; the compounds can affect the microbial community, both in negative and positive ways. Likewise, the soil type, time, and the specific compounds controlled the microbial response (Koba et al. 2016, 2017; Kodešová et al. 2016, 2020; Frková et al. 2020). Studies by Malchi et al. (2014) and Goldstein et al.(2014) found greater sorption of pharmaceutical compounds in soils with higher fractions of clay, silt and organic carbon content. An example of the different sorption coefficients of the different compounds in different soils can be seen in Table 3.

Carbamazepine. Carbamazepine occurs in the environment in the neutral form (Table 2). It was found that the interactions with H-bonding, Van der Waals-forces and organic carbon/organic matter content controlled CBZ sorption (Navon et al. 2011; Kodešová et al. 2015, 2020; Kočárek et al. 2016; Fér et al. 2018; Schmidtová et al. 2020). This mean that larger CBZ sorption was observed in soils taken from the surface horizons of different soils types, which contained larger organic matter fractions (Table 3) (Kodešová et al. 2015, 2020; Schmidtová et al. 2020). The sorption affinities for CBZ in soils decreased with increasing soil depth due to decreasing organic matter with depth (Kočárek et al. 2016). The application of biochar to spiked soils showed increase sorption of CBZ in soils (Williams et al. 2015). Therefore, the Freundlich sorption coefficients (K_F) evaluated for CBZ by Kodešová et al. (2015), Kočárek et al. (2016) and Schmidtová et al. (2020) were positively related to the organic carbon content/oxidisable carbon (Cox). The K_F values for a single solute system in the study by Kodešová et al. (2015) were significantly higher than K_F values obtained for the same soils but for the four-solute (CBZ, atenolol, trimethoprim and sulfamethoxazole) system. Similarly, mostly slightly lower K_F values were found for CBZ when applied together with other 4 compounds (sulfamethoxazole, irbesartan, fexofenadine, clindamycin) in comparison to its single-compound application (Schmidtová et al. 2020). These findings, which were obtained for the soils taken from the surface horizons, can be explained by a competition for the same sorption sites. Fér et al. (2018) found that sorption of CBZ increased when applied together with atenolol and sulfamethoxazole into soil samples taken from the subsurface Bt horizon of the Haplic Luvisol. They suggested that increased CBZ sorption can be possibly explained by ionization of molecules due to dipole - induced dipole interaction between nonpolar and polar molecules in solution. Based on its K_F values (Table 3), CBZ belongs to highly mobile compounds in the soil environment and to compounds of a very high mobility in the subsurface horizons (Kodešová et al. 2023).

Carbamazepine was observed to be relatively persistent in soils with relatively low fractions of CBZ

Table 3. Ranges of the Freundlich sorption coefficients (K_F, $cm^{3/n}$ $\mu g^{1-1/n}/g$), associated n values (i.e., $s = K_F c^{1/n}$, where s (μg/g) and c (μg/cm^3) are concentration in soil and soil solution, respectively), and dissipation half-lives, DT_{50} (days) calculated from the first-order dissipation rate constants

Substance	K_F/n	DT_{50}	Source
CBZ	1.20–4.40/1.12		Schmidtová et al. (2020)
	0.26–4.66/1.13		Kodešová et al. (2015)
		129– > 1 000	Kodešová et al. (2016)
	1.05–4.05/1.02	90.2–140.9	Kodešová et al. (2020)
	0.41–2.13/1.0		Kočárek et al. (2016)
	1.31/1.0		Williams et al. (2015)
	0.40–0.50/0.80–0.94		Fér et al. (2018)
TMD	1.00–5.23/0.96–0.98		Garduño-Jiménez et al. (2022)
STL	24.1–274/1.39		Kodešová et al. (2023)
		50–85	Li et al. (2013)
CTP	19140–501876/0.63		Schmidtová et al. (2020)
	10600–6770000/0.92	86.7–223.1	Kodešová et al. (2020)
	644–6940/1.0		Klement et al. (2018)

CBZ – carbamazepine; TMD – tramadol; STL – sertraline; CTP – citalopram metabolites (Kodešová et al. 2015, 2020; Koba et al. 2016). Carbamazepine concentrations in soils have shown not to change drastically in soils with slower degradation rates (Koba et al. 2016). The main CBZ metabolite in soils was arbamazepine 10,11-epoxide (EPC), however, it was found in low concentrations, with increasing concentrations with time, reaching up to 681 pmol/g. Under laboratory conditions with spiked soils, less than 50% of CBZ was degraded to the metabolites EPC and trans-10,11–dihydro-10,11-dihydroxy carbamazepine (RTC) (Frková et al. 2020). The formation of EPC was faster than its degradation (Koba et al. 2016). Other metabolites found in some soils, albeit in lower concentrations, included RTC and 10,11-dihydrocarbamazepine (DHC). The RTC metabolite was found slightly later than other mentioned metabolites. The C1 metabolite was found to require also a longer formation time, but once it was formed, it increased with time, thus, formation > degradation. The metabolites formed were in general relatively low in soils, due to the low degradation rate of CBZ, but maintained a similar persistency as CBZ (Koba et al. 2016).

Dissipation rates of CBZ in soils observed in different studies considerable vary. For example, CBZ half-lives (DT_{50}) in soils taken from the surface horizons of different soil types in study by Kodešová et al. (2016) were mostly larger than 1 000 days. Half-lives of CBZ in study by Kodešová et al. (2020) studied for similar soils varied between 141 and 90 days. Its persistence (DT_{50} = 171–85 days) moderately increased when applied together with other 5 compounds (sulfamethoxazole, irbesartan, fexofenadine, clindamycin, citalopram). However, this study did not revealed conditions favourable for CBZ transformation. Statistical analyses did not confirm a stimulation effect of soil properties or characteristics of the microbial community on the CBZ dissipation rates.

Assuming CBZ K_F values (Table 3) also its very high persistence in the environment, this compound can endanger the quality of groundwater and the quality of agricultural products. However, its spread and availability for plants also depends on the hydraulic conditions of soil and subsurface layers. For example, Brunetti et al. (2021) showed that the upper soil layers could have more influence in CBZ availability compared to lower layers, as root and solute distribution play a key role in the uptake of CBZ, as there is higher root water and solute uptake in the upper soil layers.

Tramadol. Under standard soil pH conditions, TMD should occur in a cationic form. Thus, in study by Garduño-Jiménez et al. (2022) a soil property that controlled TMD sorption was clay content, mainly through cation exchange capacity, meaning the higher the clay content, the higher the sorption. Another factor that controls TMD in soils is the presence of organic matter, high organic matter content leads to its higher sorption (Filep et al. 2021). Garduño-Jiménez et al. (2022) observed that higher sorption was seen in soils with the lower TMD concentrations compared to the highest TMD concentration. They also observed more sorption than desorption in their soils, meaning that TMD was accumulating. Despite that sorption of TMD is controlled by strong ionic forces its sorption was relatively low (Table 3) (Garduño-Jiménez et al. 2022). This means the TMD can potentially be as mobile as CBZ (i.e., belongs to compounds of a very high mobility in soils). Wojsławski et al. (2019) also documented the mobility of TMD in study based on packed columns, showing that TMD under static conditions was highly mobile, but in a leaching experiment, it became strongly bound to soil particles.

Sertraline. Sertraline predominantly also occurs in the soil environment in a cationic form (Table 2). Therefore, the Freundlich sorption coefficients of STL was found to be positively correlated with cation exchange capacity (CEC) and base cation saturation (Kodešová et al. 2023). The negative charges of the soil along with the positive charge of STL, creates strong ionic forces that sorb STL to the soil (Kodešová et al. 2023). Based on the K_F values > 40 $cm^{3/n}$ $\mu g^{1-1/n}/g$ it can be suggested that at in most cases STL should be immobile in soils (Kodešová et al. 2023).

Sertraline is relatively persistent in soils (Li et al. 2013) with DT_{50} = 50–85 days. In soils, Li et al. (2013) found two transformation compounds (hydroxylated sertraline, HSTL) that did not exceed 10% of the parent material, while no N-desmethylsertraline (DSTL) was found in their samples. The dissipation of STL was found to be relatively fast with highest application concentration, with negligible amounts of STL remaining in the soil after 11 days (Menacherry et al. 2022), while lower application concentrations were more stable. In our recent study (Menacherry et al. 2023b), dissipation half-lives (DT_{50}) of 35–166 days were found in 3 soils including the one studied by Menacherry et al. (2022). In this new study, we also observed that STL dissipation rates increased with the microbial abundance.

Based on the high STL K_F and DT_{50} values, leaching of STL is less probable, but this compound can remain in the soil environment and potential affect quality of the agricultural products (e.g. Kodešová et al. 2019b).

Citalopram. Finally, CTP also primarily occurs in soils as cation (Table 2) and its sorption is mainly driven by ionic bonding (Klement et al. 2018; Kodešová et al. 2020; Schmidtová et al. 2020). In all these studies, the sorption coefficients values for CTP positively correlated with base cation saturation. Its sorption in soils is very high, e.g. K_F = 644–6 940 $cm^{3/n}$ $\mu g^{1-1/n}/g$ (Klement et al. 2018), K_F = 19 140–501 876 $cm^{3/n}$ $\mu g^{1-1/n}/g$ (Schmidtová et al. 2020) and 10 600–6 770 000 $cm^{3/n}$ $\mu g^{1-1/n}/g$ (Kodešová et al. 2020).

Regarding degradation of CTP in soils, the levels observed from laboratory and greenhouse experiments are generally low (Kodešová et al. 2020; Brunetti et al. 2022). Kodešová et al. (2020) found CTP to have the largest dissipation half-life (223–87 days) compared to other compounds (sulfamethoxazole, irbesartan, fexofenadine, clindamycin, carbamazepine) in the tested soils. The dissipation half-lives increased when applied together with the other tested compounds (311–59 days).

Like for STL, the K_F and DT_{50} values for CTP indicate that leaching of CTP is not probable, but this compound can remain in the soil environment and potential affect quality of the agricultural products (e.g., Kodešová et al. 2019b). Regarding metabolites, Frková et al. (2020) found that less than 50% of CTP was degraded into the metabolite N-desmethylcitalopram (DCTP).

PSYCHOACTIVE SUBSTANCES IN PLANTS

The uptake of psychoactive substances by plants is mainly driven by the transpiration stream through plants (Dodgen et al. 2015; Kumar & Gupta 2016), and depends on the properties of the substance and the cell membrane structure of plants. It is believed that passive diffusion largely controls the uptake via roots, however, some uptake is controlled by energy consumption processes (Mackul'ak et al. 2015; Wei et al. 2023) and water is the main transporter of the compounds uptake (Malchi et al. 2014). A comparison of the psychoactive compounds and their metabolites can be observed in Table 4. Positively and negatively charged compounds could have reduced uptake due to the cations binding to the negatively charged cell walls and the repulsion of anions (Goldstein et al. 2014; Malchi et al. 2014). The type of plant plays a huge role on the uptake, accumulation and metabolization of the substances, for example there was selective uptake of compounds and different translocation in the different plant parts of spinach tissues (Kodešová et al. 2019b). Kumar and Gupta (2016) came up with a rule of three that put forward these assumptions; the uptake and translocation of compounds increase when lipophilicity (log Kow) < 3, molecular weight (MW) < 300 g/mol, H-bond donors < 3, and H-bond acceptors < 6.

The different components of plants (lipids, carbohydrates, lignin, waxes, etc.) could work as sorption sites for pharmaceuticals, therefore, their distribution within a plant part is tissue-dependent leading to different sorption coefficients (Zhang et al. 2005; Collins et al. 2006; Wei et al. 2023). The pH of soil and the xylem flow influence the electrolyte fluxes into the root membrane and control the chemicals' speciation in roots, which in turn controls the ability of the chemicals to enter the root membrane. Within the plants, the pH of the xylem and phloem affected the concentrations in the plant tissues (Brunetti et al. 2022).

Very few papers touch on the negative effects of pharmaceutical compounds in plants, however, certain studies have mentioned the difficulty of assessing whether damage to plants are directly due to the pharmaceuticals or because of the pharmaceuticals effect on soil microorganisms that then interfere with the plant-soil bacteria symbiosis (Fatta- Kassinos et al. 2011; Grassi et al. 2013).

Carbamazepine. Due to the neutral form of CBZ (and low MW, log Kow and H-bonds), its uptake and translocation in plant bodies is high, i.e. CBZ is quickly transported to the leaves of plants that is the end of the transpiration stream (Shenker et al. 2011; Goldstein et al. 2014; Malchi et al. 2014; Hurtado et al. 2016; Kumar & Gupta 2016; Montemurro et al. 2017; Kodešová et al. 2019a, b; Klement et al. 2020; Picó et al. 2020a; Menacherry et al. 2023a). However, in certain cases of reduced uptake, this could be explained by differences in root permeability to chemicals and water, where uptake of water is a lot faster than of CBZ (Brunetti et al. 2021). Despite its stability in soils, thanks to the plant cytochrome P450 enzymes CBZ is metabolized in plant tissues (Goldstein et al. 2014; Malchi et al. 2014; Kodešová et al. 2019a, b; Menacherry et al. 2023a). The application of CBZ has been found to have little to no impact on plant growth (Shenker et al. 2011; Carter et al. 2015; Kodešová et al. 2019a); however, it has been found to restrict fruiting of plants (eg. Zucchini (*Curcurbita pepe*)) when leave concentrations exceed 14 mg/kg (Knight et al. 2017). Interestingly,

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Table 4. Concentrations of the pharmaceutical compounds and their metabolites in plants

Plant species	Compound					Source
	CBZ	EPC	OXC	RTC	DHC	
Zucchini (*Curcurbita pepe*)	L > R	–	–	–	–	Knight et al. (2017)
Lambs lettuce (*Valerianella locusta*) (ng/g)	L (1 400–6 400) R (1 900–8 600)	L (5 700–20 000) R (170–1 300)	L (710–3 300) R (17–160)	L (100–580) R (< 5–98)	L (< 2.9–10) R (3.5–15)	Kodešová et al. (2019a)
Spinach (*Spinacea oleracea*) (ng/g)	L (670–4 600) R (990–5 200)	L (140–6 500) R (160–450)	L (11–750) R (12–38)	L (41–280) R (< 4.3–13)	L (< 2.6–7) R (< 2.4–9.9)	
Arugula (*Eruca sativa*) (ng/g)	L (4 300–23 000) R (1 600–4 000)	L (800–6 800) R (22–140)	L (76–830) R (< 3–16)	L (< 4.9–190) R (< 4.3 ≤ 6.1)	L (6.7–42) R (< 3.1–8.4)	
Radish (*Raphanus sativus*) (ng/g)	L (11 000–53 000) R (2 100–7 900)	L (1 500–15 000) R (67–340)	L (66–1 000) R (0.66–9.7)	L (44–620) R < 0.52 ≤ 0.82)	L (16.5–89) R (2.55–9.7)	
Spinach (*Spinacea oleracea*) (ng/g)	L (15–180) R (5.8–63)	L (28–440) R (BLOQ–33)	L (BLOQ–43) R (BLOQ)	L (BLOQ) R (BLOQ–13)	–	Kodešová et al. (2019b)
Lettuce (*Lactuca sativa*) (ng/g)	BLOQ–12.2					Mercl et al. (2021)
Corn (*Zea mays*) (ng/g)	L (0.04–1 739.6) R (0.10–2 223.6)					Mascellani et al. (2023)
Leafy greens* (ng/g)	0–247	0–187.5			0–5.2	Ben Mordechay et al. (2022b)
Apples (ng/g)	0–0.1				0–0.04	
Carrot (*Daucus carota*) (ng/g)	0–2.6				0–0.52	
Peppers (ng/g)	0.05–1.6					
Tangerine (*Citrus reticulata*) (ng/g)	0.09–1.9					
Oranges (*Citrus* × *sinensis*) (ng/g)	2.4–5.7	0–0.01			0–0.15	
Potato (*Solanum tuberosum*) (ng/g)	0–0.49					
Tomato (*Solanum lycopersicum*) (ng/g)	0–0.97	0–0.04			0–0.49	
Avocado (*Persea americana*) (ng/g)	0–1.1				0–0.46	
Banana (*Musa*) (ng/g)	0–0.51	0–0.02			0–0.13	
	CTP	DCTP				
Spinach (*Spinacea oleracea*) (ng/g)	L (BLOQ–4.6) R (7.1–68)	L (BLOQ) R (0.89–20)				Kodešová et al. (2019b)
Green pea (*Pisum sativum*) (ng/g)	L (0.41–2.76) R (50.5–212.7) S (3.12–6.36)					Brunetti et al. (2022)

Table 4 to be continued

Plant species	Compound		Source
	STL	DSTL	
Spinach (*Spinacea oleracea*) (ng/g)	L (7.7–200) R (46–550)	L (BLOQ–21) R (BLOQ–210)	Kodešová et al. (2019b)
Lettuce (*Lactuca sativa*) (ng/g)	BLOQ–9.34		Mercl et al. (2021)
Cress (*Lepidium sativum*)(ng/g)	L (520) R (4 290)		Reichl et al. (2018)
	TMD	DTMD	
Spinach (*Spinacea oleracea*) (ng/g)	L (6.6–25) R (2–8.3)		Kodešová et al. (2019b)
Lettuce (*Lactuca sativa*) (ng/g)	0.68–13.8	0.31–1.08	Mercl et al. (2021)
Barley (*Hordeum vulgare*) (ng/g)	R (4 560) S (5 410)		Khalaf et al. (2022)
Phragmites reeds (ng/g)	0.12		Picó et al. (2020b)

CBZ – carbamazepine; TMD – tramadol; CTP – citalopram; for metabolites abbreviations see Table 1;BLOQ – below limit of quantification; L – leaves; R – roots; S – shoot
*Compilation of 14 leafy greens: *Petroselinum crispum*, *Mentha*, *Anethum graveolens*, *Coriandrum sativum*, *Lactuca sativa*, *Apium graveolens*, *Beta vulgaris*, *Allium ampeloprasum*, *Spinacia oleracea*, *Corchorus olitorius*, *Thymus vulgaris*, *Eruca vesicaria*, *Aloysia*, *Foeniculum vulgare*

corn plants were found to have elevated concentrations of CBZ and its metabolites in all tissues, while showing no effect of CBZ on the biomass production but multiple physiological and chemical changes (Mascellani et al. 2023).

Carbamazepine was found to be easily taken up, accumulated and metabolized in the leaves of plants (Kodešová et al. 2019a, b; Brunetti et al. 2019, 2021; Klement et al. 2020; Ben Mordechay et al. 2021, 2022a, b), however, soil organic matter can reduce CBZ uptake (Ben Mordechay et al. 2022a). The uptake and transformation of CBZ in plants was dependent on the plant type; higher concentrations of CBZ and its metabolites were found in leaves than roots for radish and arugula than for lamb's lettuce and spinach. Interestingly, the efficiency of metabolizing CBZ follows as such Lamb's lettuce > spinach > radish and arugula (Brunetti et al. 2019; Kodešová et al. 2019a). In fact, the efficiency of radish and arugula (both family Brassicaceae) in metabolizing was very low contrary to the high and moderate efficiencies of lamb's lettuce and spinach, respectively. Ben Mordechay et al. (2021) also observed that CBZ and its metabolites were more predominately present in leafy greens compared to other studied plants. Ben Mordechay et al. (2022a) observed that the CBZ concentrations in leafy greens displayed a 'saturation-like trend' when CBZ concentrations in plants was plotted against concentrations in soils. On the other hand, the ability of green pea plants to take up CBZ, transport and high efficiency to metabolized CBZ in plant tissues was documented by Klement et al. (2020).

Four CBZ metabolites were found; EPC, oxcarbamazepine (OXC), RTC and DHC, with OXC and RTC found only in plants and not in soils (Kodešová et al. 2019a). The fractions of CBZ and its metabolite concentrations in the leaves of the lamb's lettuce, spinach, and radish/arugula were ~20, 40 and 80%, respectively (Kodešová et al. 2019a).

There are contradicting results regarding where CBZ is metabolized, whether in soil before plant uptake, or once in the plant. Kodešová et al. (2019a) observed results that most likely showed that CBZ was metabolized in plants roots. On the other hand, Malchi et al. (2014) observed CBZ was dominant in soils and roots, suggesting that plants had taken up CBZ as a parent compound and then metabolized within the leaves, with EPC being the dominant fraction. Likewise, Goldstein et al. (2014) found EPC fraction to dominate over all other CBZ metabolites in leaves of tomato and cucumber plants, Riemenschneider et al. (2017) found CBZ transformations occurring only in leaves of tomatoes, with EPC as the dominant metabolite fraction, and Menacherry et al. (2023a) found EPC to be the dominant metabolite in plant leaves. Another metabolite, OXC, was found to have lower concentrations than CBZ in tomato leaves (Riemenschneider et al. 2017), while Kodešová et al. (2019a) observed similar fractions of CBZ and OXC in lettuce. These results illustrate the persistence of these CBZ and its metabolites in the edible parts of plants. In study where dried biosolids were added to soils growing lettuce, CBZ was found in concentrations higher than 10 ng/g, with the highest in Luvisols (Mercl et al. 2021). The persistence of CBZ and its metabolites indicate the health risks that come with the use of wastewater-irrigated vegetables and fruits (Malchi et al. 2014; Paltiel et al. 2016).

Tramadol. Tramadol was found in the roots and leaves of spinach plants, however, at lower concentrations that STL (Kodešová et al. 2019b). Interestingly, despite the cationic form of TMD, it was found in higher concentrations in the leaves than in the roots, which could be explain by the low number of H-bonds and low log Kow and MW values as well (Kodešová et al. 2019b). Tramadol was found in concentrations exceeding 10 ng/g in lettuce grown in dried biosolid amended soils, with highest concentrations in the lettuce grown on Luvisols (Mercl et al. 2021). Likewise, a moderate to very high bioaccumulation (7.7–200 ng/g) was found in spinach plant tissues (Kodešová et al. 2019b). The uptake of tramadol by plants in the soil-plant continuum was also proved by Picó et al. (2020b) or by Khalaf et al. (2022) under hydrophobic conditions. Khalaf et al. (2022) found barley and cattail roots to have the ability to take up TMD with a daily uptake of 5.18 and 5.79 μg/g, respectively. However, barley seedlings under hydroponic systems displayed a TMD removal rate of 90%.

Sertraline. In spinach plants, STL was found in roots and leaves in high concentrations. Despite is positive charge and high log Kow value (5.1), STL still managed to translocate into the leaves, with high bioaccumulation in roots and in several plant leaves (dependent on soil type) (Kodešová et al. 2019b). The metabolite DSTL was found only in the roots, probably due to direct uptake from soils, little to no DSTL in the leaves was due to low transformation of STL in the leaves and low translocation of DSTL from soils (Kodešová et al. 2019b). The metabolization of STL in plants was found to be controlled by demethylation, hydroxylation and conjugation with amino acids (Reichl et al. 2018).

Citalopram. Citalopram is a cation with Kow and MW values near the limits that were described by Kumar and Gupta (2016). Citalopram belongs to the same family as STL, therefore, the metabolization of CTP in plants most likely are controlled by the same factors as mentioned for STL. Despite its high sorption in in soils, CTP is still taken up by plants. The persistency of CTP in soils, along with factors such as its lipophilicity allow for it to be translocated in plants. In spinach plants, CTP and its metabolite were present mostly in the roots of the plant, however the bioaccumulation of CTP in the roots were low, due to high sorption in soils (Kodešová et al. 2019b). In Green pea plants, Brunetti et al. (2022) observed CTP in stems and leaves, reaching concentrations of 6.36 and 2.76 ng/g, respectively. Transformation of CTP is notable in green pea plants, however, the degradation rates can be relatively low (Brunetti et al. 2022).

PSYCHOACTIVE COMPOUNDS IN FRESHWATER AND SEDIMENTS

Studies focused on the studied compounds in freshwater and their consequent implications on freshwater organisms have become more and more popular. Regarding sediments, there is limited knowledge. However, the solid-water distribution coefficient is one of the controlling factors for evaluating the fate and the mobility of compounds in water-sediment (Koba et al. 2018) and dependent on the compound and the properties of the solid particles and surrounding conditions (Hörsing et al. 2011; Al-Khazrajy & Boxall 2016). Regarding sediments, Koba et al. (2018) found 18 pharmaceutical compounds and their metabolites (OXC, RTC, EPC, DCTP) in concentrations following the order CTP > TMD > STL > CBZ (Figure 2), with CTP and STL found in all samples. The concentrations in the sediments of the pond decreased when the pond was filled, therefore, it can be implied that compounds were transported from sediments into the water (Koba et al. 2018).

The most frequently detected compound in water and sediment samples studied by Xie et al. (2015a) was CBZ, with a 100% detection rate in all water samples, ranging from 0.24 to 8.74 ng/L, and reaching up to 7 ng/g in sediments. Carbamazepine was also the most detected compound found by Fekadu et al. (2019) in both Africa and Europe. Confirming the persistence and presence of CBZ in environmental samples (Benotti & Brownawell 2009; Matamoros et al. 2009; Zhou et al. 2009; Xie et al. 2015a). Carbamazepine in river water (under laboratory stimulation) showed degradation into eight transformation products (mono-, di-, tri-hydroxy carbamazepine, hydroxylation and ring contraction, hydration of the C_{10}-C_{11} double bond and intramolecular cyclization), which totalled approximately 50% of degradation of parent compound (Calza et al. 2013). Interestingly, Grabicová et al. (2017) studied freshwater samples affected by a sewage treatment plant, and observed TMD to have the highest concentration (1.4 μg/L), followed by STL (4–100 ng/L) and CTP (24–58 ng/L).

However, the most present compound, differs depending on where in the world the study is conducted. For example, while Xie et al. (2015a) found concentrations of CBZ reaching 8.74 ng/L (China), Zhou et al. (2009) found concentrations that reached maximum values of 2 336 ng/L (England). Fekadu et al. (2019) reviewed the differences between pharmaceuticals in Europe and Africa and identified that there were large concentration variations in surfaces waters in Africa and Europe, with maximum concentrations in Africa reaching almost 20 000 times higher than concentrations found in Europe. Reasons behind these large variations throughout the world are due to different wastewater treatments, different regulations and different pharmaceutical consumptions. Therefore, the most persistent compound greatly varies on the country and the region within that country. Europe has better regulations put into place than many other continents, yet majority of studies on pharmaceuticals in freshwater is conducted in Europe. An important aspect to consider though is that whether concentrations of pharmaceuticals in freshwater systems are high or low, even at low concentrations many of the compounds and their metabolites continue to be biologically active and in turn can affect non-targeted organisms (Ebele et al. 2017).

PSYCHOACTIVE COMPOUNDS IN FRESHWATER FISH

Freshwater fish span a wide range of species, and influence the different interspecific relationships that take place (e.g., host-parasite relationship). Freshwater fish and their relationships play a vital role within the environment and any change in one species can lead to drastic change in another species or changes in their habitat (ecological effect), creating a somewhat domino effect, until eventually a balance is created (Coors & De Meester 2008; Morley 2009; Brodin et al. 2014; Hua et al. 2017). Therefore, the introduction of pharmaceutical compounds can have a dire effect in such environments. One of the impacts of pharmaceuticals on freshwater organisms is the ability to influence/change the behaviour of these organisms. For many compounds, their influence on aquatic organisms include changes in activity levels, sociability and boldness, therefore, creating change within the entire ecosystem (Krebs & Davies 1997; Schmitz 2007; Manning & Dawkins 2012). Changes in activity can go both ways: increased or decreased activity. Ecosystem and relationship instability (effecting the food chain and biodiversity) are brought about by increased activity, aggressiveness and foraging (Duffy et al. 2007; Schmitz 2007). On the other hand, decreased activity, reactions and foraging lead to animals being more prone to predators and can hinder reproduction (Krebs &Davies

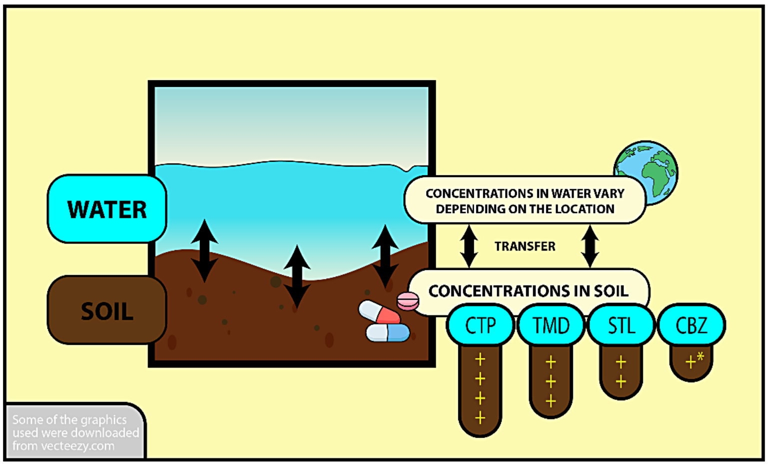


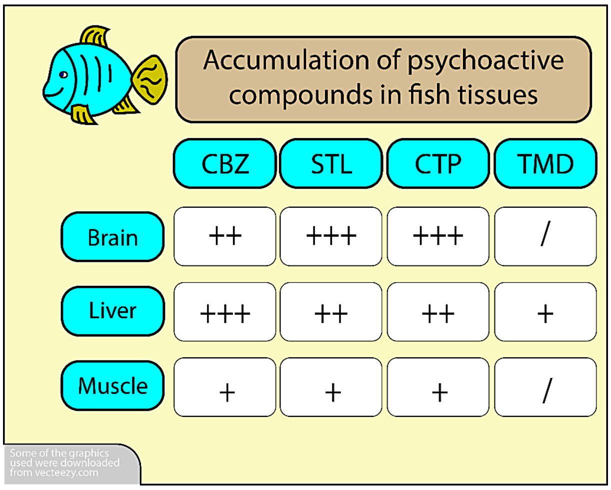
Figure 2. Presence of psychoactive compounds in soil/sediment and freshwater systems

1997; Manning & Dawkins 2012). Pharmaceuticals can disrupt the development of fish and shows to many compounds have shown to have similar metabolism in fish compared to humans (Sehonova et al. 2016, 2017; Tanoue et al. 2017). However, the efficiency of the compound depends on the metabolism of the compound itself within the fish, leading to the formation of metabolites (Zhuo et al. 2016; Tanoue et al. 2017; Santos et al. 2021). Compound consumption is highly dependent on the fish species, their personality, and their individual metabolic rates (Manning & Dawkins 2012; Metcalfe et al. 2016).

OECD (2001) formulated a criterion that stated 'if the bioconcentration factor or BAF, in our case, is ≥ 500, the compound has the potential to bioconcentrate/bioaccumulate'. Following this criterion, Grabicová et al. (2017) could conclude that STL and CTP are potential bioaccumulative compounds in the tissues of fish that live in natural conditions of freshwater streams that are affected by sewage treatment plants (Figure 3). Furthermore, Arnnok et al. (2017) stated that in their study of fish species in the Niagara River, the highest bioaccumulation of the different studied pharmaceuticals (including CTP and STL) followed the order of brain > liver > muscle > gonads, most likely attributed to the direct exposure to wastewater effluent.

Carbamazepine. Detection and concentrations of CBZ has varied in different species. Wang and Gardinali (2013) studied *G. holbrooki* that were exposed to reclaimed water (CBZ conc. = 1 229 ng/L) with a 7-day uptake phase and daily 50% renewal of water, and observed that CBZ was quickly taken up by the fish. Xie et al. (2015a) studied crucian carp, common carp, lake anchovy and yellow catfish from a lake in China. They observed highest CBZ levels in common carp (10.7 ng/g dw) with a < 40% detection rate in the organisms. Valdés et al. (2016) studied two fish species, *G. affins* and *J. multidentata* from a river and found CBZ levels in the fish were similar to that of results obtained by Wang and Gardinali (2013) and Xie et al. (2015a). Valdés et al. (2016) found, under laboratory conditions, CBZ and its metabolite EPC in gills, intestine, liver, brain and muscles of *J. multidentata*, while another metabolite (2-hydroxycarbamazepine) was found only in gills and muscle. Zebrafish (*Danio rerio*) exposed to CBZ (upto 10 000 μg/L) under laboratory conditions showed several changes in their behaviour and reproduction (Santos et al. 2018), however, significant alterations were not found, similar to results from Madureira et al. (2012). Madureira et al. (2012) exposed zebrafish to CBZ (1780 μg/L) under laboratory conditions and showed that sex played a significant role in the effects of the compound. Zebrafish showed no signs of stunted growth, increased ingestion time, eggs viability was impaired, and alterations to female gonads follicular stages (Santos et al. 2018).

Tramadol. In a study by Douda et al. (2019), they observed the effects of TMD on the relationship between parasitic larvae (glochidia) and fish (*Squalius cephalus*). The results showed slight changes in their interaction, however, no overall significant changes in their interaction nor their abundance can be found. The impact of TMD on the behaviour of fish can be found in the paper written by Santos et al. (2021). They observed that the presence of 1 μg/L of TMD in water for 42 days was enough to show significant observations in the behaviour of European chubs (*Squalius cephalus*). The changes in behaviour included anxiolytic-like behaviour, less activity/movement, less interest in exploring new environments or new items, with a correlation between the concentration of TMD in the brain and the behaviour changes (Tanoue et al. 2017; Santos et al. 2021). Ložek et al. (2019) also observed the decreased activity and lower distance moved in TMD exposed crayfish (*Pacifastacus leniusculus*), along with increased heart rate after stressor application. Likewise, Buřič et al. (2018) observed lower velocity, shorter distance moved and more time spent in shelters of crayfish (*Procambarus virginalis*) exposed to TMD. The development of the common carp (*C. carpio*) was hindered when exposed



	CBZ	STL	CTP	TMD
Brain	++	+++	+++	/
Liver	+++	++	++	+
Muscle	+	+	+	/

Figure 3. Graphic representation of accumulation of psychoactive compounds in the brains, liver and muscles of fish

to 10–200 μg/L of TMD (Sehonova et al. 2017). The changes in development and behaviour were due to the metabolism of TMD within the species, and the formation of metabolite O-desmethyltramadol (DTMD), with similar analgesic effects like in humans, however, this is dependent on the species (Zhuo et al. 2016; Tanoue et al. 2017). Tramadol in brown trout was found to accumulate in the liver and kidneys (Grabicová et al. 2017). Juvenile chubs exposed to environmentally relevant concentrations of TMD, showed positive brain concentrations from the 1st day of exposure, however, there were no signs of changes in the condition of the chubs (Hubená et al. 2020). When exposed to TMD, chubs showed no increase in aggression, but during depuration, increased aggression was observed, possibly as a side effect of withdrawals (Hubená et al. 2021).

Sertraline. In a study by Grabicová et al. (2017), STL accumulated in the liver, kidneys and brain of the exposed brown trout (*Salmo trutta* m. *fario*); STL was the only compound found in the brain probably due to its lipophilicity and specific mode of action (e.g. lipophilicity allows it to reach the brain). Likewise, positive concentrations were found in the brains of juvenile chubs (1st day mean conc. 590 ng/g to 42nd day mean conc. 1 800 ng/g) with a strong influence of the amount of STL received from the water concentrations (Hubená et al. 2020). Similarly, Schultz et al. (2010) observed STL and its metabolite, norsertraline, to be one of the few compounds that were found in the brain (albeit in low concentrations) of native white suckers (*Catostomus commersoni*) collected from a stream connected to effluent-impacted streams. Sertraline in brains of aquatic organisms could indicate that STL undergoes selective uptake into the brain tissues, with possible serotonergic effects on fish (Schultz et al. 2010, 2011; Xie et al. 2015b). Sertraline, like other compounds, showed the highest concentrations in the liver and kidney, and has a high bioaccumulation factor (Xie et al. 2015b; Chen et al. 2017; Grabicová et al. 2017; Koba et al. 2018).

The effect of STL on fish included lower food consumption, lower growth rates, heightened sertonergic activity (Murdoch & McTavish 1992; Cubitt et al. 2008; Vindas et al. 2016; Chen et al. 2017). Regarding aggression, Hubena et al. (2021) found no effect of STL (1 μg/L for 42 days) on chub aggression, however, Kania and Wrońska (2015) observed decreased aggression in Siamese fighting fish (*Betta splendens*) when exposed to concentrations ranging 0.4 to 4 μg/L after 7 and 14 days. Similarly, in further experiments, Hubená et al. (2021) found that a threshold concentration of 1 000 ng/g of STL in the brain tissue of chubs was needed in order to observe a decrease in the aggression of the fish. However, the thresholds vary depending on the species.

In the study by Minagh et al. (2009), the algae *P. subcapitata* was very sensitive to STL, which was also observed by Johnson et al. (2007). Crustaceans, such as *Daphnia* sp. also show high sensitivity to STL; the differences in the sensitivity of the *Daphnia* is attributed to the different species of *Daphnia* used and the exposure time (Henry et al. 2004; Picado et al. 2007; Christensen et al. 2007; Minagh et al. 2009). Rainbow trout was observed to be extremely sensitive to STL, with fish in waters with 320 μg/L of STL dying several days after being moved to control water, showing symptoms of decrease in respiration and loss of movement (Minagh et al. 2009). The mortality rate of chubs exposed to 1 μg/L STL for 42 days drastically increased compared to the control, with 26% of fish dying with visible signs of lowered conditions (Hubená et al. 2020), while fathead minnows exposed to 52 ng/L of STL also showed high mortality rates (Schultz et al. 2011). Exposure to concentrations of STL above environmental levels (eg. > 1 μg/L) also lead to decreased apatite and food intake, impairing energy levels of the organism and in turn decreasing the chances of survival and increasing mortality (Hedgespeth et al. 2014; Xie et al. 2015b; Chen et al. 2017; Hubená et al. 2020).

Citalopram. Crayfish (*Procambarus virginalis*) that was exposed to CTP was found to have decreased movement and velocity (Buřič et al. 2018). Citalopram in brown trout was found to accumulate in the liver and kidneys (Grabicová et al. 2017) as well as in the brain on juvenile chubs (Hubená et al. 2020). Contradicting the results observed by Buřič et al. (2018) in crayfish, Kellner et al. (2016) observed increased locomotor activity in stickleback fish that were exposed to 1.5 and 15 μg/L of CTP compared to control fish after 5–7 and 15–17 min of the start of the experiment. The study also showed an anxiolytic effect of CTP, decreasing behaviours associated with anxiety, such as bottom dwelling and freezing (Levin et al. 2007; Egan et al. 2009; Kellner et al. 2016). Similar to the results by Kellner et al. (2016), zebrafish (*Danio rerio*) spent more time in the top of the tank (decreased bottom dwelling) after a 3-min exposure to 100 000 μg/L of CTP (Sackerman et al. 2010). In the zebrafish that was exposed to 24.3 μg/L of CTP for 3 min, it took up 115 ng/g wet weight in brain and 193 ng/g wet weight in muscle tissue, indicating that acute uptake of CTP by zebrafish brain and muscle is approximately 1/100 and 1/100 of solution concentration (Sackerman et al. 2010). A study observing the effects of CTP on the aggression and sexual behaviour of rainbow trout and guppies showed that CTP doesn't cause significant aggression effects in rainbow trout and sexual behaviour in guppies, due to the low uptake of CTP from water to fish, however the exposure time of 3–7 days was too short for CTP to have an effect (Holmberg et al. 2011). Kellner et al. (2016) also observed no significant effects of CTP on the aggression of three-spined stickleback, while Lepage et al. (2005) and Kellner and Olsén (2020) observed reduced aggression in rainbow trout (intake of approx.100 μg/kg of feed) and three-spined stickleback (max dose of 0.38 μg/L). While on the other hand Hubená et al. (2021) observed that CTP exposure did increase aggression of chubs (*Squalius cephalus*). A positive linear relationship of the concentration of CTP in the brain and aggression were found for chubs, with a threshold value of 1 and 3 ng/g from which effects could be seen in their behaviour (Hubená et al. 2021) Regarding the eating behaviour of stickleback, CTP was found to decrease food intake, with threshold values for the effects of CTP to affect feeding behaviour is lower than the environmental levels of CTP (Kellner et al. 2015).

CONCLUSION

This review focused on collecting information on four different pharmaceuticals in different environmental sectors: carbamazepine, tramadol, sertraline and citalopram. The review investigated the concentrations, mobility, behaviour and fate of the compounds in soils, plants, freshwater and fish. The major source of these compounds are sludges and by-products from WWTPs that are later used in agriculture or are effluents released into freshwater bodies or used for irrigation. Majority of the articles investigated were laboratory experiments. However, they provided insightful information about the fate of each compound and the potential impacts they have in nature. The studied compounds and their metabolites were found in measurable concentrations in all studied environmental sectors as well as in freshwater fish, proving the bioaccumulation fate of these compounds through the food chain.

Many studies have focused on the effect of single compounds on aquatic species, however, in real life situations; the environmental conditions are a lot more drastic, with different doses of various compounds present in fresh water. Clearly single compounds have a significant effect on the aquatic species; therefore once can only imagine the effect of multiple compounds, all with different purposes, on aquatic organisms. One of the current significant topics researched of today is the pre-treatment and conversion of sludge into biochar. Sludge formed biochar is found to contain lower concentrations of pharmaceuticals, and therefore lower concentrations in soils and in plant. They can be high in nutrients which can also aid in plant growth, however, this is soil and plant dependant.

There is still a lot of research that must be conducted in order to truly understand the impacts of different environment of the behaviour and mobility of these compounds and ways to combat their negative impacts on the environment.

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