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Insight into the Distribution of Pharmaceuticals in Soil-Water-Plant Systems

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ABSTRACT

Pharmaceuticals in agricultural soils originating from irrigation with treated wastewater and land-applied biosolids can enter field crops. However, little is known about the role of pore water in plant uptake of pharmaceuticals from soil. In this study, the fate, uptake and distribution of fifteen commonly used pharmaceuticals in soil-water-radish systems were investigated to examine the relationship between the accumulation and their physicochemical processes in soils. The results indicate that the distribution of pharmaceuticals between soil and pore water, as well as their biodegradation, combined to govern the bioavailability of pharmaceuticals to plant uptake. Fourteen out of 15 pharmaceuticals could enter radish tissues in which the accumulation ranged from 2.1 to 14080 ng/g. Comparison of bioconcentration factors (BCFs) on the basis of pharmaceutical concentration in bulk soil vs. in pore water implies that pharmaceuticals present in soil pore water are the major bioavailable fractions to plant uptake. The pore water-based BCFs exhibited a positive linear relationship with log D_{ow} for the pharmaceuticals with > 90% as neutral species in soil pore water, while such relationship was not observed between bulk soil-based BCFs and log D_{ow} mainly due to sorption by soil. Other than hydrophobicity, the dissociation of ionizable pharmaceuticals in the soil pore water and (or) root cells may lead to the "ion-trap" effects and thus influence the uptake and translocation process. The large molecular size pharmaceuticals (e.g., tylosin) manifested a minimum uptake due plausibly to the limited permeability of cell membranes.

Keywords: Plant uptake; Soil pore water; Bioavailability; Bioaccumulation; Translocation.

1. Introduction

Some pharmaceuticals have been recognized as chemicals of emerging concern because they are widespread in the environment, and have the potential adverse effects on non-target organisms and humans (e.g., endocrine disruption and preservation of antibiotic resistance) (Carvalho et al., 2014; Daughton and Ternes, 1999; Kolpin et al., 2002; Madikizela et al., 2018). Conventional wastewater treatment processes cannot effectively remove all pharmaceuticals from the influents, leaving the pharmaceuticals in the effluents at the levels of ng/L to low μg/L (Gros et al., 2010; Sui et al., 2011; Vanderford and Snyder, 2006) and in biosolids at μg/kg to low mg/kg (dry weight) (Clarke and Smith, 2011; McClellan and Halden, 2010). Irrigation with the treated wastewater and land application of biosolids are common agricultural practices, which lead to the dissemination of a wide range of pharmaceuticals in agricultural soils with concentration up to mg/kg levels (Carter et al., 2014; Durán-Alvarez et al., 2009; Kinney et al., 2006; Vazquez-Roig et al., 2010). For example, land application of biosolids at a rate of 5 kg/m^2 caused triclosan concentration of 0.77-0.95 mg/kg in the farm soils located in Bedfordshire, UK (Butler et al., 2012). One major consequence of the soil contamination is that these pharmaceuticals could enter food chain after plant uptake, and pose potential risks to human and animal health via dietary consumption (Christou et al., 2017; de Boer et al., 2018; Sallach et al., 2015; Wu et al., 2014). Paltiel et al. (2016) recently found that carbamazepine and its metabolites were detected in human urine after consuming the fresh produce irrigated with treated wastewater.

In soil-plant systems, the amount of organic chemical uptake by plant roots depends largely on sorption/desorption of contaminants in soils and their physicochemical properties. It is assumed that organic chemicals present in soil pore water are readily bioavailable to plant uptake (Miller et al., 2016), and soil water serves as the carrier to move the chemicals into plants. The distribution of pharmaceuticals in soil-water-plant systems is commonly characterized by bioconcentration

67 factor (BCF) which is typically calculated as the ratio of pharmaceutical concentration in plant to
68 that in bulk soil (Hurtado et al., 2016; Karnjanapiboonwong et al., 2011; Pan et al., 2014; Shenker
69 et al., 2011; Wu et al., 2010). However, pharmaceuticals present in soil pore water vs sorb by soil
70 could manifest different bioavailability to plant uptake. Therefore, BCFs calculated on the basis
71 of pharmaceutical concentration in bulk soil are not comparable among the studies using different
72 soils because of the varying affinities of pharmaceuticals to soils. For instance, soil-based BCFs
73 of seven benzodiazepines in radish could vary by up to 86.0 times between two soils (Carter et al.,
74 2018). The difference of soil-based BCFs between three soils for caffeine, carbamazepine, and
75 lamotrigine in tomato or cucumber can up to 20.0, 7.8, and 245 times, respectively (Goldstein et
76 al., 2014). In fact, BCFs calculated by pharmaceutical concentration in soil pore water are believed
77 to provide more accurate information to describe the uptake process since pharmaceuticals in soil
78 pore water are directly available to plant root uptake. For example, Blaine et al. (2014) used pore
79 water-based BCFs of perfluoroalkyl acids in four vegetables grown in soils to explore the
80 relationship between bioaccumulation and chemical properties, and found the consistent results
81 with the vegetables grown in hydroponic solution but not for soil-based BCFs. Despite numerous
82 greenhouse and field studies that have been conducted, very limited studies were conducted to
83 systematically evaluate the contribution of pharmaceuticals in soil pore water to the
84 bioaccumulation in plants (Boxall et al., 2006; Carter et al., 2014).

85 Water is believed to carry xenobiotic chemicals (e.g. pharmaceuticals) to cross plant root
86 cortex by symplastic (intracellular space) and apoplastic (extracellular space) pathways
87 (McFarlane and Trapp, 1994; Trapp and Pussemier, 1991). In plant roots, Casparian strip
88 composing primarily of hydrophobic suberin and lignin functions as a water-impermeable barrier
89 to prevent water and pharmaceuticals from passing through the endodermis via the apoplastic route

(Naseer et al., 2012; Schreiber, 2010). Therefore, pharmaceuticals have to reenter the symplastic pathway to cross cell membranes and enter the xylem. For many nonionic organic compounds, the accumulation in plants is positively related to their lipophilicity as indicated by the linear relationship between BCFs and octanol−water partition coefficient (K_{OW}) (Briggs et al., 1982; Briggs et al., 1983). However, plant uptake of ionic compounds is determined by the combination of hydrophobicity, chemical speciation and surrounding solution pH (Briggs et al., 1987; Trapp, 2000). Most pharmaceuticals are ionizable compounds and have low hydrophobicity (e.g., log D_{OW} < 2). Therefore, the relations developed for nonionic organic contaminants may not be applied to the uptake of pharmaceuticals. For example, no apparent relationship was observed between log BCF and log D_{ow} (pH-adjusted K_{ow} to neutral species) for 20 pharmaceuticals (including acids, bases and neutral compounds) in hydroponically grown lettuce, spinach, cucumber and pepper (Wu et al., 2013). However, strong correlations were observed when the data were limited to neutral pharmaceuticals. The relationship between plant uptake of ionic pharmaceuticals and their physicochemical properties still remain largely unknown in the complex soil-water-plant systems, where the dissociation in soil and plant at relevant pHs has been considered as an important factor (Carter et al., 2014; Goldstein et al., 2014; Hyland et al., 2015; Malchi et al., 2014).

This study aims to investigate the fate, uptake and distribution of fifteen diverse pharmaceuticals in soil-radish systems. Radish plants grew in soil with the soil moisture levels at 75%, 60% and 45% of maximum water holding capacity (MWHC), which represent the common range of soil water contents in agricultural field. BCF values, calculated on the basis of pharmaceuticals concentration in bulk soil vs. in pore water, were compared to gain more insight into the bioavailable fractions of pharmaceuticals in soil to plant root uptake. The selected physicochemical properties of pharmaceuticals were evaluated to examine the relation to their

uptake and translocation in plants. This study provided experimental results to verify and improve the understanding of plant uptake of pharmaceuticals from soils in terms of pore water, which delivers the useful information on the risk assessment of human exposure to pharmaceutical-contaminated vegetables from the reuse of treated wastewater and biosolids in agriculture.

2. Experimental Section

2.1. Chemicals and Materials

Acetaminophen, caffeine, carbamazepine, sulfadiazine, sulfamethoxazole, lamotrigine, carbadox, estrone, 17 β-estradiol, triclosan, trimethoprim, lincomycin, oxytetracycline, monensin and tylosin were purchased from Sigma-Aldrich (St. Louis, MO, USA). These fifteen pharmaceuticals (Table 1) were selected because they are commonly present in treated wastewater and biosolids, as well as in agricultural lands. Ceramic homogenizers, octadecylsilane (C18), and primary secondary amine (PSA) were purchased from Agilent Technologies (Santa Clara, CA, USA). Disodium ethylenediaminetetraacetate (Na_2EDTA), formic acid, and sodium chloride (NaCl) were purchased from J.T. Baker (Phillipsburg, NJ, USA). Organic solvents (HPLC grade) were purchased from Fisher Scientific (Fair Lawn, NJ). Ultrapure water was produced from a Milli-Q water purification system (Millipore, Billerica, MA, USA).

A sandy loam soil was collected from Michigan State University Research and Teaching Farm located in Lansing, Michigan. The sampling site had not previously irrigated with treated wastewater or amended with biosolids and manure. The soil contained 79.0 % sand, 12.6 % silt, and 8.4 % clay. The soil was mixed with a portion of peat to achieve soil organic matter content

136 of 2.8 %. The soil had a cation exchange capacity of 9.2 cmol/kg. The soil was air-dried and passed
137 through 2-mm sieve before use.
138
139 *2.2. Experimental Setup*
140
141 A mixture of the fifteen pharmaceuticals (Table 1) in acetone was spiked to soil (1.0 kg)
142 and thoroughly mixed in a fume hood. After acetone was evaporated, the soil with spiked
143 pharmaceuticals was mixed thoroughly with 32.0 kg of clean soil using a motorized concrete mixer
144 to achieve the final concentration of 1 μg/g for each pharmaceutical. Five radish (*Raphanus sativus*)
145 seeds (Burpee & Co., Warminster, PA) were planted in each plastic pot containing 1.2 kg of the
146 soil. The pots were irrigated daily with deionized water to maintain water content at 75 %, 60 %
147 and 45 % of MWHC by monitoring the pot weights. No additional fertilizer was added. All
148 experimental pots were prepared in triplicate, including the pharmaceutical-free and radish-free
149 controls. The pots were randomly placed in a climate-controlled greenhouse under sunlight at
150 25 °C during daytime and 21 °C during night. After seed germination (at day 8), the plants were
151 thinned to two radish seedlings per pot.
152 For the radish-free controls, soil and pore water samples were collected at 4 hours after
153 irrigation at day 0, 1, 3, 7, 14, 21, 28 and 35. For the uptake experiments, radish were sampled at
154 day 28 (premature stage) and day 35 (mature stage). The radish plants were thoroughly rinsed with
155 deionized water to remove the attached soil particles, wiped with tissue paper, and separated into
156 roots (including bulb) and leaves. Plant samples were weighed, cut into small pieces, freeze-dried
157 and ground to fine powders. All samples were stored at −20 °C prior to extraction. At the same
158 time, soil samples were also collected from the plant pots at day 28 and 35 for the analysis of

159 pharmaceuticals in soil and pore water. The pH of collected pore water was measured using a
160 Fisher Scientific Accumet AB15 pH meter (Pittsburgh, PA, USA).
161
162 *2.3. Sample Extraction and Analysis*
163
164 Pharmaceuticals in radish and soil samples were extracted using a modified QuChERS
165 method (Chuang et al., 2015). In brief, dry radish (0.5 g) or soil sample (2.5 g) was placed in
166 polypropylene centrifuge tube to which 2.0 mL of 150 mg L^{-1} of Na_2EDTA was added with two
167 pieces of ceramic homogenizers and vortexed for 1 min. The sample was then extracted with 5.0
168 mL of acetonitrile and methanol mixture (v/v = 65/35) by vigorously shaking for 3 min. Then,
169 Na_2SO_4 (2.0 g) and NaCl (1.0 g) were added and vortexed for another 2 min. The tubes were
170 centrifuged at 2990 g for 10 min, and 1.3 mL of supernatant was transferred into clean 1.5-mL
171 centrifuge tubes containing 250 mg of Na_2SO_4 and d-SPE sorbents (25 mg of C18, and 25 mg of
172 PSA). The samples were vortexed for 1 min, and centrifuged at 9240 g for 10 min. The supernatant
173 was filtered through a 0.22 μm polytetrafluoroethylene (PTFE) filter and stored at −20 °C prior to
174 analysis.
175 Soil pore water was collected immediately after soil sampling using the protocol described
176 by Carter et al. (2014). Briefly, 25 g of soil was placed in a 20-mL disposable plastic syringe with
177 a glass wool insert at the bottom. The syringes were placed in 50-mL centrifuge tubes and
178 centrifuged at 4300 g for 40 min. The collected pore water was passed through a 0.22-μm PTFE
179 membrane, and an aliquot of the pore water (0.5 mL) was diluted to 1.0 mL with methanol in clean
180 HPLC glass vials for LC-MS/MS analysis.

The LC-MS/MS system consisted of a Shimadzu prominence high-performance liquid chromatography (Columbia, MD, USA) coupled to a Sciex 4500 triple quadrupole mass spectrometer (Foster City, CA, USA), and a 50 mm × 2.1 mm Agilent C18 column (Torrance, CA, USA). Detailed information about the LC-MS/MS optimized condition is provided in the supporting information (SI). Multiple reaction monitoring (MRM) parameters used for the analysis are listed in Table S1. Extraction efficiency and method detection limits (MDLs) of pharmaceuticals are summarized in Tables S2 and S3.

2.4. Data Analysis

Soil−pore water distribution coefficient *(K_d)* was calculated using equation 1. BCF was calculated by measured pharmaceutical concentration in soil and in pore water using equation 2 and 3. Translocation factor (TF) was calculated using equation 4. The first-order dissipation rate constant (k) of pharmaceuticals in soil was estimated by fitting the time-dependent concentration to the first-order decay model using equation 5. The dissipation half-life ($T_{1/2}$) was calculated using equation 6.

$$K_d = \frac{C_s}{C_{pw}} \quad (1)$$

$$\mathrm{BCF_{soil}} = \frac{C_{root}}{C_{soil}} \quad (2)$$

$$\mathrm{BCF_{pore\ water}} = \frac{C_{root}}{C_{pw}} \quad (3)$$

$$\mathrm{TF} = \frac{C_{leaf}}{C_{root}} \quad (4)$$

$$C_t = C_0\, e^{-kt} \quad (5)$$

$$T_{1/2} = \frac{\ln(2)}{k} \quad (6)$$

where C_s is pharmaceutical concentration in soil solid phase (total amount of pharmaceuticals in soil subtracted by that present in pore water) (ng/g, dry weight), C_{pw} is pharmaceutical concentration in pore water (ng/mL), C_{soil} is pharmaceutical concentration in bulk soil (ng/g, dry weight). C_{root} and C_{leaf} are pharmaceutical concentration in radish roots and leaves (ng/g, dry weight), respectively. BCF_{soil} and $BCF_{pore\ water}$ are the BCFs calculated on the basis of pharmaceutical concentration in bulk soil and in pore water, respectively. C_0 and C_t are pharmaceutical concentration at the beginning of the incubation and time t (d) in soil, respectively. Statistical analysis (All Pairs, Tukey HSD, $p = 0.05$) of experimental results for significant analysis was carried out using SPSS 22.0 software for Windows (IBM Corp., Armonk, NY).

3. Results and discussion

3.1. Plant Uptake

Radish grew well in the soil with the three water content at 75%, 60%, and 45% of MWHC, and appeared in good health. The associated radish biomass showed no significant difference at the three water contents in the presence and absence of pharmaceuticals ($p > 0.05$) (Figure S1). The radish plants were separated into leaves and roots, and analyzed individually for the accumulated pharmaceuticals (Table S4). All the pharmaceuticals except 17 β-estradiol were detected in the radishes sampled at both day 28 and 35. Pharmaceutical concentration in roots ranged from 2.4 to 1774 ng/g. Carbamazepine demonstrated the highest accumulation, which was up to 738 times greater than estrone (the least accumulated compound in roots) at day 35. In the leaves, thirteen out of the fifteen pharmaceuticals (except 17 β-estradiol and monensin) were

226 detected with the concentration range of 2.1 to 14080 ng/g. Carbamazepine, caffeine, lamotrigine
227 and trimethoprim were measured at relatively high concentrations in leaves (462-14080 ng/g),
228 while tylosin and estrone were detected at low concentrations (2.1-12.3 ng/g). Monensin was found
229 to accumulate in the roots only, which was not detected in the leaves.

230 Pharmaceuticals accumulated in plants may be metabolized, thus further influence their
231 accumulation and distribution in plant organs. In our previous study, we found that 17 β-estradiol,
232 sulfamethoxazole, sulfadiazine, estrone, triclosan, acetaminophen, caffeine, carbadox and
233 lamotrigine were extensively metabolized in the radish plants with the mass recoveries ranging
234 from 3.0 to 32.1% after 7 days of hydroponic exposure (Li et al., 2018). In some cases, the amount
235 of formed metabolites can even be greater than the accumulated parent compounds (Goldstein et
236 al., 2014; LeFevre et al., 2017; LeFevre et al., 2015; Macherius et al., 2012a; Malchi et al., 2014;
237 Riemenschneider et al., 2017). For example, Macherius et al. (2012a) reported that the total amount
238 of eight phase-II triclosan conjugates was about 5 times that of triclosan in carrot roots after two-
239 month growth in soil.

240 The transpiration stream is considered as the main driving force for uptake and transport
241 of pharmaceuticals from soil to plants (Dodgen et al., 2015). In this study, the three common soil
242 water contents (75, 60 and 45 % of MWHC) did not have an apparent impact on the accumulation
243 of pharmaceuticals in the radish tissues. As shown in Table S4, the concentrations of all detected
244 pharmaceuticals (except caffeine) in radishes showed no significant difference ($p > 0.05$) among
245 three soil water contents. This could be due to the factor that the water present in soil at the three
246 soil water contents could be sufficient for radish growth, and the variation in three soil water
247 contents had barely impact on the water use efficiency by radishes. This is evidenced by the fact
248 that there was no significant difference in the amount of transpired water through the radish

249 growing at the three soil water contents ($p > 0.05$, Figure S2). As a result, the uptake of
250 pharmaceuticals from soil pore water could be similar, and the corresponding BCFs or TF values
251 at both harvesting times demonstrated no significant difference for all measured pharmaceuticals
252 in radish growing at the three soil water contents ($p > 0.05$, Figures S3 and S4).
253
254 *3.2. Bioconcentration Factor*
255
256 To better understand the accumulation potential of pharmaceuticals in radish from soil
257 system, the BCF values were calculated on the basis of pharmaceutical concentration in bulk soil
258 (BCF_{soil}) and in soil pore water ($BCF_{pore\ water}$). The BCF values were averaged across all radish
259 samples growing at the three soil water contents ($n = 9$), and are shown in Figure 1. The BCF_{pore}
260 $_{water}$ values ranged within 0.26-45.9 mL/g, and the BCF_{soil} values were within the range of 0.02-
261 5.4 g/g. Triclosan manifested the highest $BCF_{pore\ water}$ value 45.9 mL/g at day 28, and
262 acetaminophen had the greatest BCF_{soil} 5.4 g/g at day 28. Tylosin demonstrated the lowest BCF_{soil}
263 and $BCF_{pore\ water}$ compared to the other pharmaceuticals. Other than the two sulfonamide antibiotics
264 (sulfadiazine and sulfamethoxazole), the $BCF_{pore\ water}$ values of the pharmaceuticals were 1.2-423
265 and 1.3-281 times greater than their corresponding BCF_{soil} values at day 28 and 35, respectively.
266 The greater $BCF_{pore\ water}$ than BCF_{soil} values could be due to the less bioavailability of soil-sorbed
267 pharmaceuticals to radish root uptake than pharmaceuticals in soil pore water. For the instance of
268 triclosan, the BCF_{soil} value was < 0.12 g/g at day 28, and its corresponding $BCF_{pore\ water}$ was 45.9
269 mL/g. The strong sorption of triclosan by soil (K_d = 316.2 mL/g) could reduce the bioavailability
270 of sorbed chemical, resulting in the substantially diminished BCF_{soil}. Different soils
271 manifest varying sorption for pharmaceuticals hence the bioavailability for plant uptake (Fu et al.,

2016b; Goldstein et al., 2014; Malchi et al., 2014). For example, the uptake of triclosan from soils by root vegetables such as radish and carrot demonstrated a wide range of BCF_{soil} from 0.12 to 6.6 g/g (Carter et al., 2014; Fu et al., 2016b; Macherius et al., 2012b; Pannu et al., 2012; Prosser et al., 2014). Such difference in BCF_{soil} among the soils (up to 55 times) could be attributed mainly to the varying sorption by soils that lead to the different available fractions of triclosan in pore water to plant uptake. The BCF_{soil} tends to be elusive as evidenced by that the chemical concentration in bulk soil does not reflect its bioavailability in soil (Hung et al., 2009), and thus the BCFs of pharmaceuticals with different soils give no direct insight to the efficiency of pharmaceutical uptake into plants. In contrast, the concentration in pore water serves as a reasonable basis to evaluate the accumulation potential of pharmaceuticals in soil-plant systems. $BCF_{pore\ water}$ could also facilitate the comparison of pharmaceuticals uptake by plants from soils by minimizing the effects of soil sorption. To further clarify this point, BCF_{soil} data of triclosan in radish from this test and a previous study were thus compared in five different soils (Fu et al., 2016b). As illustrated in Figure S5, the BCF_{soil} of triclosan in radish roots varied among five soils by up to 17.5 times between soil A (BCF_{soil} = 2.10 g/g) and soil D (0.12 g/g), with the detailed data given in Table S6. On the other hand, the corresponding $BCF_{pore\ water}$ data could also obtained from Fu et al. 2016b, by using $BCF_{pore\ water} = BCF_{soil} \times K_d$, where the soil K_d values were provided from another report of the same authors using the same soils (Fu et al., 2016a). As shown in Figure S5, the triclosan $BCF_{pore\ water}$ values (41.1-87.7 mL/g) varied within a factor of 2.2 among five soils (detail in Table S6), which sharply narrowed the variation relative to that of the corresponding BCF_{soil} data.

3.3. Relationship between Pharmaceutical Properties and Root Uptake

295 The previous hydroponic studies suggested that the neutral form of organic chemicals
296 generally favors root uptake (Briggs et al., 1982; Tanoue et al., 2012; Trapp, 2000; Wu et al., 2013).
297 To further characterize the relationship between the uptake and pharmaceutical properties in soil-
298 plant systems, pH-adjusted octanol-water partition coefficient (D_{ow}) was used to account for the
299 lipophilicity of neutral speciation of pharmaceuticals in soil pore water (Table 1). Both soil and
300 pore water-based log BCF values are plotted against log D_{ow} for all studied pharmaceuticals. The
301 relationship of log $BCF_{pore\ water}$ vs. log D_{ow} (R^2 = 0.48) or log BCF_{soil} vs. log D_{ow} (R^2 = 0.04) is
302 showed in Figures 2A and 2B. These results suggest that partitioning of pharmaceuticals in neutral
303 speciation is not the singular uptake driving force for the accumulation of the investigated
304 pharmaceuticals in roots. The ionic pharmaceutical species could also contribute to the uptake and
305 accumulation in the radish roots.
306 Root uptake of anionic chemicals could be inhibited by the negative electrical potential
307 across plant cell membranes (between −71 and −174 mV), which might repulse anionic
308 pharmaceuticals to approach the cell surfaces (Trapp, 2009). In this study, soil pore water pH value
309 was ~8.1 at which the majority of sulfadiazine (92.5%), sulfamethoxazole (99.6%) and monensin
310 (100%) were anionic, thus limiting their penetration into plant cells, as evidenced by a low
311 bioaccumulation in radish roots ($BCF_{pore\ water}$ < 1.0 mL/g). Carbadox, acetaminophen, and estrone
312 were present in soil pore water primarily in neutral form (> 95%). These chemicals could pass
313 through the cell membrane resulting in relatively higher $BCF_{pore\ water}$, 1.5 mL/g for carbadox (log
314 D_{ow}= -1.22), 6.6 mL/g for acetaminophen (log D_{ow}= 0.44), and 23.1 mL/g for estrone (log D_{ow}=
315 3.13).
316 Cationic chemicals could be attracted to plant root cell membranes via electrostatic
317 interaction with negatively-charged plasmalemma (Inoue et al., 1998; Trapp, 2009). Ion trapping

could enhance the accumulation of cationic pharmaceuticals in plants due to the alteration of chemical speciation in cell organelles (Trapp, 2004). For example, trimethoprim (weak organic base with pK_a = 7.12) existed primarily in neutral form (> 90%) in soil pore water (pH = 8.1). The neutral trimethoprim could easily enter plant root cells, and be ionized in vacuole where pH is ~5.5 (Trapp, 2000, 2009). The majority of trimethoprim is present as cationic species (> 97%) in the vacuole, and could be trapped in vacuole because less effective to cross the membranes. This could be responsible for the observed relatively high accumulation of trimethoprim in roots ($BCF_{pore\ water}$ = 4.3 mL/g) in spite of its low log D_{ow} = 0.86.

Among the 14 pharmaceuticals measured in radish roots, acetaminophen, caffeine, carbamazepine, lamotrigine, carbadox, estrone and trimethoprim were present primarily in neutral form (> 90%) in soil pore water. A strong positive correlation was found between log $BCF_{pore\ water}$ and log D_{ow} (R^2 = 0.94) (Figure 2C), suggesting that partitioning could be the primary factor affecting their accumulation in radish roots. This is consistent with the findings from the previous study of uptake of neutral pharmaceuticals by vegetables from hydroponic solution (Wu et al., 2013). Hyland et al. (2015b) calculated the BCFs based on the chemical concentration in irrigation water, and found the positive correlation between log BCF and log D_{ow} for six pharmaceuticals and three flame retardants in both lettuce and strawberry roots grown in soils (R^2 = 0.78). However, in this study, the poor relationship was observed between log BCF_{soil} and log D_{ow} for these neutral pharmaceuticals (R^2 = 0.03) (Figure 2D), revealing that $BCF_{pore\ water}$ is more appropriate to describe the distribution of pharmaceuticals in soil-water-plant systems, rather than the bulk soil-based BCF.

In addition to charged species and hydrophobicity, the bioaccumulation of pharmaceuticals could also be affected by chemical molecular weight (MW), plant physiology, metabolism, exposure time, and plant growth rates, etc. For example, MW is considered as another factor that

associate with the membrane permeability (Kumar and Gupta, 2016; Topp et al., 1986). Studies on diffusion have indicated that the compounds with MW > 500 g/mol have the restricted membrane permeability (Camenisch et al., 1998), while the compounds with MW > 1000 g/mol are impossible to be absorbed by cells (Sanderson et al., 2004). In this study, the MW of 15 pharmaceuticals is in the range of 151.16-916.10 g/mol (Table 1), among the 14 measured chemicals, 12 compounds with MW < 500 g/mol and 2 compounds with MW > 500 g/mol. Ten out of 12 compounds with MW < 500 g/mol (acetaminophen, caffeine, carbamazepine, lamotrigine, estrone, triclosan, trimethoprim, lincomycin, and oxytetracycline) had the greater $BCF_{pore\ water}$ (1.34-45.9 mL/g) than that of the 2 compounds with MW > 500 g/mol (monensin and tylosin) (0.26-1.0 mL/g). As shown in Figure 2A, tylosin with the highest MW (916.10 g/mol) showed the lowest $BCF_{pore\ water}$ (< 0.32 mL/g) even though the most of this antibiotic presented in the pore water as neutral form (~69%) with the intermediate lipophilicity (log D_{ow}, 1.47). The low $BCF_{pore\ water}$ of tylosin was also reported in lettuce (< 0.1 mL/g) and carrot (< 0.54 mL/g) (Boxall et al., 2006). The relative high MW of tylosin limiting its permeability across the cell membranes may account for the low bioaccumulation in vegetables.

3.4. Pharmaceuticals Translocation

Many pharmaceuticals in plant roots can be transported upwards to aerial tissues via xylem driven by transpiration stream, and the magnitude can be quantified by translocation factor (TF). In this study, acetaminophen, oxytetracycline, triclosan and tylosin showed less translocation from roots to leaves with TF < 1 (Figure 3A). Monensin and 17 β-estradiol were not detected in radish leaves. The TF values for other nine pharmaceuticals were > 1, indicating their strong translocation

364 from roots to leaves. No apparent relationship was observed between log TF and log D_{ow} (Figure
365 3B). This is consistent with the previous hydroponic study in which no correlation between log TF
366 and log D_{ow} was found for the pharmaceuticals with log D_{ow} between -3 and 4 (Wu et al., 2013).
367 However, Tanoue et al. (2012) observed that the root-to-leaf translocation is more effective for the
368 pharmaceuticals with moderate hydrophobicity i.e. $1 < \log D_{ow} < 3$. However, our experimental
369 results showed that the hydrophilic caffeine manifested the highest translocation (TF = 36.1). The
370 relatively high transpiration stream concentration factor of caffeine could lead to the higher
371 accumulation in plant leaves (Garvin et al., 2015).

372 The poor relationship between log TF and log D_{ow} suggests that other factors could
373 influence the translocation processes such as the electrostatic interaction with ionizable
374 pharmaceuticals (e.g., ion trapping), plant physiology, molecular size, and in-plant metabolism.
375 For example, ion trapping may decrease the translocation of lamotrigine from roots to leaves.
376 Carbamazepine and lamotrigine exhibit the similar log D_{ow} (2.45 and 2.57, respectively) and MW
377 (236.27 and 256.10 g/mol, respectively). Both chemicals existed as neutral form in the pore water
378 and had the similar $BCF_{pore\ water}$ (~11 mL/g). However, the TF of carbamazepine (~8.0) was about
379 4 times greater than that of lamotrigine (~2.0). Lamotrigine is a weak organic base ($pK_a = 5.34$);
380 after neutral species entered the root cell, lamotrigine could be dissociated and accept protons in
381 the cell vacuole (pH ~5.5). In the vacuoles, ~41% of lamotrigine was positively charged, which
382 could be trapped in vacuoles or interact with the negatively charged cell walls. This process could
383 largely reduce the translocation of lamotrigine to radish leaves, compared to the neutral
384 carbamazepine. The less translocation of lamotrigine relative to carbamazepine was also observed
385 in sweet potato, carrot, tomato, and cucumber (Goldstein et al., 2014; Malchi et al., 2014).
386 Goldstein et al. (2018) demonstrated that the transpiration stream concentration factor of

carbamazepine (~0.7-0.9) in cucumber was about 4.6 times higher than that of lamotrigine (~0.1-0.25), which is similar to the TF difference (~4 times) in radish between the two chemicals. The TF values of intermediate hydrophobic compounds monensin (log D_{ow} = 1.65) and tylosin (log D_{ow} = 1.47) was 0 and 0.4, respectively, which are much less than the predicted transport based on the hydrophobicity (Tanoue et al., 2012). The relatively large-sized monensin and tylosin with MW> 500 g/mol could limit their transport across the cell membrane and enter xylem, hence decrease their accumulation in leaves (Limmer and Burken, 2014).

3.5. Pharmaceutical Distribution in Soil and Relation to Plant Uptake

The K_d, $T_{1/2}$, and residual fractions of pharmaceuticals at day 35 are reported in Table 2. The tested soil demonstrated a range of sorption capacity for the fifteen pharmaceuticals as indicated by the K_d values from 0.3 to 316 mL/g. The half-lives ranged from 5.0 to >35 days, and the concentration profiles of pharmaceuticals in bulk soil and pore water over time are plotted in Figure S6. Pharmaceutical with strong sorption to soil and/or short half-life is generally less bioavailable to plant uptake. For example, 17 β-estradiol had relatively strong sorption to soil (K_d = 34.9 mL/g) and a rapid degradation rate ($T_{1/2}$ = 7.5 days), as a result, little 17 β-estradiol was found in radish. In contrast, carbamazepine was weakly sorbed by soil (K_d = 4.2 mL/g) and highly persistent in soil ($T_{1/2}$ > 35 days, 78.4 % remained after 35 days). Therefore, a large fraction of carbamazepine remained in soil and pore water, which is readily available to root uptake leading to the relatively high accumulation of carbamazepine. This could partially explain the high concentration of carbamazepine (e.g., up to 400 ng/g) found in various vegetables irrigated with treated wastewater (Goldstein et al., 2014; Malchi et al., 2014; Paltiel et al., 2016; Wu et al., 2014).

Soil pore water is the media to move pharmaceuticals into plants. Pharmaceutical concentration in soil pore water could be estimated using sorption cofficient (*K)* obtained from another independent batch equilibration experiment (detailed in SI) in which $C_{pore\ water} = C_{soil} / K$ (Chiou et al., 2001). The *K* values used here were calculated from the slope of sorption isotherm of pharmaceutical by the tested soil (Figure S7 and Table S6). To evaluate the impact of sorption and desorption of pharmaceuticals in soils to the uptake by radish, the $BCF_{pore\ water}$ values were estimated using $BCF_{soil} \times K$, and then compared to the measured $BCF_{pore\ water}$ (Figure 4). The predicted $BCF_{pore\ water}$ values are within 3.0 times of difference compared to the measured $BCF_{pore\ water}$ for all the measured pharmaceuticals at both day 28 and 35, except for estrone and lincomycin are within 3.0-5.5 times of difference. Recall that the measurement of sorption isotherm (to obtain *K* values) was equilibrated for 48 hours, while plant uptake experiment was conducted for 35 days. The sorption of pharmaceuticals in the pot experiments (without plant) at different sampling intervals during the 35-day studies are also compared to the 48-hour sorption equilibration isotherms (Figure S7). The results revealed that distribution of most pharmaceuticals between soil and water in the 35-day study is similar to the sorption of 48-hour equilibration. The good agreement between the measured and the predicted $BCF_{pore\ water}$ indicates that soil-sorbed pharmaceuticals could quickly establish sorption/desorption equilibrium with soil pore water (< 48 hours). Therefore, pharmaceutical desorption from soil is not the limiting factor governing the uptake of pharmaceuticals from soil to radish. These results provide the basis for assuming the fast sorption equilibration of pharmaceuticals between soil and pore water when modeling the movement of pharmaceuticals from soil to pore water for plant uptake.

4. Conclusion

This study reveals that pharmaceuticals could enter plant from contaminated soil, and sorption and biodegradation in soil are the determinants of the bioavailable amounts of pharmaceuticals to plant uptake. The comparison of the bulk soil-based BCF_{soil} and pore water-based $BCF_{pore\ water}$ suggests that the pharmaceuticals in pore water represent the more effective fractions for plant uptake than those sorbed by soil. In addition, the good positive correlation (R^2 = 0.93) between $\log BCF_{pore\ water}$ and $\log D_{ow}$ vs. the poor correlation between $\log BCF_{soil}$ and $\log D_{ow}$ (R^2 = 0.03) for neutral pharmaceuticals indicate that pharmaceuticals in pore water is more appropriate for developing the relationships for predicting the accumulation in plants. We therefore highly recommend $BCF_{pore\ water}$, instead of BCF_{soil}, be used to evaluate the distribution of pharmaceuticals in soil-plant systems. Anionic pharmaceuticals generally showed less uptake than neutral pharmaceuticals. "Ion trapping" effects may enhance the accumulation of basic pharmaceuticals accumulation in the roots but limit the transport to leaves. Our results indicate that pharmaceutical in pore water is an important factor to control their uptake by food crops from contaminated agricultural soils. The results help to better understand the common processes of pharmaceutical transport and distribution in soil-water-plant systems through land application of biosolids or animal manure. However, the experiment may not well mimic the processes of plant uptake of pharmaceuticals via irrigation with treated wastewater. The human dietary intake of these pharmaceuticals via radishes seems to be small, as the measured amounts are much lower than the amount of single medical dose (usually in the range of 10–200 mg). However, little is known about the long-term risks of exposure to the mixture of pharmaceuticals and metabolites. Therefore, more studies are still needed to warrant better understanding of pharmaceutical transport, uptake and metabolism in soil-plant systems.

Acknowledgement

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Appendix A. Supporting Information

Additional description is available regarding analytical methods, soil-pore water distribution coefficient, pharmaceuticals concentration in plant tissues, sorption measurement using batch equilibration method, radish biomass, BCF values, TF values, and water transpiration, Comparison between the 48 hours sorption isotherms and long term (35 days) sorption isotherms in greenhouse experiment.

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Tables and Figures

Table 1. Summary of molecular weight (MW), *n*-octanol–water partition coefficient (log K_{OW}), pH-adjusted octanol–water partition coefficient to the basis of neutral speciation (log D_{OW}), acidic dissociation constant (pK_a), and fraction of neutral and ionic pharmaceutical speciation in soil pore water (pH ≈ 8.1).

Pharmaceutical	MW (g/mo1)	log K_{ow}[a]	log D_{ow}	pK_a	Neutral fraction (%)[i]	Ionic fraction (%)[i]
Acetaminophen	151.16	0.46	0.44	9.38 (acid)[a]	95.2	4.8 (anion)
Caffeine	194.19	-0.07	-0.07	–	100	–
Carbamazepine	236.27	2.45	2.45	2.3 (acid), 13.9 (base)[b]	100	–
Sulfadiazine	250.28	-0.09	-1.21	2.01 (base),6.99 (acid)[c]	7.5	92.5 (anion)
Sulfamethoxazole	253.28	0.89	-1.49	1.6 (base), 5.7 (acid)[d]	0.42	99.6 (anion)
Lamotrigine	256.10	2.57[e]	2.57	5.34 (base)[e]	99.8	0.2 (cation)

Carbadox	262.22	-1.22	-1.22	1.8 (base), 10.5 (acid)[c]	99.6	0.4 (anion)
Estrone	270.37	3.13	3.13	10.77 (acid)[h]	99.8	0.2 (anion)
17 β-estradiol	272.38	4.01	4.01	10.71 (acid)[h]	99.8	0.2 (anion)
Triclosan	289.54	4.76	4.36	7.9 (acid) [a]	39.8	60.2 (anion)
Trimethoprim	290.32	0.91	0.86	7.12 (base) [a]	90.1	9.9 (cation)
Lincomycin	406.54	0.2	0.08	7.6 (base) [a]	75.1	24.9 (cation)
Oxytetracycline	460.43	-0.9	-1.76	3.23 (acid), 7.32 (acid), 9.11 (base)[f]	13.7	86.3 (anion)
Monensin	692.87	5.43	1.65	4.3 (acid) [a]	0.02	100 (anion)
Tylosin	916.10	1.63	1.47	7.73 (base)[g]	69.1	30.9 (cation)

[a] From TOXNET database: http://toxnet.nlm.nih.gov/index.html, [b] Dodgen et al.(2015), [c] Chuang et al. (2015), [d] Tanoue et al. (2012), [e] Malchi et al. (2014), [f] Sassman and Lee (2005), [g] Boxall et al. (2006), [h] Lewis and Archer (1979), and [i] calculated on the pH-pK_a relationship.

Table 2. Soil-water distribution coefficient (K_d), half-life ($T_{1/2}$), and residual fractions of pharmaceuticals in soil at the end of experiment (35 days). The values are the average of nine soil samples at three soil water contents (mean ± standard deviation, n = 9).

Pharmaceutical	K_d (mL/g)[a]	$T_{1/2}$ (days)	Residual fraction (%)
Acetaminophen	0.5 ± 0.1	6.1 ± 0.1	1.6 ± 0.1
Caffeine	7.5 ± 1.3	8.6 ± 0.5	7.5 ± 1.1
Carbamazepine	4.2 ± 0.5	>35	78.4 ± 2.4
Sulfadiazine	0.8 ± 0.1	8.0 ± 0.2	2.1 ± 0.2
Sulfamethoxazole	0.3 ± 0.0	7.2 ± 0.4	1.5 ± 0.2
Lamotrigine	3.0 ± 0.2	27.8 ± 1.1	31.5 ± 3.1
Carbadox	15.4 ± 0.6	>35	58.5 ± 1.4
Estrone	116.3 ± 20.3	10.5 ± 0.2	9.9 ± 0.9
17 β-estradiol	34.9 ± 1.8	7.5 ± 0.1	3.6 ± 0.3

Triclosan	316.2 ± 21.9	>35	70.7 ± 2.7
Trimethoprim	25.2 ± 3.1	>35	55.0 ± 0.8
Lincomycin	1.9 ± 0.2	5.0 ± 0.2	0.6 ± 0.1
Oxytetracycline	33.6 ± 1.5	29.0 ± 1.2	33.9 ± 1.4
Monensin	3.5 ± 0.3	14.3 ± 0.5	18.5 ± 0.8
Tylosin	9.7 ± 0.3	>35	50.9 ± 2.7

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682 [a] Average the data sampled at day 1, 3, 7, 14, 21, 28 and 35 of the radish-free controls.
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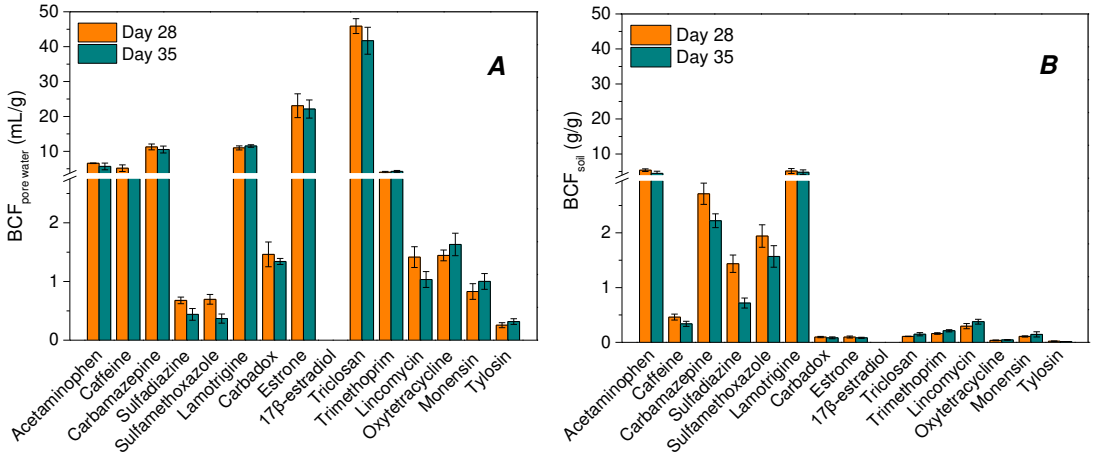

684

685 **Figure 1**. Bioconcentration factors (BCF) of pharmaceuticals in radish roots on the basis of their
686 concentrations in pore water (A) and in bulk soil (B). The values are the average of nine radish roots samples
687 collected at the three soil water contents (one sample per pot, n = 9). The error bars represent the standard
688 deviations.

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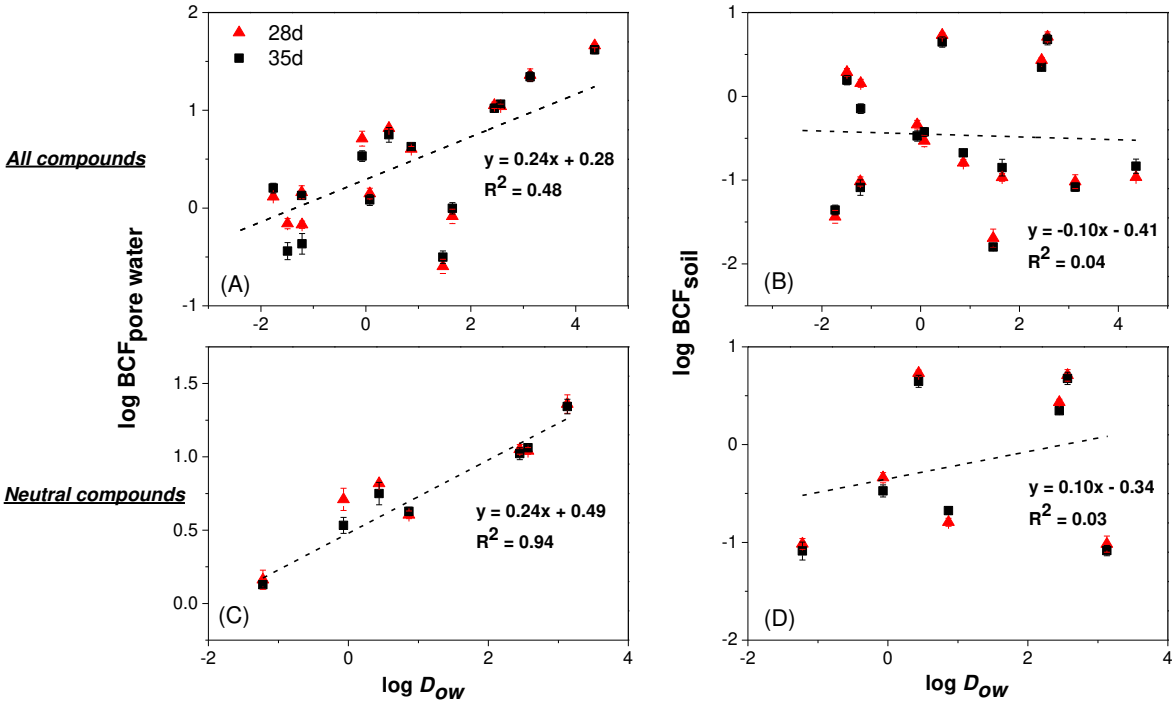

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691 **Figure 2**. Linear relationship between log BCF of radish roots and log D_{ow} for all measured pharmaceuticals

692 (A and B) and the neutral pharmaceuticals (C and D).

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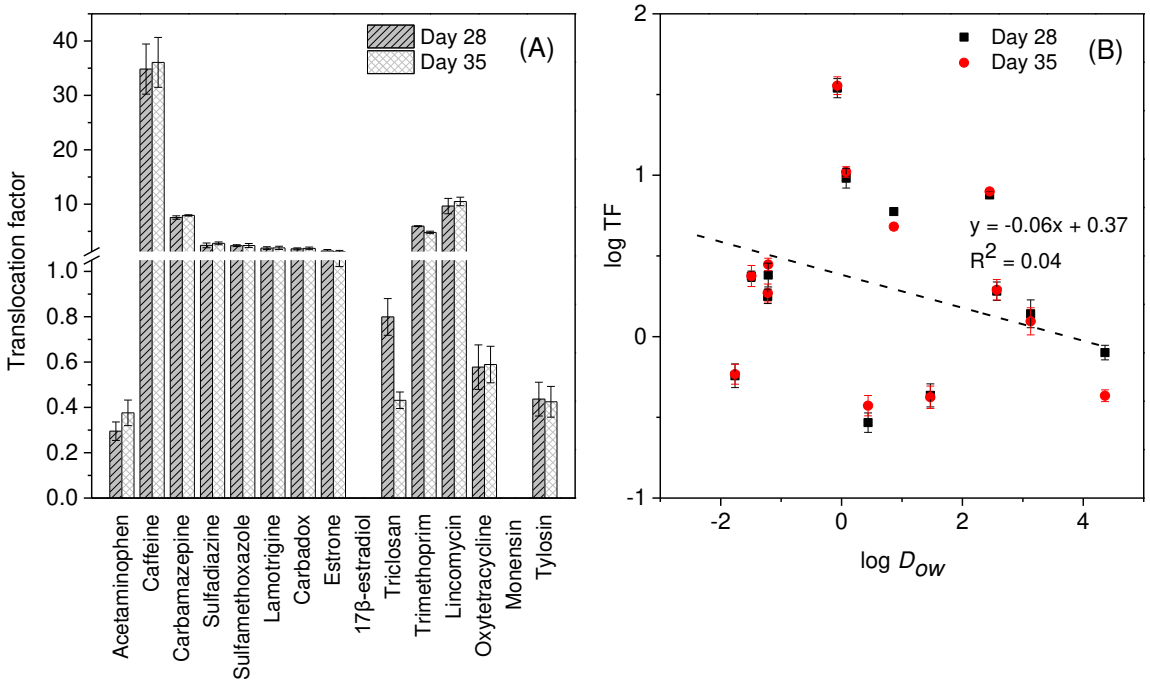

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705 **Figure 3**. (A) Translocation factor (TF) of pharmaceuticals, and (B) relation between log TF and log D_{ow}.
706 The values are the average of nine radish growing at three soil water contents. The error bars represent the
707 standard deviation (one sample per pot, n = 9).
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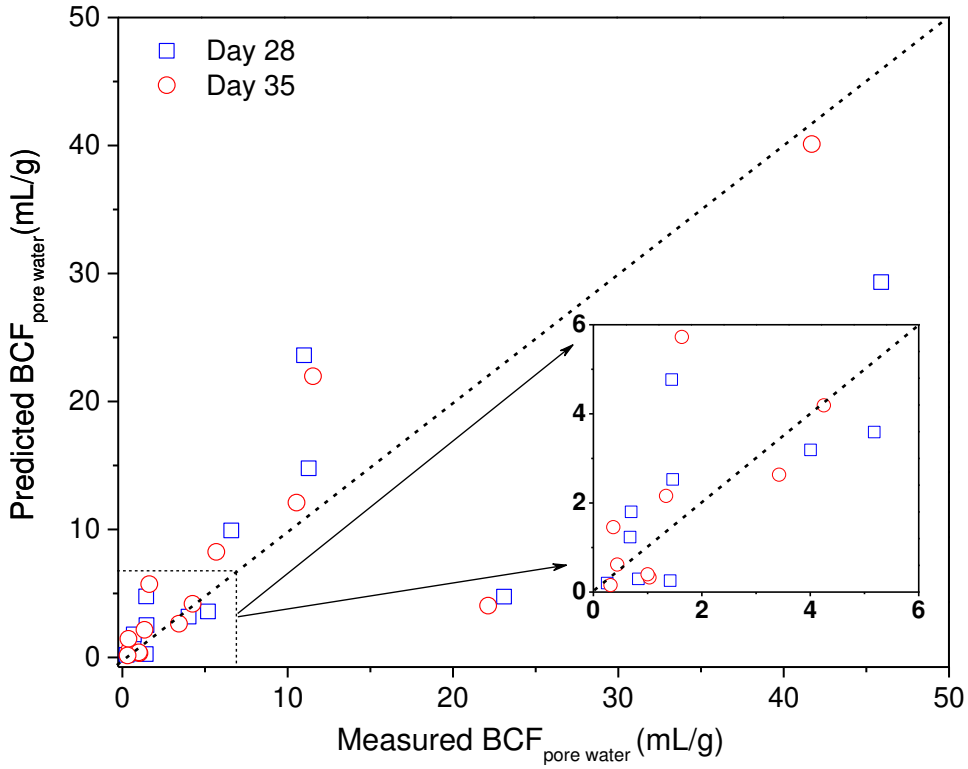

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724 **Figure 4.** Comparison between predicted and measured pore water-based bioconcentration factors (BCF

725 $_{pore\ water}$) of pharmaceuticals in radish roots.

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