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Fate and Uptake of Pharmaceuticals in Soil–Plant Systems

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Supporting Information

ABSTRACT: Pharmaceuticals have been detected in the soil environment where there is the potential for uptake into crops. This study explored the fate and uptake of pharmaceuticals (carbamazepine, diclofenac, fluoxetine, propranolol, sulfamethazine) and a personal care product (triclosan) in soil–plant systems using radish (*Raphanus sativus*) and ryegrass (*Lolium perenne*). Five of the six chemicals were detected in plant tissue. Carbamazepine was taken up to the greatest extent in both the radish (52 μg/g) and ryegrass (33 μg/g), whereas sulfamethazine uptake was below the limit of quantitation (LOQ) (<0.01 μg/g). In the soil, concentrations of diclofenac and sulfamethazine dropped below the LOQ after 7 days. However, all pharmaceuticals were still detectable in the pore water at the end of the experiment. The results demonstrate the ability of plant species to accumulate pharmaceuticals from soils with uptake apparently specific to both plant species and chemical. Results can be partly explained by the hydrophobicity and extent of ionization of each chemical in the soil.

KEYWORDS: *plant uptake, pharmaceuticals, fate, soil, bioavailability, carbamazepine, diclofenac, fluoxetine, propranolol, sulfamethazine, triclosan*

INTRODUCTION

Worldwide, pharmaceutical use has been on the increase for the past century[1−3] and will continue to increase into the future with the development of new medicines to cure recently discovered diseases as well as previously untreatable conditions. Following use by the patient, active pharmaceutical ingredients (APIs) and their metabolites are excreted to the sewerage system. They are then typically transported to a wastewater treatment works, where, depending on their molecular structure and physicochemical properties, they can be either degraded by biological treatment processes or released to the environment in effluents or sorb to sludge.[4−8] The soil environment will therefore be exposed to APIs and their metabolites when sludge from treatment processes is applied to land as an agricultural fertilizer or when soil is irrigated with reclaimed wastewater effluent.[9−13] While only a few studies have explored the occurrence of APIs in the soil environment, available data indicate that a range of API classes, including nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants, and antibacterial agents do occur in soils in concentrations up to the low mg/kg level.[9−15]

Because of detection of pharmaceuticals in soils, concerns have been raised over the potential for these substances to be taken up into human food items and to pose a risk to human health.[16,17] A number of studies have demonstrated the uptake of pharmaceuticals used in human and veterinary medicine into plants.[16−24] Studies have explored the uptake and translocation of a variety of APIs with a particular focus on the antidepressant drug fluoxetine and antibacterial chemicals including sulfamethazine, sulfamethoxazole, and trimethoprim into numerous plant species including root and shoot crops such as soybean, lettuce, and carrot.

Many of the previous plant uptake studies have been done at unrealistic exposure concentrations. Studies typically have looked at uptake only with no attempt being made to understand the temporal fate of the pharmaceutical in soil matrices. Without understanding the dynamics of the distribution and fate of the pharmaceuticals in the soil, it is difficult to establish relationships between the properties of pharmaceuticals and uptake. This study was therefore initiated to explore the fate, distribution, and uptake of a range of pharmaceuticals in soil–plant systems. This work consisted of a fate study (with no plants) and an uptake study performed on two crop species with five pharmaceuticals and an antimicrobial personal care product. The compounds were selected to cover a diverse range of physicochemical properties (Table 1).

MATERIALS AND METHODS

Analytical grade carbamazepine (>98% purity), diclofenac (>98% purity), fluoxetine (>98% purity), propranolol (>99% purity), sulfamethazine (>99% purity), and triclosan (>97% purity) were obtained from Sigma-Aldrich (Sydney, Australia). Deuterated forms of selected study compounds (carbamazepine-d_{10} (99.8% purity), diclofenac-d_4 (98.5% purity), fluoxetine-d_5 (99.4% purity), propranolol-d_7 (99.6% purity), and triclosan-d_3 (98.6% purity) were purchased

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Table 1. Selected Properties of Test Chemicals

test chemical	therapeutic use	chemical formula	molecular weight (g/mol)	pK_a	log K_{ow} [a]	log D_{ow} [b]
carbamazepine	anticonvulsant	$C_{15}H_{12}N_2O$	236.27	N/A	2.5	N/A
diclofenac	anti-inflammatory	$C_{14}H_{11}Cl_2NO_2$	296.15	4.0	4.5	2.30
fluoxetine	antidepressant	$C_{17}H_{18}F_3NO$	309.33	10.1	4.1	0.19
propranolol	beta-blocker	$C_{16}H_{21}NO_2$	259.34	9.5	3.5	0.19
sulfamethazine	antibacterial	$C_{12}H_{14}N_4O_2S$	278.32	7.4	0.9	0.87
triclosan	antimicrobial	$C_{12}H_7Cl_3O_2$	289.54	8.1	4.8	4.80

[a]Un-ionized form of the drugs; [b]at pH 6.25.

from TLC Pharmachem (Vaughan, Canada) for use as internal standards in the chemical analyses.

Tepko soil (obtained from near Tepko township in South Australia) was used for both the plant uptake and fate studies (pH 6.25, EC 0.09 dS/cm, OC 1%, CEC 5.2 cmol(+)/kg, 0.6% moisture, clay 8%, 3% silt and 89% sand). The soil was not cropped and had not previously received biosolid or wastewater applications. Test soil was obtained from the top 10 cm depth and prior to testing was air-dried and then sieved to 2 mm to ensure homogeneity.

Ryegrass seeds (*Lolium perenne*, Guard variety) were obtained from Seed Services (SARDI, South Australian Research and Development Institute) and radish seeds (*Raphanus sativus*, Cherry belle variety) were from Mr Fothergills (Sydney, Australia).

Fate Study. For each study chemical, duplicate pots of soil (200 ± 5 g) were spiked with aliquots of 1 g/L (in acetone) solution to give a nominal concentration of test compound of 10 mg/kg. This concentration, which is higher than concentrations expected in the environment, was chosen to enable detection of the study compounds in the soil pore water. Following spiking, soil was mixed by hand to ensure a homogeneous distribution of the test chemicals; pots were then left for 2 h in a fume cupboard to evaporate off any solvent. Blank control pots were also prepared. Plants were omitted from fate study pots because previous research has demonstrated that the presence of plants results in no significant differences in compound dissipation in soils either by uptake or enhanced degradation and therefore would not significantly influence our fate study.[17] Pots were then kept in controlled conditions (14 h light (23 °C) 10 h dark (15 °C)) until time of sampling. Moisture content adjustments were made on a daily basis, by addition of deionized water (DI), to ensure levels remained at 60% of the soil maximum water holding capacity (MWHC) (for methods see Supporting Information, section 1.1). Sampling points were 0 h, 1, 3, 7, 14, 40 days. At each sampling point, duplicate pots were removed, and the soil pore water was extracted. Extractions were done by taking 2 × 25 g portions of soil from each pot and placing these on top of a glass wool insert in 2 × 25 mL disposable plastic syringes. Syringes were placed in plastic centrifuge tubes and centrifuged at 3500 rpm for 45 min. The resulting pore water collected in the two centrifuge tubes for each single sample was combined into one sample and centrifuged again at 15 000 rpm for an additional 30 min and then transferred to vials ready for analysis. Soil samples (sampled directly from the fate pots) were also taken and stored at −20 °C for later analysis.

Uptake of Pharmaceuticals into Plants. Plastic pots containing 500 ± 5 g and 200 ± 5 g were prepared for use in uptake studies with radish and ryegrass respectively. Pots were prepared in triplicate for each pharmaceutical and plant type and spiked as per the fate study to give a final soil concentration of 1 mg/kg. This concentration, which is at the high end of reported concentrations for pharmaceuticals in soil and at the lower end of concentrations used in previous uptake studies, was chosen to maximize the likelihood of detection in plant tissue while maintaining a degree of realism. Solvent and blank controls were also prepared in triplicate. Soils were then left for 48 h to equilibrate before a total of 6 and 16 seeds were initially added to each pot for radish and ryegrass respectively, which were then lightly covered in test soil.

Plants were left to grow for 6 weeks in a growth chamber under the same conditions as the pots in the fate study. Pots were arranged in a randomized order (specific positions were determined based on a random number generator in Microsoft Excel). A similar watering regime to that used in the fate study was adopted to maintain moisture levels at 60% of the MWHC. After 50% germination (when the seedling was visible through the soil), plants were fed Ruakura nutrient solution, where 5 mL was applied per 250 g soil twice weekly (for three weeks) instead of the DI water. After 3 weeks, addition of nutrient solution continued with one 5 mL application of nutrient solution per 250 g of soil per week (for nutrient solution preparation, see Supporting Information, section 1.2). When 80−90% of plants had germinated (approximately day 11), the radish plants were thinned to leave behind three seedlings. This was to ensure maximum for growth potential in order to gather enough biomass for the chemical analysis.

At harvest, loose soil was removed from around the radish plant to allow for the intact removal of the whole radish. The radish plant was thoroughly rinsed in deionized water to remove any soil residues, patted dry with paper towel, weighed, and divided up into root and above ground biomass, and these were then reweighed separately. For the ryegrass, after the maximum height of the plants from each treatment was measured, the above ground plant material was cut away, rinsed in DI water, patted dry, and then weighed. All plant samples were cut into smaller pieces and then freeze-dried and stored at −20 °C until extraction for residue analysis. Soil was also taken from the plant pots, at the end of the uptake study, for analysis.

Pharmaceutical Analysis. *Extraction from Soil and Plant Material.* Pharmaceutical compounds were extracted from soils and plants using validated methods chosen for their high percentage recoveries (Supporting Information, section 1.3). Prior to plant and soil extractions, 1 mg/g of deuterated stable isotope standard was added to their respective samples (100 μg/L stock solution in acetone). Since stable isotopes were unavailable for sulfamethazine, control plants and control soil samples were spiked with a known amount of sulfamethazine to determine recoveries. For the soil extraction (i.e., soil taken directly from the pots), 5 mL of methanol was added to 1 g of soil (wet weight) and 1 g of sand. After addition of the solvent, the test tubes were vortexed for 1 min and then ultrasonicated for 15 min. Lastly, the tubes were centrifuged for 30 min at 1500 rpm, and the supernatant was removed. The extraction process was repeated with a further addition of 5 mL of methanol and then 5 mL of acetone. The supernatants from the three extractions were combined and then evaporated to dryness before being reconstituted in 1 mL of methanol, sonicated for 5 min and then transferred into LC-MS/MS vials for analysis.

For the plant extractions, sand (1 g) was added to 1 ± 0.1 g of plant material for each of the samples and 5 mL of extraction solvent (70:30 acetonitrile/Milli-Q water solution) was then added to the test tube. After addition of the solvent, the test tubes were vortexed for 1 min and then ultrasonicated for 15 min. The samples were then centrifuged for 30 min at 1500 rpm, and the supernatant was removed and the process was repeated for two further extractions. The combined extracts (15 mL) were diluted with Milli-Q to make a maximum solvent concentration of 10%, and the extract was then applied to an Oasis HLB (Waters Corporation) 6 mL 200 mg solid phase extraction (SPE) cartridge that had been preconditioned with Milli-Q water and methanol. The cartridges were left to dry under a vacuum, washed with 10% methanol in Milli-Q water, and eluted with 2× methanol (3 mL) and 1× dichloromethane (3 mL). The eluates were combined and evaporated to dryness under a nitrogen stream and reconstituted in 1

mL of methanol. Lastly, the test tubes were sonicated for 5 min ready for the extract to be transferred into LC-MS/MS vials.

LC-MS/MS Analysis. Cleaned-up extracts were analyzed for the pharmaceuticals by LC-MS/MS using a ThermoFinnigan TSQ Quantum Discovery Max (Thermo Electron Corporation). HPLC separation was performed with a Kinetex C18 100 × 2.1 mm i.d. (2.6 μm particle size) column (Phenomenex, USA) with a mobile phase flow rate of 0.3 mL/min. The mobile phase composition consisted of two eluents which were (A) formic acid (0.1%) and (B) acetonitrile using a binary gradient program over 12 min. The relative flow of 0.1% formic acid was 95% for 2 min, 20% after 3 min, 2% at 4 min, and held for 3 min until 7 min before returning to 95% by 9.5 min. MS/MS analysis was undertaken using atmospheric pressure electrospray ionization (ESI) in both positive and negative ionization modes. Spray voltage was 5000 V, and source collision induced dissociation was −12 V in positive ESI and −4000 and 10 V for negative ESI, with the ESI capillary line maintained at 350 °C and collision gas (Ar) pressure set at 1.5 mTorr. More details of the analytical method pertaining to each compound are summarized in Supporting Information, section 1.4. Qualitative and quantitative analysis of compounds was based on retention time, multiple reaction monitoring (MRM) of two product ions, and the ratios between the product ions.

Isotopes were used to account for recovery (loss of analytes during sample preparation and matrix effects); however, isotopes were unavailable for sulfamethazine. Sulfamethazine spiked matrix samples were extracted and run throughout the analysis and compared with sulfamethazine standards in a clean matrix to determine the extent of ion suppression or enhancement. Lower limits of quantitation (LOQs) were derived using guidelines proposed by the USEPA.[25]

Data Analysis. *Soil Degradation.* Concentrations of pharmaceuticals in soil and pore water were plotted against time of sampling. Where there was a significant difference in concentration to that measured at 0 days (for methods see Statistical Analysis section), three kinetic models were used to fit the data: a simple first-order degradation kinetic (SFO; eq 1) model, a first-order multicompartment model (FOMC; eq 2),[26] and a biexponential first-order model (BFO; eq 3).[27] Model parameters were optimized according to recommendations by FOCUS using the least-squares method with Microsoft Excel Add-Inn Solver.[27]

$$C_t = C_0 e^{-kt} \tag{1}$$

$$C_t = C_0(1 + \beta t)^{-\alpha} \tag{2}$$

$$C_t = C_{t1} + C_{t2} = C_{01}e^{(-k1t)} + C_{02}e^{(-k2t)} \tag{3}$$

where C_t is the concentration of pharmaceutical remaining in soil (μg/g) after t (days), C_0 is the initial concentration of pharmaceutical (μg/g), k is the rate of degradation (day^{-1}), β is the location parameter, α is a shape parameter determined by coefficient of variation k values. For eq 3, $C_{t1} + C_{t2}$ is the total amount of pharmaceutical applied at time t = 0 (in two compartments), C_{01} and C_{02} is the amount of chemical applied to compartment 1 and 2 respectively, and k_1 and k_2 are independent decay rate constants for compartments 1 and 2 respectively. Models used specific to each pharmaceutical, parameter, and measurement to assess the goodness of fit for the optimized parameters are outlined in Supporting Information, section 1.5. For SFO and FOMC model fits, the time it took for a 50 or 90% decline in the concentration of the pharmaceutical (DT_{50}, DT_{90}) could then be calculated from the model fits (Supporting Information, section 1.5.1). For BFO models, no analytical solution exists to calculate degradation end points.

Uptake Factors. Measured concentrations for each of the pharmaceuticals taken up by the radish and ryegrass were used to calculate soil and pore water-based uptake factors (UFs). UFs were derived using concentrations in the soil, pore water, and plant material (eqs 4−6).

$$UF_{soil} = \frac{C_p}{C_s} \tag{4}$$

$$UF_{pore\ water} = \frac{UF_{soil}}{K_d} \tag{5}$$

$$K_d = \frac{C_s}{C_{pw}} \tag{6}$$

where UF_{soil} is the soil-based UF, $UF_{pore\ water}$ is the soil pore water-based UF, C_p is the concentration in plant material, C_s is the concentration associated with the soil particles (i.e., total soil concentration corrected for the concentration in the pore water), C_{pw} is the concentration in the pore water, and K_d is the average soil sorption coefficient for each pharmaceutical calculated across seven sampling points in the fate study.

Statistical Analysis. Statistical analysis of the data was performed using Sigma Plot (v.11.0). A one-way ANOVA (significance level 0.05) was employed to assess differences in plant biomass (dry weight) between plants grown under treated soil and controls. Additionally, a one-way ANOVA (p = 0.05) was employed to assess any differences in concentration of the pharmaceuticals in the soil and pore water over 40 day exposures, with additional comparisons between sampling points assessed by Holm−Sidak pairwise comparison. To determine which pharmaceuticals showed a significant difference in concentration between radish leaf and ryegrass, t test's were performed. Prior to all tests, the data were tested for normality and equal variance by performing a Shapiro−Wilk and Levene−Mediane test, respectively.

RESULTS AND DISCUSSION

Fate Study. Over 40 days, average K_d values ranged from 0.99 to 121.88 L/kg and increased in the order of sulfamethazine < carbamazepine < fluoxetine < diclofenac < propranolol < triclosan (Table 2). Some of the study compounds persisted in the soil throughout the 40 day uptake period, while others were readily dissipated (Figure 2; Table 3). There was no significant difference between measured concentrations at 0 and 40 days for carbamazepine (p = 0.026), fluoxetine (p = 0.162), and propranolol (p = 0.757). Triclosan dissipated from the soil after 14 days (p = 0.004). Concentrations of diclofenac (p = 0.032) and sulfamethazine (p = 0.013) significantly decreased after 1 day and were undetectable after 3 days. The dissipation rates of these three compounds was fast (0.06−1.4 day^{-1}; Table 3); compound degradation followed single first-order kinetics, and corresponding DT_{50} values were 0.5, 0.99, and 11.55 days for diclofenac, sulfamethazine, and triclosan respectively.

The persistent nature of carbamazepine, fluoxetine, and propranolol is consistent with previous research findings.[9,28−30] The observed degradation of triclosan is also consistent with previous research which has suggested a half-life of 18 days.[31] Results presented in this study show that in less than 40 days only 10% of the applied triclosan remained in the soil (Supporting Information, section 1.5). This is probably due to the transformation of triclosan to methyl triclosan.[13,32] Previous fate studies have also shown that diclofenac is not persistent and readily biodegradable from soils as a result of chemical mineralization.[15,33] The half-life observed in this study (0.5 days) is therefore comparable to previous findings of <5 days[33] and considerably faster than observations by Xu et al.,[34] who reported DT_{50}'s ranging from 3.1 days (loamy sand) to 20.4 days (silty loam) (Table 3). Dissipation of sulfamethazine has been observed in previous research, although the average half-life was longer at 18.6 days than reported in this study (Table 3).[35]

Even though diclofenac and sulfamethazine were not detectable in whole soil extracts after 3 days, detectable concentrations of these chemicals in the pore water were seen

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Table 2. Average Soil Concentrations Measured at the End of the Experiment from Soils Collected from the Plant Pots, Soil–Water Partition Distribution Coefficients (K_d) Values Calculated during Fate Study and Calculated Uptake Factors (UF) for Ryegrass, Radish Bulb, and Leaf[a]

pharmaceutical	radish soil (μg/g)	ryegrass soil (μg/g)	soil K_d (L/kg: average 21 days)	ryegrass UF_{soil}	radish leaf UF_{soil}	radish bulb UF_{soil}	ryegrass $UF_{pore\ water}$	radish leaf $UF_{pore\ water}$	radish bulb $UF_{pore\ water}$
carbamazepine	0.71	0.46	7.85	65.26	60.59	8.28	8.31	7.71	1.05
diclofenac	0.07	0.05	12.40	6.82	11.53	5.39	0.55	0.93	0.43
fluoxetine	0.47	0.55	8.39	0.08	0.10	0.36	0.01	0.011	0.043
propranolol	0.16	0.21	79.44	11.04	0.91	1.20	0.14	0.011	0.015
sulfamethazine	<LOQ	0.01	0.99	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
triclosan	9.31	0.05	121.88	37.59	0.10	0.12	0.31	0.0008	0.001

[a]Plant concentrations used for calculations are on a dry weight basis.

Table 3. Summary Statistics from Soil and Pore Water Dissipation Modeling[a]

	pore water					soil				
pharmaceutical	model	DT_{50} (days)	DT_{90} (days)	rate constants	r^2	model	DT_{50} (days)	DT_{90} (days)	rate constants	r^2
carbamazepine	*b*	>40	>40			*b*	>40	>40		
diclofenac	FOMC	19.65	2.57×10^3	$\alpha = 0.79$, $\beta = 0.34$	0.88	SFO	0.50	1.64	(1.4)	0.99
fluoxetine	*b*	>40	>40			*b*	>40	>40		
propranolol	*b*	>40	>40			*b*	>40	>40		
sulfamethazine	BFO			C01 = 91 C02 = 9 $k_1 = 0.85$ $k_2 = 0.017$	0.99	SFO	0.99	3.29	(0.7)	0.99
triclosan	*b*	>40	>40			SFO	11.55	38.38	(0.06)	0.97

[a]More detailed table including model fit provided in Supporting Information, section 1.5. [b]No significant difference between 0 and 40 day measured concentrations; therefore, data were not modeled to determine degradation rates.

for the full duration of the fate study (Figure 2). By 40 days, concentrations of all test chemicals remaining in the pore water decreased in the order carbamazepine > fluoxetine > sulfamethazine > propranolol > triclosan > diclofenac (Figure 2). With the exception of sulfamethazine on 0 days, carbamazepine concentrations were consistently the highest in the pore water (1321–3129 μg/L) over 40 days (Figure 2). Sulfamethazine concentrations were initially high (2932–6502 μg/L); however after 1 day, concentrations dropped to 832–2683 μg/L, after which they decreased at a slower rate. Unlike soil dissipation, pore water dissipation did not follow first-order kinetics. Models instead included first-order multicompartment model (FOMC; eq 2)[26] and a biexponential first-order model (BFO; eq 3) (Table 3). Pore water concentrations decreased significantly in the diclofenac ($p = 0.016$) and sulfamethazine studies ($p = < 0.001$) resulting in DT_{50}'s < 20 days (Table 3) in comparison to DT_{50}'s for the remaining compounds of >40 days. While triclosan dissipated rapidly from the soil, pore water concentrations were not significantly different at any of the sampling points over 40 days ($p = 0.266$).

Plant Uptake. Plants contain ion channels and enzymes which could also be potentially targeted by pharmaceuticals and may initiate a response such as inhibition in the transport of essential elements required for plant growth for example.[36] Previous research has highlighted the potential for pharmaceuticals to induce toxic effects on plants.[22] Dose response relationships with plants grown under triclosan treatment have been noted starting at 0.44 mg/L in hydroponic studies[24] and low observed effect concentrations (LOECs) seen at 0.74 mg/kg after plant growth in quartz sand.[37] In this study, however, no observed effect on plant growth was noted for any of the treatments in comparison to the controls ($p = 0.08–0.966$) for both radish and ryegrass, probably due to the more realistic exposure concentrations that were used. This is in support of previous research where concentrations of carbamazepine in root tissue ranging between 202–426 μg/kg yielded no observed effect on ryegrass aerial plant growth (Supporting Information, section 1.6).[38]

Previous research has demonstrated metabolism of carbamazepine within the bean and leaf.[17,39] Therefore, in our study it is possible there may have been some transformation of parent compounds; however potential metabolite products were not quantified, and the results presented focus on the parent compounds. Five of the six test chemicals were taken up in detectable quantities into radish and ryegrass (Table 2; Figure 1). The degree of uptake varied across pharmaceuticals and plant species. With the exception of propranolol, greater uptake into radish was seen after combining the concentrations in the bulb and leafy parts compared to ryegrass. For both radish and ryegrass, carbamazepine was taken up to the greatest extent with measured concentrations of up to 52 μg/g dwt in radish leaf (Figure 1). While sulfamethazine was taken up by both plants, this was consistently below the LOQ (Supporting Information, section 1.4.1). Therefore, both radish leaf and radish bulb accumulated chemicals in the order of carbamazepine > triclosan > diclofenac > propranolol > fluoxetine, whereas chemicals accumulated in the ryegrass in the order of carbamazepine > propranolol > triclosan > fluoxetine > diclofenac (Figure 1).

In the propranolol exposure, there was very high uptake into the ryegrass, but this was not mirrored in the radish leaf where concentrations were some 16 times lower ($t_{(4)} = 6.38$, $p = 0.003$) (Figure 1). For the remaining pharmaceuticals, concentrations in the radish leaf and ryegrass were not significantly different (carbamazepine $t_{(4)} = 2.28$, $p = 0.09$;

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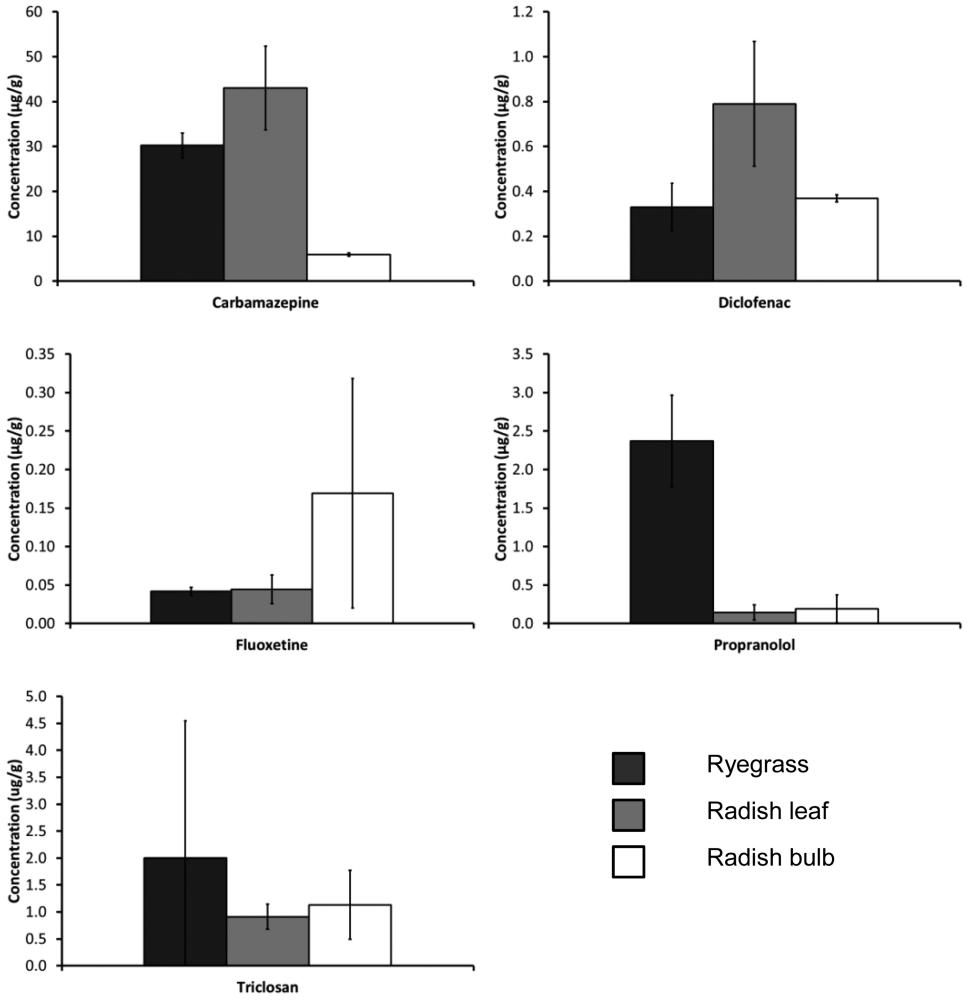

Figure 1. Uptake of carbamazepine, diclofenac, fluoxetine, propranolol, and triclosan into ryegrass, radish leaf, and radish bulb after plants were grown from seed in pharmaceutically spiked soil for 40 days. Average concentrations (dry weight) provided with error bars representing the standard error. Sulfamethazine uptake was below LOQ.

diclofenac $t_{(4)} = 2.69$, $p = 0.06$; fluoxetine $t_{(4)} = 0.24$, $p = 0.82$; triclosan $t_{(4)} = 0.34$, $p = 0.75$).

Greater fluoxetine uptake into the roots was observed in this study (170 ng/g dwt) in comparison to research by Wu et al.[17] where fluoxetine root concentrations were <22.2 ± 5.3 ng/g after exposure via biosolids application. The amended soil concentration in the Wu et al.[17] study was lower (0.07 mg/kg) than the current study, whereas in an earlier study Redshaw and colleagues saw fluoxetine uptake by *Brassicaceae* tissue cultures from a hydroponic setup comparable to the results from our study at 0.26−0.49 µg/g.[23]

Uptake Factors. The greatest UF_{soil} values for the ryegrass, radish leaf, and radish bulb were obtained in the carbamazepine treatments, with values of 65.3, 60.6, and 8.28, respectively (Table 2). In comparison, relatively small UF_{soil} values were found for fluoxetine (0.08−0.36) (Figure 1). Calculated $UF_{pore\ water}$ range between 0.01−8.31, 0.0008−7.71, and 0.001−1.05 for the ryegrass, radish leaf, and radish bulb respectively (Table 2). Similar to UF_{soil} carbamazepine exposure resulted in the highest $UF_{pore\ water}$ in the ryegrass, radish leaf, and radish bulb. Triclosan had the lowest $UF_{pore\ water}$ in the radish leaf (0.0008) and bulb (0.001), whereas fluoxetine had the lowest $UF_{pore\ water}$ in ryegrass (0.01).

In comparison to results generated from field experiments (via biosolid application) for carbamazepine uptake into roots and shoots, the results presented in this study are just over double those observed in the field study.[21] Specifically for triclosan, work by Karnjanapiboonwong et al.[40] found greater UFs between the soil and the root in the pinto bean (*Phaseolus vulgaris*), which ranged between 9 and 12, in comparison to UF_{soil} (0.12) and $UF_{pore\ water}$ (0.001) values generated in this study for the radish root. However, in the ryegrass exposure the triclosan UF_{soil} is considerably larger in the present study at 37.6, demonstrating that plant uptake is dependent on both species and compound; such factors are discussed in more detail below.

Potential Factors Influencing the Uptake of Pharmaceuticals. Plant uptake is thought to be heavily dependent on the physicochemical characteristics of the chemical, including Henry's Law constant, water solubility, and octanol−water partition coefficient.[41−44] Dissociation constants are important because they can describe whether a chemical is neutral or ionizable at environmentally relevant pH values. A clear distinction has been made between the plant uptake of neutral chemicals and chemicals that are ionized (electrically charged), and separate models exist to predict uptake of chemicals in both these forms.[45] However, it is important to note the total

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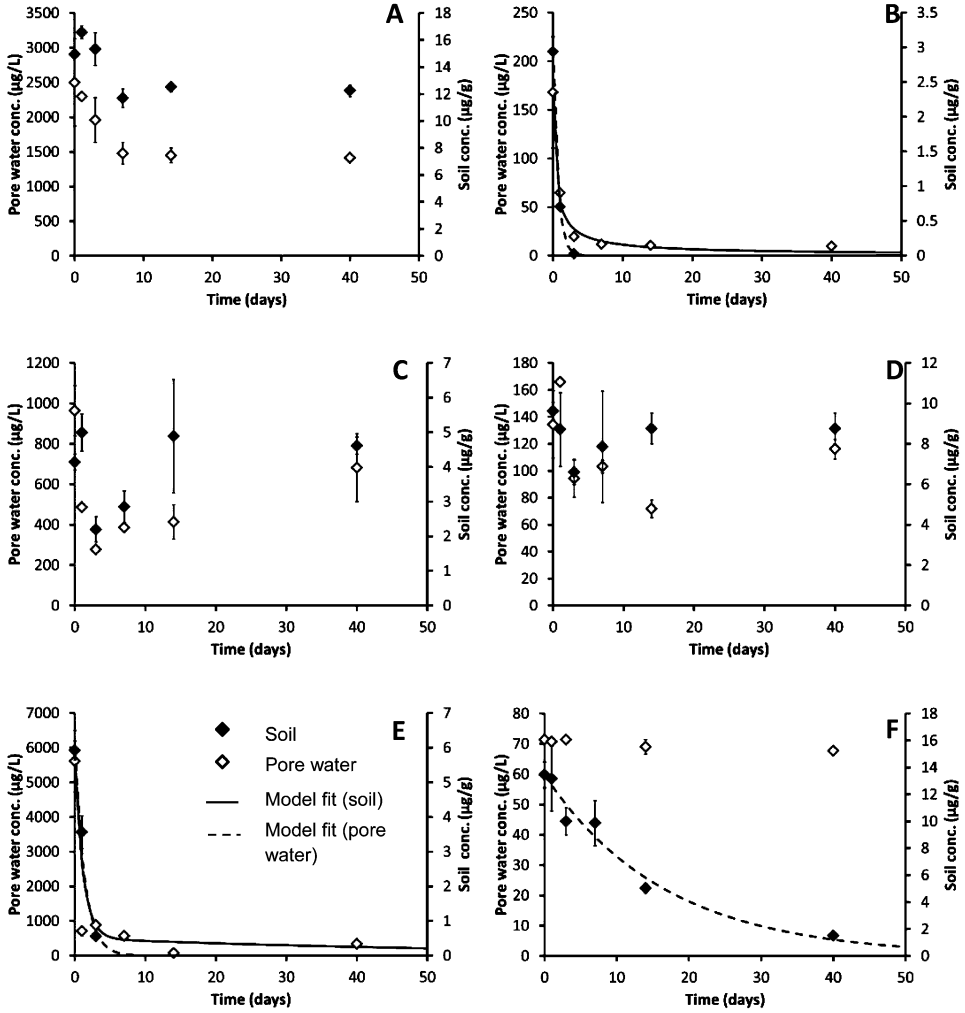

Figure 2. Average measured soil (closed) and pore water (open) concentrations during fate study (40 days) for test pharmaceuticals: carbamazepine (A), diclofenac (B), fluoxetine (C), propranolol (D), sulfamethazine (E), and triclosan (F). Best model fit provided by dashed line for soil and a solid line for pore water where necessary and error bars represent standard error of mean.

concentration in a plant cell comprises neutral, ionic, and complexed forms of a compound.[45] In this study, carbamazepine was the only neutral chemical, whereas the remaining pharmaceuticals were ionizable (Table 1).

For neutral chemicals, hydrophobicity (usually expressed as log K_{ow}) has been postulated to be the most important property involved in the uptake of chemicals into a plant from the soil medium[46] as the degree of uptake appears to be proportional to the octanol–water partition coefficient.[47,48] Briggs et al.[47] proposed that plant uptake of neutral chemicals can be represented by a Gaussian distribution (bell-shaped curve) where maximum translocation of chemicals can be seen at a log K_{ow} ~1.78 in comparison to particularly hydrophobic (high log K_{ow}) and hydrophilic (low log K_{ow}) chemicals which are taken up to a lesser extent.

Carbamazepine is hydrophilic in nature preferring to reside in the aqueous phase rather than attached to the soil particles as demonstrated by the low K_d values discussed above (Table 2). The high concentrations in pore water for the carbamazepine exposure may have played a crucial role in the large amount of uptake observed. However, the consistently high carbamazepine uptake into leafy parts of the plants (<52 μg/g) can more likely be attributable to the log K_{ow} of this neural compound which is similar to the K_{ow} values where maximum uptake of neutral organics is observed.[47] Greater carbamazepine concentrations were noted in the leaf material in comparison to the roots (Figure 1; Table 2) which is in agreement with previous research findings.[17,19,21,38] It appears that the uptake of carbamazepine is passive and not restricted by root membranes. The relatively low hydrophobicity of carbamazepine enables it to be transported by mass flow from the roots and concentrate in the mature and older leaves.[19]

Even though triclosan is slightly ionized at the test soil pH of 6.19 (1.2%), most of the compound will be in the nonionized form. The un-ionized molecule has a log K_{ow} of 4.80, so the low observed uptake for triclosan can be also explained by the fact that it falls on the upper tail of the Gaussian distribution.[47] Small radish $UF_{pore\ water}$ (0.0008–0.001) and UF_{soil} (0.10–0.12) values for triclosan uptake demonstrate that particularly hydrophobic chemicals are not taken up to a great extent in the plant material.

Similar to triclosan, only a small proportion of sulfamethazine (5.8%) would be in the ionized form. On the basis of the Gaussian distribution,[47] the neutral form of sulfamethazine (log K_{ow} of 0.9) would not be expected to enter the root system; it is therefore not surprising that concentrations of sulfamethazine were below the LOQ and that UFs could not be calculated. The rapid dissipation from the soil in the first of the study 3 days

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may have also contributed to the lack of detection of sulfamethazine in plant tissue (Figure 2).

Diclofenac, fluoxetine, and propranolol are expected to be extensively ionized in the test soil (>99%). Previous research demonstrates that plant uptake of the dissociated species of an ionizable compound is lower compared to the un-ionized species.[49,50] As demonstrated in Figure 1, there was up to 600 times less uptake of diclofenac, fluoxetine, and propranolol in the ryegrass in comparison to the neutral pharmaceutical carbamazepine. Specifically for diclofenac, the large ionization combined with the results from the fate study which show extensive dissipation from both the soil and pore water and low measured concentrations can probably explain the minimal uptake of diclofenac into the radish and ryegrass.

Previous research findings demonstrate that some pharmaceuticals have a tendency to accumulate in the roots with the roots acting as a sink for hydrophobic neutral compounds.[17,24] In general, organic chemicals with log K_{ow} > 4 are expected to have high potential for root retention and low translocation capacity.[44] Even though diclofenac and fluoxetine have log K_{ow} > 4 (Table 1), this is in their un-ionized form. As both diclofenac and fluoxetine are extensively ionized at test soil pH log K_{ow} is not applicable and thus cannot explain plant uptake. However log D_{ow} (pH corrected log K_{ow}) could be a better descriptor for ionized chemicals as our results show a general increase in log D_{ow} corresponds to an increase in $UF_{pore\ water}$ and UF_{soil}. For example, fluoxetine and propranolol have low log D_{ow} values (Table 1) and smaller $UF_{pore\ water}$ (<0.14) than diclofenac ($UF_{porewater}$ < 0.93) at log D_{ow} 2.3.

Similar to other studies, our results found differences in uptake between the two crop species.[16,21] Differences may be explained by factors such as degree of root growth, transpiration rates, and the size and shape of the leaf material. Differences in plant lipid contents may also be important as this can affect the sorption of hydrophobic chemicals.[51,52] The reported lipid content of perennial ryegrass ranges between 2−4%,[53] whereas radish bulbs only contain trace amounts of lipid which may explain the lower observed uptake of carbamazepine, diclofenac, and propranolol in the radish (Figure 1). However, similarly to results in the Wu et al.[21] study, differences in plant uptake behavior could not be solely attributable to differences in lipid content between plants.

On the basis of the results presented, the factors that affect the uptake of pharmaceuticals into plants include physicochemical properties of the pharmaceuticals, species type including lipid content, and distribution between above and below ground plant. Previous work has also highlighted that plant uptake can vary between a mixture and single compound exposure,[54] and additional research has also demonstrated that soil properties and the application of biosolids or wastewater irrigation can also affect plant uptake.[17,21,55−57] Interestingly, the persistence of pharmaceuticals in soil can also be influenced by the presence of biosolids, which can ultimately affect plant uptake as well.[29] Therefore to conclude, the uptake of chemicals into plants is a complex process governed by a combination of soil, plant, and chemical factors. However on the whole, the uptake behavior observed in this study makes sense based on the knowledge from previous research.

Human Exposure. Uptake into plants, especially edible crops, may represent an important exposure pathway of these chemicals into the food chain and thus present a risk to humans and livestock which feed on them.[16,58−60] An acceptable daily intake (ADI) value can be used to calculate the amount of a substance, for example, pharmaceuticals, that can be consumed by a human without resulting in appreciable risk to health. For a full explanation of calculated methods to determine the risk to humans from consuming contaminated crops from results in the present study see Supporting Information, section 1.7.

Results show that if all crops consumed were grown in soil containing the selected pharmaceuticals, then humans would not consume levels greater than the ADI for any of the pharmaceuticals in this study (Table 4). It should also be noted

Table 4. Results from a Comparison of Acceptable Daily Intake (ADI) Values for Study Chemicals and Theoretical Crop Concentration (Based on Measured Soil Concentrations and UF_{soil} Calculated in This Study) Shown As a Percentage of ADI[a]

		ryegrass	radish
	soil (mg/kg)	% of ADI in 359.5 g crop	% of ADI in 159 g crop
carbamazepine	0.0065[b]	3.81	0.21
diclofenac	0.00054[c]	0.18	0.06
fluoxetine	0.0067[c]	0.09	0.19
propranolol	0.0004[d]	0.20	0.01
triclosan	0.019[b]	83.80	0.12

[a]With exception of sulfamethazine as plant concentrations were below LOQ. Ryegrass was used as a representative above ground crop species and radish as a representative below ground crop species. [b]Measured soil concentration reference = Duran-Alverez et al., 2009. [c]Measured soil concentration reference = Dalkmann et al., 2012. [d]Measured soil concentration reference = Vazquez-Roig et al., 2012.[10,14,15]

that all crops eaten must be grown in the contaminated soil as our analysis assumed radish leaf and bulb to be representative of all above and below ground crops consumed, which is not currently the case. A safety factor of 100 was also applied to the minimum therapeutic dose to calculate the ADI, and for a large proportion of the population this is not needed, which would make the actual ADI higher than the current threshold.

To date, the health risks from pharmaceuticals in drinking water have been reviewed, and several papers have also computed levels in crops fit for human consumption.[16,61,62] For fluoxetine, a comparison of measured concentrations in drinking water and predicted no effect concentrations in children yielded a ratio of 2.8×10^{-4}, which would infer the risk to humans drinking water contaminated with fluoxetine would be minimal. Indeed, for all APIs evaluated, approximate margins of safety for potential exposures ranged from 30 to 38000.[61] Presently, the risk to humans in terms of contaminated crops is therefore similar to drinking water exposures, in that it is highly unlikely.

However, an important note for the future is that with the growing demand for alternative irrigation resources in water stressed regions and projected increases in the application of sewage sludge on land, pharmaceutical loadings in soil will inevitably increase. The threat posed by pharmaceuticals taken up into crops may therefore be of more concern in the future than based on current exposure levels.

In conclusion, radish and ryegrass can take up a variety of pharmaceuticals and personal care products from spiked soil. On the basis of current exposure levels, however, this uptake does not pose a risk to humans consuming crop grown in contaminated soil. Using a combination of fate study and plant uptake data, it is clear that relationships between plant uptake

and the available fraction of the chemical are key. While a chemical may have a log K_{ow} that fits within the Gaussian distribution correlating with a high propensity for uptake, this clearly is not the only property influencing uptake into plants. The ionizable state of the chemical together with its potential for degradation may result in diminishing concentrations in the soil matrix. The fraction available for uptake may therefore be very small, and, correspondingly, the measured concentrations in the plant material will also be minimal. Interestingly, fate studies data show that while a chemical may dissipate from the soil it can still remain in the pore water. This may hold wider implications for risk assessments and screening techniques as chemicals present in the pore water may still be bioavailable for uptake into an organism.

Our results demonstrate that in some circumstances uptake and distribution of pharmaceuticals and personal care products in a plant can be related to hydrophobicity (K_{ow}) and generally follows a Gaussian distribution, although this is not always the case. The results presented here would suggest that there are different drivers responsible for the uptake between different plant species. It is instructive to note that pharmaceuticals are predominantly ionizable organic chemicals, and in contrast to neutral organics, this is a characteristic that is likely to affect their partitioning behavior in terms of bioavailability, plant uptake, and molecular interaction with soil matrices of variable pH. It therefore may be important to question previous assumptions on plant uptake, and specific models may be required to accurately predict plant uptake which account for species differences, distribution of chemicals in the plant, chemical properties, and the fate of the pharmaceutical in different soil matrices.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed information on preparation of nutrient stock solution, LC-MS/MS methods, parameters for dissipation modeling, and human exposure calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, this article published January 17, 2014 with an incorrect version of Figure 1. The correct version published January 21, 2014.