FACTORS AFFECTING THE CONCENTRATIONS OF PHARMACEUTICALS RELEASED TO THE AQUATIC ENVIRONMENT

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ABSTRACT

Although recent research has demonstrated that pharmaceuticals are widely distributed in the aquatic environment, it is difficult to assess the threat that they pose to drinking water supplies or their rate of attenuation in natural systems without an adequate understanding of the sources of contamination. To identify pharmaceutical compounds of significance to water supplies in the United States, we have reviewed available data on the use of prescription drugs. Results of our analysis indicate that approximately 40 compounds could be present in municipal wastewater effluent at concentrations above 1,000 ng/L and at least 120 compounds could be present at concentrations above 1 ng/L. Important classes of prescription drugs include analgesics, beta-blockers, and antibiotics.

Analysis of a group of the most commonly used pharmaceuticals in the United States indicates that they are ubiquitous in wastewater effluents. We have detected concentrations ranging from approximately 10-3,000 ng/L for high use pharmaceuticals such as beta-blockers (*e.g.,* metoprolol, propranolol) and acidic drugs (*e.g.,* gemfibrozil, ibuprofen). The concentration of pharmaceuticals in effluent from conventional wastewater treatment plants is similar. Advanced wastewater treatment plants equipped with reverse osmosis systems reduce concentrations of pharmaceuticals below detection limits. In addition to removal during biological wastewater treatment, pharmaceuticals also are attenuated in engineered natural systems (*i.e.,* treatment wetlands, ground water infiltration basins). Preliminary evidence suggests limited removal of pharmaceuticals in engineered treatment wetlands and nearly complete removal of pharmaceuticals during ground water infiltration.

INTRODUCTION

During the 1990s, researchers in Germany and Switzerland reported the occurrence of numerous pharmaceuticals in municipal wastewater and in surface waters that receive wastewater effluent (Stan et al., 1994; Hirsch et al., 1996; Stan & Heberer, 1996; Stumpf et al., 1996; Buser et al., 1998a; Buser et al., 1998b; Hartmann et al., 1998; Ternes, 1998; Buser et al., 1999; Hartig et al., 1999; Hirsch et al., 1999; Ternes & Hirsch, 2000). Preliminary results from studies conducted in North America have confirmed the presence of many of the same compounds (Metcalfe & Koenig, 2000; Sedlak et al., 2000; USGS 2001). Despite these findings, our ability to predict the concentrations of pharmaceuticals in receiving waters and in potable water supplies is limited by a lack of understanding of the attenuation mechanisms of pharmaceuticals. To predict the concentrations of pharmaceuticals in the aquatic environment and to design strategies to minimize exposure to pharmaceuticals, scientists and engineers must understand the processes that result in attenuation of pharmaceuticals both in wastewater treatment plants and in engineered receiving waters.

Organic contaminants present in municipal wastewater, such as pharmaceuticals, may be removed or transformed by a variety of mechanisms. In conventional wastewater treatment plants, pharmaceuticals can be removed by sorption to particles or by biotransformation. In advanced wastewater treatment plants, such as those employed prior to indirect potable reuse, pharmaceuticals may be removed by physical separation processes (e.g., reverse osmosis). Finally, when wastewater effluent is discharged to engineered receiving waters, attenuation of pharmaceuticals also could occur through a combination of physical, biological, and photochemical processes.

To develop a better understanding of the factors controlling concentrations of pharmaceuticals in the aquatic environment in the United States, we have studied the sources of pharmaceuticals in municipal wastewater and the effect of different treatment processes on concentrations of some of the most common pharmaceuticals present in municipal wastewater. Results of our research suggest that it may be possible to design cost-effective approaches for minimizing concentrations of pharmaceuticals in the aquatic environment. However, further research will be required to optimize these treatment systems.

ESTIMATION OF PHARMACEUTICAL CONCENTRATIONS IN MUNICIPAL WASTEWATER

As mentioned previously, most available data on concentrations of pharmaceuticals have been collected in Europe. To assess the occurrence of pharmaceuticals in the United States, it is necessary to identify those compounds that are most likely to be present. To accomplish this goal, we have reviewed data on pharmaceutical use in the United States and studies on the occurrence of pharmaceuticals in Europe. The purpose of our review is to identify compounds likely to be present at relatively high concentrations that can serve as indicators for the larger suite of pharmaceuticals.

The first step in identifying pharmaceuticals meriting further study requires us to predict the concentrations of compounds present in water discharged by municipal and agricultural sources. To achieve this goal, we have estimated concentrations in untreated wastewater for the most popular U.S. pharmaceuticals. Estimates were not made for less popular drugs, nonprescription drugs, and drugs used mainly in hospitals (e.g., X-ray contrast media, cancer chemotherapy drugs) because sales data were unavailable.

Our approach for estimating the concentrations of prescription drugs involved dividing the mass of drug excreted by patients by the volume of wastewater discharged to municipal wastewater treatment plants. Calculations were performed for the top 200 prescription drugs listed in a 1998 survey conducted by IMS Health (1999). The top 200 prescription drugs include 136 compounds because some of the drugs contain the same active ingredient. Because numerous assumptions are needed to convert the number of prescriptions administered to the concentration of pharmaceuticals in municipal wastewater, considerable uncertainty is associated with these estimates. Despite the uncertainties, the estimates are useful in identifying pharmaceuticals that are candidates for further study.

Estimation of the concentrations of pharmaceuticals in municipal wastewater required the conversion of the number of prescriptions administered into the mass of compound discharged. Because several formulations are available for each prescription drug, the mass of active ingredient in a dose varies between prescriptions. For example, the β-blocker timolol is prescribed at 40 mg/prescription in an oral formulation and 6 mg/prescription in an eye ointment. To estimate the mass of active drug associated with each dose, we consulted medical reference books (Katzung 1998, PDR 1999) and interviewed a practicing pharmacist who provided information on the most popular form of each prescription of interest. After estimating the mass of active ingredient in each dose of the most popular form of the drug, we estimated the number of doses per prescription. Estimates were made for the maximum and minimum masses per prescription assuming the most common drug formulations. For drugs that were given on a one-time basis (e.g., antibiotics), we assumed that each prescription included a sufficient number of doses to treat the ailment (typically 10 days). For drugs administered on a continuing basis (e.g., beta-blockers, birth control pills) we assumed that each prescription was renewed monthly. The basis for this assumption was the current practices of many health maintenance organizations (HMOs) to refill prescriptions once per month.

After estimating the mass of each drug prescribed, we estimated the concentration present in untreated wastewater (results for those compounds predicted to be present at concentrations above 1,000 ng/L are included in Table 1). The values given in Table 1 represent the geometric mean of estimates based on the upper and lower bound estimates. When excretion data were readily available, we estimated the fraction of the dose excreted in its original form. However, excretion data were not readily available for many drugs, or when the data were available, it was unclear if glucuronide or sulfate conjugates were considered to be transformation products. Since the conjugates appear to be converted back into their original unconjugated forms prior to, or during wastewater treatment, conjugated forms of drugs should be included with the parent compound. As a result of missing or ambiguous data, information on metabolism was only available for 30 percent of the pharmaceuticals in the top 200 list. Therefore, comparisons between estimated concentrations of PhACs are made without consideration of metabolism. No attempts were made to quantify active metabolites.

Estimated concentrations of prescription drugs in untreated wastewater (only the top 49 drugs are included in Table 1) range from less than 1 ng/L to approximately 133,000 ng/L. The estimated concentrations are distributed over a wide range with the majority of compounds estimated to be present at concentrations between 100 and 1,000 ng/L. In general, the compounds expected to be present at the highest concentrations consisted of analgesics (e.g., acetominophen, ibuprofen) and antibiotics (e.g., amoxicillin, cephalexin). Because some of the analgesics on the list also are available as over-the-counter products, their concentrations in wastewater could be considerably higher. Compounds estimated to be present at the lowest concentrations tended to be potent drugs such as hormones (e.g., medroxyprogresterone, equilin). Therefore, compounds

Table 1: Estimated concentrations of popular prescription drugs in untreated wastewater in the United States.

		Excluding Metabolism	Including Metabolism	
Name	**Classification**	**Predicted Wastewater Conc. (1) (ng/L)**	**Predicted Wastewater Conc. (1) (ng/L)**	**Excretion (2)**
acetominophen	analgesic	61,000	53,000	C
ibuprofen	analgesic, anti-inflammitory	37,000		B
amoxicillin	antibiotic	27,000	16,000	D
metformin	antidiabetic	24,000	21,000	D
cephalexin	antibiotic	14,000	12,000	D
nabumetone	analgesic, anti-inflammitory	12,000		F
azithromycin	antibiotics	9,200		J
oxaprozin	analgesic, anti-inflammitory	6,600		B
sodium valproate	anticonvulsant	6,000	2,400	H
gabapentin	anticonvulsant	5,400	5,400	D
carisoprodol	skeletal muscle relaxant	5,100		J
penicillin	antibiotic	4,000		J
sulfamethoxazole	antibiotic	3,800	3,200	G
gemfibrozil	cholesterol lowering	3,400		D
metoprolol	β-blocker	3,100	160	B
ciprofloxacin	antibiotic	3,100	1,400	G
ranitidine	H_2-receptor antagonist	3,000		J
mupirocin	antibiotic	2,800		A
clarithromycin	antibiotic	2,800	680	F
phenytoin	anticonvulsant	2,700		A
diltiazem	calcium channel blocker	2,600	79	A
naproxen	analgesic, anti-inflammitory	2,400		C
verapamil	calcium channel blocker	2,400	85	J
ipratropium	bronchiodiolater	2,400		E
trimethoprim	antibiotic	2,200	1,500	J
tramadol	analgesic	2,200	640	E
cimetidine	H_2-receptor antagonist	2,200	1,000	D
clavulanic acid	antibiotic	2,100	680	E
propoxyphene	opiod analgesic	2,100		J
bupropion	antidepressant	2,100		F
hydrochlorothiazide	diuretic	1,900	1,200	D
troglitazone	antidiabetic	1,800		B
cefprozil	antibiotic	1,700	1,000	J
pseudoephedrine	decongestant	1,600		J
erythromycin	antibiotic	1,500	75	I
atenolol	β-blocker	1,500	1,500	D
sertraline	antidepressant	1,400	180	F
triamterene	diuretic	1,400		J
nefazodone	antidepressant	1,300	13	F
tetracycline	antibiotic	1,200		J
allopurinol	antigout	1,000		F

(1) This calculation was made assuming that the population of the U.S. is 250 million, that each person produces 320 L of wastewater per day, and that the excreted pharmaceuticals are evenly distributed among all wastewater in the U.S.

(2) (A) Extensive metabolism to inactive metabolites
(B) Extensive metabolism, possibly to conjugates
(C) Excreted mostly as conjugates
(D) Excreted mostly in original form (>50%)
(E) Excreted partially in original form (25-50%)
(F) Extensive metabolism to active metabolites
(G) Excreted as mixture of conjugates/original form
(H) Excreted partially as conjugates (25-50%)
(I) Little excreted in urine
(J) Data on metabolism not obtained

References for doses and metabolism:
Katzung, B.G. 1998. *Basic and Clinical Pharmacology.* Stamford, CT: Appleton and Lange.

Physicians' Desk Reference. 1999. Montvale, NJ: Medical Economics Company, Inc.

estimated to be present at low concentrations should not be eliminated from further consideration without considering issues related to potency. However, such compounds will be extremely difficult to detect using conventional analytical techniques.

After considering the predicted concentrations of pharmaceuticals, the availability of suitable analytical techniques and data on the occurrence of pharmaceuticals in Europe, we identified a subset of compounds to serve as indicators for pharmaceuticals in wastewater effluent. In several cases, compounds were included even though they were not expected to be present at high concentrations because they could be analyzed readily with the selected analytical methods. Excluding antibiotics, which are be discussed elsewhere (Huang *et al.*, 2001), our list included six acidic drugs (i.e., diclofenac, gemfibrozil, ibuprofen, indometacine, ketoprofen and naproxen) and three beta-blockers (i.e., metaprolol, nadolol and propranolol).

MATERIALS AND METHODS

Samples collected from wastewater treatment plants and engineered receiving waters were subjected to solid-phase extraction and were analyzed for pharmaceuticals using gas chromatography/tandem mass spectrometry (i.e., GC/MS/MS) and immunoassays. Details of the analytical methods have been, or will be, reported elsewhere. Therefore, we have only provided a brief description of our approach.

Between 1 to 4 liters of samples were filtered through 0.45-µm glass fiber filters followed by solid phase extraction. For the acidic drugs, the sample pH was adjusted to pH less than 2 with sulfuric acid followed by extraction using endcapped C-18 resin. For neutral drugs and beta-blockers, the solid phase consisted of C-18 resin. For hormones, a C-18 Empore disc was used for solid phase extraction.

Samples to be analyzed for acidic drugs or beta-blockers were eluted from the resins using methanol followed by derivitization. For the acidic drugs, we used a diazomethane/diethylether mixture for derivitization. The beta-blockers were derivitized using MSTFA followed by MBTFA. Samples were analyzed by GC/MS/MS using a 30-meter DB-5 column. Internal standards were added to each sample to monitor extraction and derivitization efficiency as well as GC performance. Typical detection limits for pharmaceuticals in wastewater effluent were around 10 ng/L.

Analysis of hormones was performed by modification of a previously published immunoassay approach (Huang & Sedlak, 2000). Samples were eluted from the Empore disc using a methanol water mixture followed by dual column cleanup using gel permeation chromatography followed by reverse-phase chromatography. The detection limit for 17β-estradiol and 17α-ethinyl estradiol was approximately 0.02 ng/L. Confirmatory analysis was conducted using GC/MS/MS.

ATTENUATION OF PHARMACEUTICALS

To assess factors controlling the concentrations of pharmaceuticals in receiving waters, we measured concentrations of pharmaceuticals present after different treatment processes. Additional analyses are underway and we plan on publishing complete results of these studies during the coming year. Therefore, the results presented here should be considered preliminary. However, they do illustrate the relative significance of different mechanisms that can be pursued in more detail as part of future investigations. In the following sections, we describe the attenuation mechanisms and available data for each of the different treatment processes.

Conventional Wastewater Treatment Plants

Two attenuation mechanisms are potentially important for the removal of pharmaceuticals in conventional wastewater treatment plants: (1) sorption to particles followed by settling and removal; and, (2) biotransformation. The relative importance of these mechanisms will be controlled by the configuration of the treatment plant, the physical and chemical properties of the compounds and the concentrations of the compounds.

During primary and secondary wastewater treatment, particles are efficiently removed. Therefore, any pharmaceutical with a high affinity for particles also will be removed in the sludge. (If these compounds are not transformed prior to sludge disposal, they could lead to an additional exposure pathway that is not considered further in this paper.) Sorption of pharmaceuticals to particles present in wastewater treatment plants can occur either via hydrophobic or electrostatic interactions (e.g., ion exchange, surface complexation).

For hydrophobic interactions, the octanol/water partition coefficient is a good predictor of the affinity of the compound for the solid phase. Under the conditions encountered in conventional wastewater treatment plants, only those compounds with octanol/water

partition coefficients greater than approximately 100 will be removed to an appreciable degree (Sedlak et al., 2000). With the exception of the steroid hormones, which have octanol/water partition coefficients of approximately 10,000, few pharmaceuticals meet this criterion. Therefore, we do not expect this mechanism to result in substantial removal of pharmaceuticals.

Sorption of pharmaceuticals via other interactions usually requires the presence of acidic, phenolic, or amino functional groups. Although many of the pharmaceuticals contain such functional groups, removal via these mechanisms is not expected to be significant under the conditions encountered in municipal wastewater. However, some antibiotics appear to undergo sorption via ion exchange reactions.

Removal of pharmaceuticals also can occur via biotransformation. Predicting the relative importance of biotransformation from chemical structure is notoriously difficult. Furthermore, compounds that are metabolized by microorganisms at relatively high concentrations may not be transformed to an appreciable degree when present at the extremely low concentrations encountered in wastewater. Available data from full-scale wastewater treatment plants suggest that certain compounds, such as ibuprofen, are readily degraded while other compounds, such as and carbamazepine, are removed to a much smaller extent (Ternes, 1998; Buser et al., 1999).

Preliminary results from our survey of wastewater treatment plants are consistent with these findings (Figure 1). The horizontal lines included in the figure, which represent our estimate of pharmaceutical concentrations in untreated wastewater (i.e., Table 1), allow us to compare expected influent concentration with observed effluent concentrations. These results indicate that more than 99 percent of the ibuprofen is removed during secondary wastewater treatment while less than half of the gemfibrozil and propranolol are removed during secondary treatment.

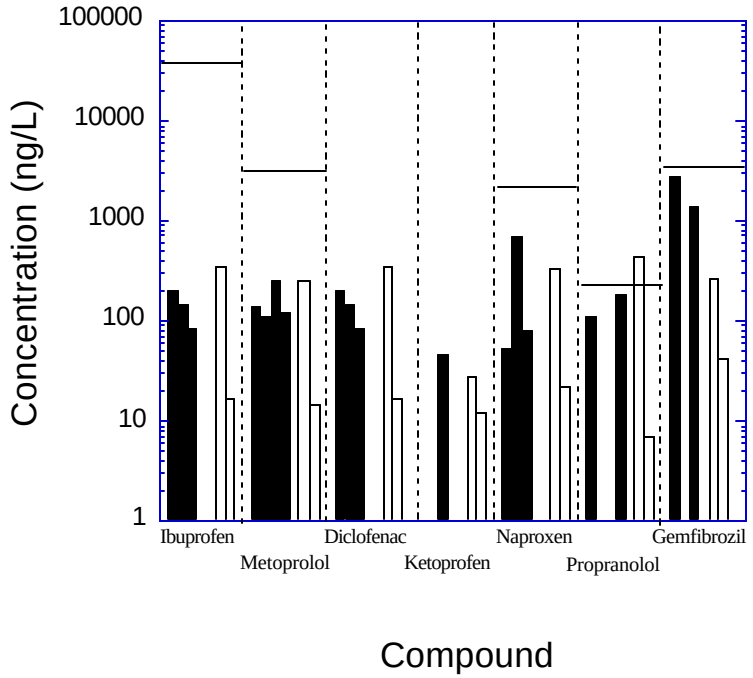

Figure 1: Concentrations of selected pharmaceuticals detected in final effluent collected from secondary (filled bars) and tertiary (hollow bars) municipal wastewater treatment plants. Horizontal lines indicate estimated concentrations in untreated wastewater.

The six pharmaceuticals depicted in Figure 1 were detected in wastewater effluent samples at concentrations ranging from approximately 10 to 3,000 ng/L. Concentrations detected in secondary effluent samples (filled bars) were similar for all four sites. For the two sites that also employed nitification (hollow bars) concentrations at the first site, which is a trickling filter followed by a nitrification tower, were comparable to those detected in the secondary effluent samples; while concentrations detected at the second site, which employed activated sludge followed by nitrification, exhibited significantly lower concentrations.

Advanced Wastewater Treatment Plants

Indirect potable reuse projects equipped with state-of-the-art advanced wastewater treatment plants have been operated in several locations in the United States for over twenty-five years (NAS, 1998; Sedlak et al., 2000). To remove pathogens and chemical contaminants, many of these facilities employ membrane treatment. Currently, the most common configuration for these systems involves the use of lime coagulation or microfiltration to remove colloids followed by reverse osmosis. Because the polar pharmaceuticals should not be associated with particles, we expect little removal to occur during lime clarification or microfiltration. In contrast, reverse osmosis should remove most of the pharmaceuticals that have molecular weights above approximately 200 gm/mole.

Measurements of the concentrations of pharmaceuticals at the West Central Basin Ground water Replenishment Project, an advanced wastewater treatment plant that uses microfiltration and thin-film composite reverse osmosis membranes, are consistent with these expectations (Figure 2). Concentrations of pharmaceuticals measured before and after microfiltration are nearly identical. Concentrations of pharmaceuticals decrease to levels below detection limits after reverse osmosis treatment. These results suggest that full-scale reverse osmosis systems effectively remove these polar pharmaceuticals.

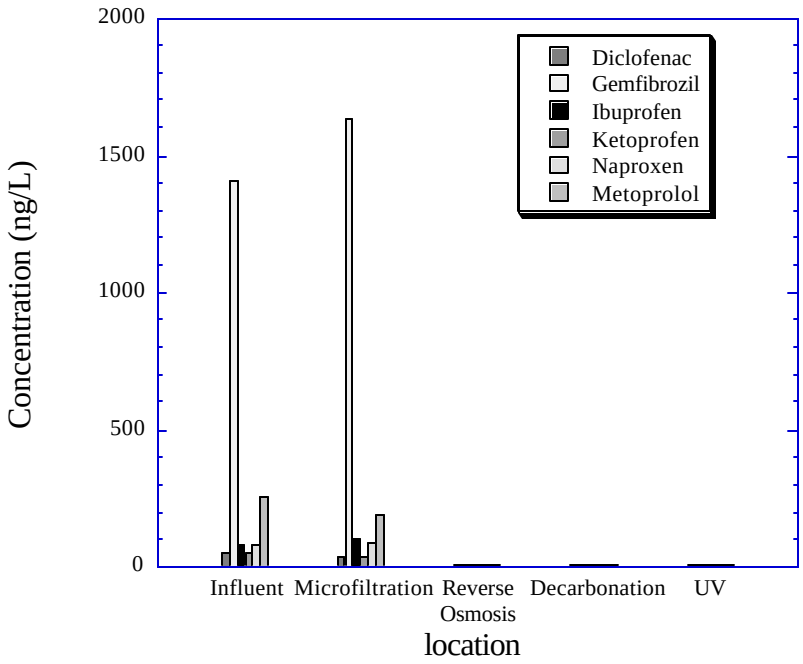

Figure 2: Concentrations of pharmaceutical measured after different unit processes at the West Central Basin Ground water Replenishment Project. After reverse osmosis treatment concentrations, of all pharmaceuticals are below 10 ng/L.

Engineered Receiving Waters

After conventional or advanced wastewater treatment, engineered receiving waters may be used to further attenuate contaminants, especially when water is being reused or discharged into a sensitive aquatic habitat. In the United States, the most common types of engineered receiving waters are surface engineered treatment wetlands and ground water infiltration basins. Although most of the attenuation mechanisms found in wastewater treatment plants also will occur in these systems, changes in environmental conditions (e.g., less organic matter available for metabolism) could alter the rates of transformation reactions. Furthermore, new attenuation mechanisms may also be important in these systems (e.g., phototransformation in wetlands). To assess these processes, we have analyzed concentrations of pharmaceuticals in samples from engineered receiving waters.

In ground water infiltration basins, the microbial community metabolizes many organic compounds (Drewes & Fox, 1999). The biological processes occurring during infiltration, which are sometimes referred to as soil aquifer treatment, could provide a means of removing pharmaceuticals that pass through conventional wastewater treatment systems. To assess the efficacy of soil aquifer treatment systems, we collected samples from the Sweetwater Ground water Recharge Facility, located in Tuscon, Arizona. The facility consists of an infiltration basin that receives secondary wastewater effluent that replenishes a deep aquifer. Samples collected from the recharge pond, a shallow well (screened at 5 meters below the basin) and a deep well (screened at 40 meters below the basin) indicate that little removal occurs during the initial stages of infiltration and that all of the compounds are removed between the shallow and deep well. Because previous studies have indicated that almost all of the water sampled by the deep well originated in the infiltration basin, these data suggest that the pharmaceuticals are attenuated during passage through the aquifer. However, it should be noted that previous sampling of the deep well indicated the presence of several pharmaceuticals at concentrations as high as 50 ng/L (data not shown).

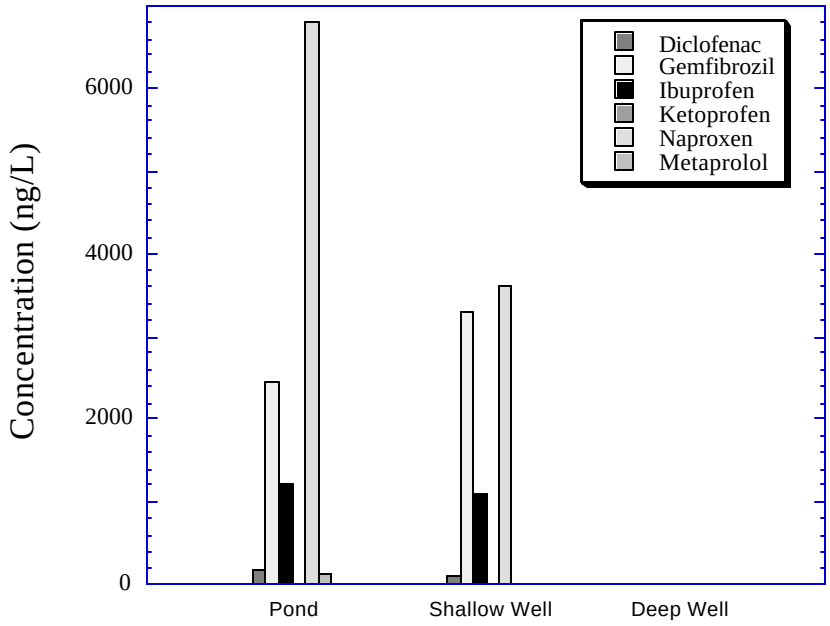

Figure 3: Concentrations of pharmaceuticals measured after ground water infiltration at the Sweetwater Ground water Recharge Site in Tuscon, Arizona. Concentrations of all compounds measured in the deep ground water well were below detection limits.

Pharmaceuticals also could be removed during passage through engineered treatment wetlands. Attenuation mechanisms of potential importance in engineered treatment wetlands include biotransformation, photolysis, and hydrolysis. To assess losses of contaminants during passage through treatment wetlands, we have measured concentrations of pharmaceuticals at locations throughout an engineered treatment wetland that receives nitrified wastewater effluent. Samples were collected at the exit weirs from several wetland cells located along the flow path of the water. Previous tracer studies at the wetland indicate a hydraulic residence time of approximately seven days. Little or no loss of pharmaceuticals was observed during passage through the treatment wetland (data not shown). In contrast, significant losses of the estrogenic hormone, 17α-estradiol were observed: influent concentrations decreased from approximately 2 ng/L in the first pond to less than 0.5 ng/L in the final pond. Because ethinyl estradiol is resistant to biotransformation in activated sludge treatment systems, we hypothesize that the observed transformation is attributable to some other process, such as indirect photolysis.

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