Pharmaceutically Active Compounds in Residential and Hospital Effluent, Municipal Wastewater, and the Rio Grande in Albuquerque, New Mexico

by

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ABSTRACT

This project investigated: 1) the contribution of pharmaceutically active compounds (PhACs) from residential and hospital effluent sources, 2) resultant concentrations of PhACs in the Albuquerque Southside Water Reclamation Plant (SWRP) raw influent and treated effluent, and 3) concentrations of PhACs in the Rio Grande, which receives SWRP effluent. PhACs present in surface waters have been shown to adversely impact organisms (Jobling et al., 1998) and, in the case of antibiotics, perhaps increase resistance to these drugs (Ash, 1999; Eichorst, 1999; Guardabassi et al, 1998; Sternes, 1999).

In this study, ten sample sites were identified and samples collected and analyzed for the presence of 39 PhACs, consisting of 29 non-antibiotic PhACs and 10 antibiotics. The Scientific Laboratory Division of the New Mexico Department of Health (SLD) conducted all analyses. Antibiotic analyses involved solid phase extraction, high performance liquid chromatography, and tandem mass spectrometry while the non-antibiotic PhACs were analyzed using liquid-liquid extraction, gas chromatography, and tandem mass spectrometry.

Six antibiotics (sulfamethoxazole, trimethoprim, ciprofloxacin, ofloxacin, lincomycin, and penicillin G) and caffeine were detected in hospital wastewater (300-35,000 ng/l), while only one antibiotic, ofloxacin, was detected in wastewater from one of the two residential sites (1,300 ng/l). Three antibiotics: sulfamethoxazole, trimethoprim, and ofloxacin were present in both SWRP influent and treated effluent in concentrations ranging from 110 ng/l to 470 ng/l. However, concentrations in the treated effluent were

reduced 20 to 77 percent. No PhACs were detected in the Rio Grande sample upstream of the SWRP discharge, and only one antibiotic, sulfamethoxazole, was detected in the two Rio Grande samples below SWRP.

These results reveal that most of the PhACs analyzed for were absent or at undetectable concentrations in wastewater. However, antibiotics, particularly some sulfonamides and fluoroquinolones, were found at relatively high concentrations in hospital wastewater and were not completely removed by wastewater treatment. In particular, the sulfonamide antibiotic, sufamethoxazole, displayed high persistence and was detected at concentrations of 300 ng/l in the Rio Grande.

1.0 INTRODUCTION

Pharmaceutically active compounds (PhACs) such as analgesics, anti-convulsants, anti-depressants, anti-inflammatories, hormones, and antibiotics can enter municipal and natural water systems via residential or commercial discharges, including hospital effluent. Although PhACs are intended to be utilized by the human body, in some instances as much as 50 to 90 percent of an administered drug may be excreted by the body in a biologically active form (Raloff, 1998). Wastewater treatment facilities vary in their ability to remove PhACs. Consequently, PhACs are released into surface waters where they may adversely impact aquatic organisms (Jobling et al., 1998) and, in the case of antibiotics, perhaps increase resistance to these drugs (Ash et al., 1999; Eichorst et al., 1999; Guardabassi et al., 1998; Sternes, 1999).

In 2000, the New Mexico Environment Department (NMED) and the Scientific Laboratory Division of the New Mexico Department of Health (SLD) initiated a study of PhACs in New Mexico waters. NMED detected a variety of drug residues in 11 of 15 sewage effluent samples and in 4 of 23 surface water samples (McQuillan et al., 2000, 2001, and 2002). Estrogenic hormones were detected in trout and silvery minnow habitats in the San Juan and Rio Grande rivers respectively (McQuillan et al., 2002), at levels that have been shown to cause sexual disruption of wild fish in Europe (Jobling et al., 1998). Antibiotics like those found by NMED in New Mexico sewage effluents (McQuillan, 2002), and in streams worldwide (Heberer et al., 2001; Sedlak and Pinkston, 2001) are of concern due their possible connection to the development of antibiotic-resistant

organisms, the potential for disruption of microbial ecology, complications surrounding development of water reuse technologies, and even increased human health risks (Daughton and Ternes, 1999; Guardabassi et al., 1998; Huang et al., 2001).

The development of antibiotic-resistant bacteria is an increasing concern. Recent studies have found widespread antibiotic-resistant bacteria in the Rio Grande (Sternes, 1999), in several major U.S. rivers (Eichorst et al., 1999), and in wild Canada geese (Ash et al., 1999). The widespread and often inappropriate administration of antibiotics in livestock, pets, and humans has been shown to result in the development of antibiotic-resistant bacteria and is generally accepted to be the primary pathway for proliferation of antibiotic-resistant bacteria in the environment (Shagum, 2003, personal communication, unreferenced).

However, there is concern that long-term, low dose concentrations (ng/l-µg/l) of antibiotics, such as those present in wastewater and surface water, could also result in the development of antibiotic-resistant organisms. Although there is a paucity of literature addressing this potential pathway, one study has shown increased prevalence of antibiotic-resistant Acinetobacter spp. in sewers receiving wastewater effluent from a hospital and a pharmaceutical plant (Guardabassi et al., 1998). Specifically, sewers downstream from the hospital displayed an increased prevalence of bacteria resistant to oxytetracycline, while sewers downstream from the pharmaceutical plant showed an increased prevalence of bacteria resistant to multiple drugs, including sulfamethoxazole. The results of this study and in particular, the findings at the pharmaceutical plant, seem

to lend credence to the concern that antibiotic-resistant bacteria could develop from environmental exposure to pharmaceuticals. However, although concerning, this study alone is not sufficient to determine the relative risk. Consequently, while the presence of antibiotics in wastewater and surface water is discussed widely in the literature as an area of concern it is also identified as a topic in much need of further investigation.

Additionally, in hospital effluent, ciprofloxacin was detected at levels from 3 μg/l to 87 μg /l (Hartmann et al., 1998). Ciprofloxacin, a fluoroquinolone antibiotic, was shown to display high genotoxicity at these concentrations. Genotoxic substances are often also mutagenic and carcinogenic and are therefore especially concerning. Furthermore, the presence of genotoxic antibiotics in hospital effluent is of particular concern for its possible connection to proliferation of antibiotic-resistant organisms. Although several studies have detected the occurrence of antibiotics in hospital effluent (Alder et al., 2003; Feldmann et al., 2003; Hartmann et al. 1998), little is known about their fate or effects in the environment (Guardabassi et al, 1998; Hartmann et al. 1998)

This study investigated hospital and residential effluents for their potentially significant contribution of PhACs to wastewater systems, such as the Albuquerque Southside Water Reclamation Plant (SWRP). Wastewater effluent has been shown to be a primary contributor of PhACs to surface water (Daughton and Ternes, 1999). Surface run-off, mainly from confined animal feed operations, is also a significant contributor of PhACs to surface water, but is not specifically addressed in this study (Daughton and Ternes, 1999).

This professional project was conducted in collaboration with NMED and SLD to investigate: 1) the contribution of PhACs from residential and hospital effluent sources and, 2) the resultant PhAC concentrations in Albuquerque's SWRP raw influent, treated effluent, and in the Rio Grande, which receives SWRP effluent. While it is generally accepted that hospitals are a primary point source for PhACs in water, there is little literature documenting the quantities contributed (Hartmann et al., 1998). In fact, the EPA website identifies the issue of hospital vs. residential contributions of PhACs as one of its top research needs (Daughton, 2002). Additionally, research indicates that sunlight can degrade some PhACs, notably fluoroquinolone and tetracycline antibiotics (Buser et al., 1998; Huang et al., 2001). Given New Mexico's prevalent sunlight, and wide and shallow river morphology, this degradation process is of particular significance.

In prior studies, concentrations of PhACs ranging from 1 ng/l to 100 ng/l seemed to correlate with a region's population density (Raloff, 1998). Similarly, the highest concentrations tended to show up in the smallest rivers, where 50 percent of the water could be sewage treatment effluent (Raloff, 1998). The SWRP effluent is a major contributor of flow in the Rio Grande and is considered the fifth largest tributary to the Rio Grande (Stomp, 2003, personal communication, unreferenced).

The City of Albuquerque plans to divert additional Rio Grande water as part of the San Juan-Chama Diversion Project and Albuquerque Drinking Water Program (City of Albuquerque, 2003). The diversion of approximately 94,0000 acre-feet/year (af/y) will occur in Albuquerque north of Paseo del Norte Blvd. and the return flow of

approximately 47,000 af/y will occur in the Albuquerque South Valley via the SWRP effluent. Operation of the diversion is only planned for conditions when the river flow is large, hence although 15 miles of the Rio Grande will have a diminished flow, this reduction will be small.

Predicting the actual reduction in Rio Grande flow attributed to this change from ground to surface water diversion is a complicated hydrologic process involving connections between the river and groundwater aquifers. However, the City of Albuquerque predicts the effective loss of water in this stretch of the Rio Grande to be only 34,000 af/y, not the full 94,000 af/y. This prediction is based on the expected contribution of additional water to the Rio Grande from the surrounding aquifer once groundwater pumping is reduced.

Ultimately, however, flow in the Rio Grande through Albuquerque will be diminished to some extent while the quantity of SWRP effluent remains the same. Consequently, the flow contribution from the SWRP effluent will be a higher percentage of total river flow, resulting in a greater impact to the water quality of the river. (See Appendix A for calculations of SWRP effluent and Rio Grande flow rates and dilution)

As part of the Albuquerque Drinking Water Program, surface water will be used for drinking. This raises the questions of whether PhACs might be present in the surface water to be used and, if present, will treatment techniques be capable of removing them? Because very little is known about safe allowable limits for drinking water or about the temporal and spatial fluctuations of PhACs in surface waters, this is a significant concern.

While previous studies have found no detectable concentrations of PhACs in drinking water samples in New Mexico (McQuillan, 2000), PhAC have been detected in U.S. municipal drinking water revealing that at least some conventional treatment processes are not fully effective in removing all PhACs (Stackelberg et al., 2003). Additionally, the combined effects of drought and increased diversions could push concentrations of PhACs to levels of concern.

2.0 METHODS

2.1 Selection of PhACs

A total of 10 antibiotics and 29 other non-antibiotic PhACs were selected for testing (Table 1). Selection of PhACs was based on five factors: 1) analytical capabilities of SLD, 2) data identifying the most commonly prescribed drugs in the US (Table 2) and at UNM Hospital in Albuquerque, NM (Achusim, 2003, personal communication; unreferenced), 3) classes of drugs with known and suspected environmental and species impact (Ash et al., 1999; Eichorst et al., 1999; Jobling et al., 1998; McQuillan et al., 2002), 4) classes of drugs that persist in aqueous environments and have previously been detected in wastewater and natural waters (Huang et al., 2001), and 5) PhACs included in previous NMED studies that will offer a comparison group (McQuillan et al., 2001).

Table 1: PhACs investigated in this study

Drug Class	**Non-antibiotic PhACs (29 Total)**
Analgesics	propoxyphene (Darvon)
Anti-Convulsants	phenytoin (Dilantin)
Anti-Depressants	fluoxetine (Prozac), sertraline (Zoloft), amitriptyline, protriptyline, trimipramine maleate, nortriptyline, desipramine, imipramine, doxepin, nordoxepin, paroxetine
Anti-Inflammatory	methyprednisolone, prednisone
Hormones	equilin, 17β-estradiol, estrone, 17α-ethynyl estradiol, medroxyprogesterone, megestrol acetate, mestranol, progesterone, norethindrone, norethynodrel, norgestrel, cholesterol
Other	caffeine, tamoxifen
	Antibiotics (10 Total)
Antibiotics	norfloxacin, lincomycin, oxytetracycline HCl, ciprofloxacin, ofloxacin, trimethoprim, penicillin G. 1/2 – benzathine salt, sulfamethoxazole, penicillin V potassium salt, tylosin tartrate

Table 2: Most commonly prescribed drugs in the United States
(McQuillan et al., 2001; RxList, 2003).

Drug Class	Specific Drugs
Analgesics	hydrocodone, ibuprofen, propoxyphene (Darvon), acetaminophen
Antibiotics	amoxicillin, azithromycin, cephalexin, ciprofloxacin, clarithromycin, penicillin VK
Anti-Convulsants	diazepam, phenytoin (Dilantin)
Anti-Depressants	fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), amitriptyline
Cardiovascular	amlodipine, digoxin, enalapril, lisinopril, furosemide, diltiazem
Hormones	thyroxine, estrogen hormones
Lipid Lowering Agents	atorvastatin, lovastatin, simvastatin

2.2 Selection of Sampling Sites

Locations of sampling sites are presented in Table 3. Sampling sites were selected to address three primary objectives: 1) investigate point source contributions of PhACs from hospital and residential sources, 2) determine removal of PhACs by a well run treatment plant and 3) investigate the occurrence and fate of PhACs in the Rio Grande, upstream and downstream of SWRP.

Contributions of PhACs from hospital and residential sources to wastewater have not been well documented (Daughton, 2002). In this study, sample sites 1-5 were selected to address this issue (Table 3). Hospitals were selected because, while it is generally accepted that they are a significant point source contributor of PhACs, there is little literature documenting the quantities contributed (Hartmann et al., 1998). Three hospitals were selected based on their patient population profiles, ease of accessibility to effluent pipes, and willingness to participate in study. Two residential sites were selected to

Table 3: Locations of sampling sites

Site No.	Sample Site Name	Details of Site Location
1	Presbyterian Hospital	Hospital effluent at NE corner of Silver and Oak St. (manhole)
2	University Hospital	Hospital effluent at NE corner of Lomas Blvd and hospital entrance road (sewer access)
3	VA Hospital	Hospital effluent under overhang at main entrance to hospital (manhole)
4	UNM Alvarado Dormitory	Dormitory effluent south of Campus Dr. and west of loading ramp (manhole)
5	Vista del Rio Assisted Living/Retirement Community	Facility effluent via cleanout pipe located off north side of building at the edge of the NW parking lot (clean-out)
6	SWRP influent	City of Albuquerque laboratory official daily influent sample (called T.P. 2.3 by city)
7	SWRP effluent	City of Albuquerque laboratory official daily effluent sample (called T.P. 2.7 by city)
8	Rio Grande 1	At Los Calabacitas Arroyo, north of Paseo del Norte Bridge; upstream of SWRP discharge
9	Rio Grande 2	Approximately 1.0 mile downstream from SWRP discharge
10	Rio Grande 3	Approximately 1.5 miles north of I-25 interstate bridge; approximately 4.0 miles downstream from SWRP

represent potential contributions from the population at large. The UNM Alvarado dormitory was selected to represent a relatively young population, while Vista del Rio Assisted Living/Retirement Community was selected to represent a more elderly population. The sample collection times for hospitals were selected based on prior research showing that concentrations of PhACs in hospital wastewater vary throughout the day with peaks between 6 a.m. and 10 a.m., and between 6 p.m. and 8 p.m. (Guiliani et al., 1996; Feldmann, 2003, personal communication; unreferenced). By selecting collection times during the potentially peak hours of 6 a.m. to 10 a.m., samples were more likely to contain PhACs.

The SWRP influent and effluent were selected to allow comparison of PhAC concentrations before and after wastewater treatment. Rio Grande 1 sampling site was selected to measure the occurrence of PhACs in the river upstream from the SWRP effluent location. Rio Grande 1 is also near the proposed intake for the City of Albuquerque Drinking Water Program (City of Albuquerque, 2003). The Rio Grande 2 sampling site was located downstream of SWRP effluent, and intended to be just far enough below the discharge point to allow mixing of effluent with river water. The comparison of Rio Grande 1 with Rio Grande 2 allows comparison of Rio Grande waters before and after the addition of SWRP discharge. Rio Grande 3 was selected to offer insight into the fate and persistence of PhACs in the Rio Grande.

2.3 Sampling Protocol

This study was conducted in accordance with the EPA-approved Quality Assurance Project Plan (QAPP) for the NMED (New Mexico Environment Department, 2003). Samples were collected between March 30, 2003 and May 7, 2003.

The sampling at sites 1-5 was performed using an ISCO GLS automated composite sampler (Table 3). At these five sites, forty-eight 125 ml samples were collected in 5-minute increments between 6 a.m. and 10 a.m., resulting in 6-liter composite samples. Each collection was compiled in a 2.5 gallon glass bottle inside the ISCO sampler, surrounded by ice and protected from sunlight. After collection, the composite samples

were transferred to six 1-liter brown glass bottles, stored on ice, and delivered to SLD within 24 hours.

For sampling sites 6 and 7, samples were collected by City of Albuquerque as part of the official sampling events at SWRP (Table 3). Each of these approximate 6-liter composite samples was comprised of approximate 1-liter samples that were collected every four hours and compiled over two consecutive 24-hour periods. The City of Albuquerque lab used three of six liters from each 24-hour sample and donated the remaining three liters for use in this study. Since approximately six liters were required for this study, three liters from the first 24 hour sample remained refrigerated at 4º C and out of sunlight at the City of Albuquerque lab while awaiting the second 24-hour sample. The two 3-liter 24-hour samples were composited and mixed in a large glass jar and then redistributed into six 1-liter brown glass bottles, stored on ice, and delivered to SLD within 24 hours. Although the collection times were dictated by the City of Albuquerque's established protocol, the 48–hour composite sample was ideal as it allowed for capture of a representative sample that accounted for high and low flow periods within a day (Kearsey, 2003, personal communication; unreferenced).

For sampling sites 8-10, six 1-liter grab samples were collected in brown glass bottles, composited and mixed in a large glass jar, and then redistributed into six 1-liter brown glass bottles (Table 3). Samples were collected across the channel and at variable depth profiles (shallow to deep) at each river sampling site based on accepted USGS technique (Kolpin et al., 2002). Samples were stored on ice and delivered to SLD within 24 hours.

Attempts were made by SLD to extract all samples within 48 hours of collection; however, the Rio Grande samples remained refrigerated at 4º C for four days before being extracted.

Equipment and field blanks were collected and analyzed based on the NMED QAPP (New Mexico Environment Department, 2003). The equipment blank involved sampling of three liters of de-ionized water from a glass jar using the ISCO composite sampler. The collected sample was then redistributed into three 1-liter brown glass bottles, and immediately stored at 4º C at SLD. A field blank was collected at the VA hospital site by placing three 1-liter brown glass bottles of de-ionized water (open to the environment) next to the ISCO sampler for the duration of the sampling event. The three 1-liter equipment blank samples were stored on ice and delivered to SLD along with the VA sample. Sample temperature, pH, specific/electrical conductance, and total dissolved solids concentrations were collected and are presented along with other sample site collection details in Appendix B. Rio Grande flow rates were obtained from USGS gage data (USGS, 2003).

2.4 Analytical Methods

In the process of developing the analytical techniques used in this study, SLD encountered difficulties associated with analyses of very low concentrations of PhACs in raw wastewater. Several PhACs originally intended for analysis had to be eliminated due to difficulties associated with extraction and recovery. For instance, erythromycin

appeared to dehydrate resulting in poor recovery due to multiple product formation during MS/MS analyses. Tetracyclines tended to complex with metals making them difficult to extract with Solid Phase Extraction (SPE). Additionally, many of the PhACs were very sensitive to pH such that two different pH extractions had to be conducted for optimum recovery to occur. Although clogging of SPE cartridges was anticipated for the raw sewage samples, no centrifuging was necessary to achieve optimal extraction. Similar difficulties arose with analyses of non-antibiotic PhACs; however, these issues were resolved with prior NMED/SLD studies (Chapman, 2003, personal communication, unreferenced).

Antibiotic samples were extracted using Solid Phase Extraction (SPE) at two pHs. The first set was brought to a pH of 9.5 using 2M ammonium hydroxide, while a pH of 3.5 was achieved for the second set using formic acid. All samples were extracted at both pHs to determine optimum extraction. Extracted samples were concentrated to 1ml. and analyzed by high performance liquid chromatography (HPLC) and tandem mass spectrometry (MS/MS) using Agilent 1100 liquid chromatograph interfaced to Applied Biosystems API 4000 mass spectrometer. (Chapman and Mawhinney, 2003, manuscript in preparation; unreferenced).

The non-antibiotic PhACs were analyzed using techniques developed in previous NMED/SLD studies (McQuillan, 2001). Samples were extracted with a dichloromethane liquid-liquid extraction (LLE) and then concentrated down to 1 ml. Sampling was performed using a Varian 8200 automatic sampler. Samples were analyzed by gas

chromatography (GC) and MS/MS using a Varian 3800 gas chromatograph coupled to Saturn 2000 mass spectrometer (Chapman and Mawhinney, 2003, manuscript in preparation; unreferenced).

Each sample batch was analyzed along with lab reagent blanks, lab fortified blanks, and lab fortified matrices as controls. All positive results were quantified using freshly prepared chemical standards.

The sample detection limit (SDL) for all antibiotics and non-antibiotic PhACs was10 ng/l. Recoveries ranged from 80 to120 percent. Conjugate forms of the PhACs, such as glucuronides and sulfates, were treated as transformation products and are not accounted for in the concentrations detected. Since some conjugates can be converted back into the original PhAC form before or during wastewater treatment processes, this may result in an underestimation of the concentration of PhACs present in samples (Huang et al., 2001). Chemical characteristics and pharmacokinetics for several of the detected antibiotics are presented in Appendix C.

3.0 RESULTS AND DISCUSSION

First, it is important to note that this study does not quantify the total load of PhACs contributed from any sample source because flow volume during sample collection was not known. Instead, what can be determined is a concentration of parent compound present in the sample at the time of collection. Secondly, the study design did not allow PhACs to be tracked temporally (i.e. from hospital to SWRP to river). Consequently, while results do reflect occurrence concentrations at time of collection, it is not feasible to definitively claim that differences in concentrations detected from source to river actually reflect removal of the PhACs within the system. Finally, only the parent compounds of the 39 PhACs were investigated. Conjugates and metabolites of the parent compounds, while sometimes pharmaceutically active, were not included in analytical testing. Consequently, by tracking only parent compounds, these results likely underestimated the concentration of PhACs present in the samples.

Ten sampling sites were investigated for the presence of thirty-nine PhACs comprised of 29 non-antibiotic PhACs and 10 antibiotics. Analytical results of all PhACs detected are presented in Table 4. Of the 29 non-antibiotic PhACs tested, only caffeine was found and only at the Presbyterian Hospital site (3000 ng/l). However, a number of antibiotics were detected, with six of the ten antibiotics found (Figure 1). Each of the six antibiotics detected were found at two or more sites (Figure 1). Additionally, of the ten sampling sites investigated, eight sites had at least one of the 39 PhACs present while five sites had three or more PhACs present (Figure 2).

Table 4: PhACs detected at sampling sites (ng/l). Blank boxes indicate no detection.

PhAC *drug class*	**Presbyterian Hospital**	**University Hospital**	**VA Hospital**	**UNM Dormitory**	**Vista del Rio Assisted Living**	**SWRP Influent**	**SWRP Effluent**	**Rio Grande 1**	**Rio Grande 2**	**Rio Grande 3**
sulfamethoxazole *antibiotic-sulfonamide*	800	2100	400	ND	ND	390	310	ND	300	300
trimethoprim *antibiotic-other*	5000	2900	ND	ND	ND	590	180	ND	ND	ND
ciprofloxacin *antibiotic-fluoroquinolone*	2000	ND	850	ND	ND	ND	ND	ND	ND	ND
ofloxacin *antibiotic-fluoroquinolone*	25500	34500	35500	ND	1300	470	110	ND	ND	ND
lincomycin *antibiotic-lincosamine*	2000	300	ND	ND	ND	ND	ND	ND	ND	ND
penicillin G *antibiotic- β-lactam*	ND	5200	850	ND	ND	ND	ND	ND	ND	ND
caffeine *other-stimulant*	3000	ND	ND	ND	ND	ND	ND	ND	ND	ND

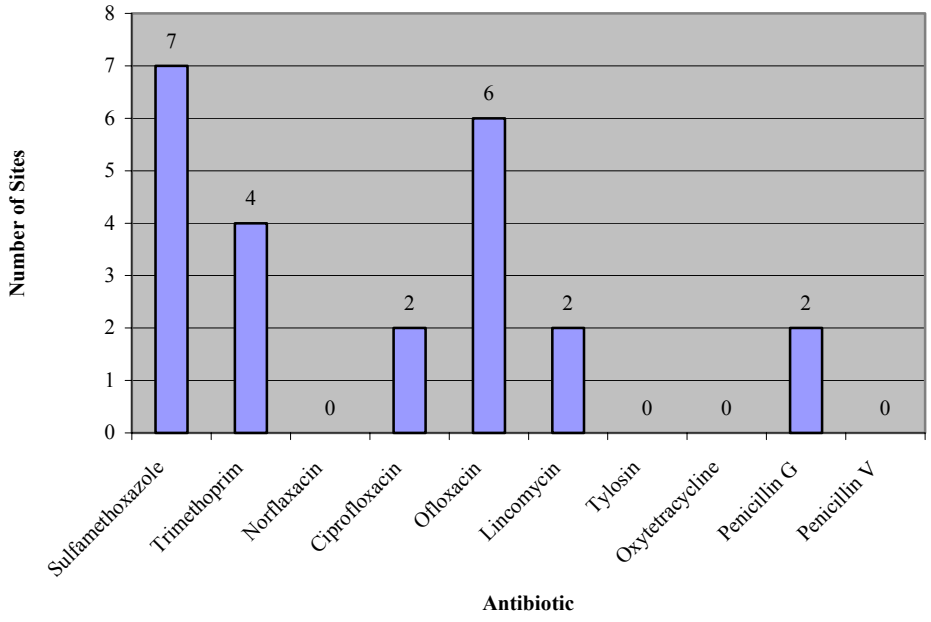

Figure 1: Number of sites where a particular antibiotic was detected. This graph also shows that six of the ten antibiotics were detected while four were absent from all sampling sites.

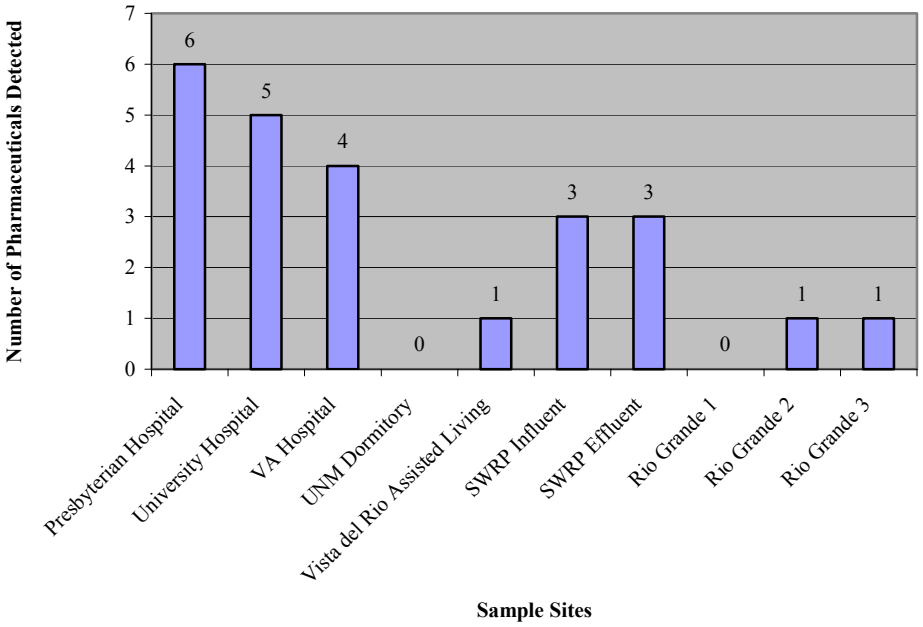

Figure 2: Number of PhACs detected at each sampling site. As expected, hospitals had the most PhACs detected and the river the least. Also, eight of the ten sampling sites had at least one PhAC present and two sites had none.

3.1 Fate and Persistence of PhACs in the Environment

Once a PhAC enters wastewater or natural waters, several processes affect its fate and transport in the environment. These processes include 1) sorption, 2) biotic transformation, and 3) abiotic transformation (Huang et al., 2001). The fate and persistence of PhACs in the environment is affected by their sensitivity to these processes. Research based on the chemical properties and structures of PhACs has improved our ability to predict the sensitivity of PhACs to these processes and hence, their expected fate and persistence (Huang et al., 2001). Furthermore, it is now understood that classes of drugs that have similar chemical properties and characteristics tend to behave similarly in the environment. See Appendix D for details regarding

specific chemical properties and pharmacokinetics of the three antibiotics detected in SWRP influent and effluent.

The likelihood of detecting specific drugs can be predicted by combining knowledge regarding the concentrations and fate of PhACs within the same class (Huang et al., 2001). Regarding antibiotics, their persistence and transport in the environment has been predicted by Huang et al. (2001), as follows: sulfonamides and fluoroquinolones are the most persistent followed by macrolides; tetracyclines can persist for relatively long periods if sunlight is not present, but tend to be less mobile, and aminoglycosides and β - lactam antibiotics show the least persistence. However, it is important to realize that it is not essential for a PhAC to be persistent in the environment in order for it to have significant impact. Instead, the PhAC could be present at concentrations of concern simply by continual infusion into the environment (Daughton and Ternes, 1999).

With regard to antibiotics in wastewater and surface water, previous studies have shown tendencies for some classes of antibiotics to be detected while others are not. In wastewater and surface waters, tetracycline and β-lactam antibiotics have been found rarely, trimethoprim occasionally, and sulfonamide, fluoroquinolone, and macrolide antibiotics frequently (Huang et. al, 2001). Research by Huang et al. (2001), identified antibiotics that were most likely to be found in wastewater sources by combining information concerning environmental fate with predicted concentration levels of different antibiotics. From their respective classes, sulfamethoxazole, ciprofloxacin, and azithromycin were predicted to be the leading wastewater effluent antibiotics (Huang et

al., 2001). This predictability of detection is largely related to stability of these compounds in the environment. As such, the sulfonamides and fluoroquinolones, followed by macrolides, are the least susceptible to transformation and more likely to persist and transport in aqueous environments (Huang et al., 2001). Additionally, the fluoroquinolones and tetracyclines degrade very slowly as long as sunlight is limited (Huang et al., 2001). Tetracyclines adsorb to soils and sediments most readily, fluoroquinolones and macrolides moderately, sulfonamides moderately to weakly, and aminoglycosides and β-lactams weakly (Huang et al., 2001). In addition to predictions regarding fate and persistence, Huang et al. (2001) also estimated antibiotic concentrations in untreated wastewater to range from 3.9 ng/l to approximately 27,000 ng/l. Interestingly, these predictions regarding fate, persistence, and concentrations are similar to the results obtained in this project (Table 4). See Appendix D for additional fate, transport and persistence characteristics for common antibiotic classes.

3.2 Detection of Antibiotics vs. Other PhACs

While antibiotics were detected in all hospital samples, it is surprising and not well understood why none of the non-antibiotic PhACs were detected, or why caffeine was detected at only one site. Although beyond the scope of this study, the absence of these non-antibiotic PhACs from all samples may be due to 1) lower prescribed use, 2) differences in excretion and metabolism of parent compound, 3) lower persistence and transport due to differences in chemical properties and structures of non-antibiotic drugs, and/or 4) analytical error/inaccuracies associated with the analytical techniques used for the non-antibiotic drugs compared with that used for antibiotics.

3.3 Occurrence of PhACs in Hospital and Residential Effluent

The first objective of this study was to investigate the occurrence of PhACs in hospital and residential wastewater and, when present, to document their concentrations. In this regard, data reveals that all three hospitals are in fact significant source contributors of several antibiotics but not of non-antibiotic PhACs (Figure 3). In addition, one hospital was also a source contributor of the PhAC, caffeine. Six of the ten antibiotics investigated were detected at the hospital sites (Figure 3). As predicted by Huang et al., 2001, the drug classes of fluoroquinolones and sulfonamides are well represented. This is reflected by the presence of ofloxacin and sulfamethoxazole at all three hospital sites, and ciprofloxacin at two hospital sites. Ofloxacin was found at particularly high levels in all three hospital's wastewaters.

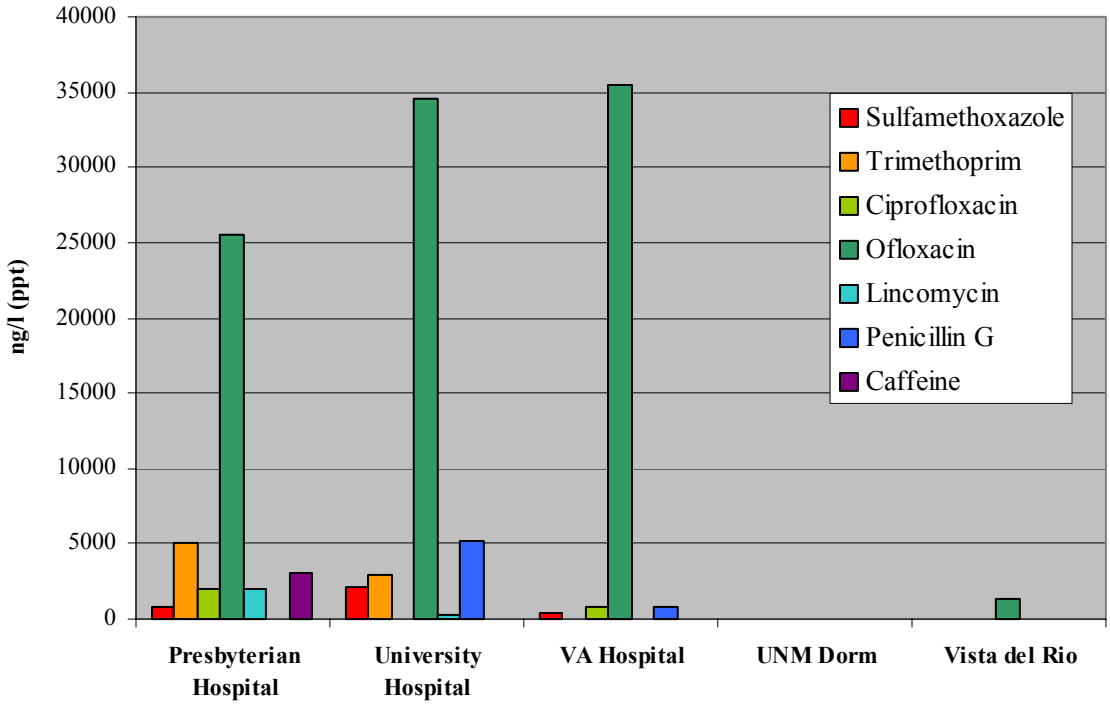

Figure 3: PhACs detected in effluent from hospital and residential sites

In contrast to hospital effluents, residential point source contributions were minimal as indicated by the absence of PhACs at the UNM Alvarado Dormitory, and the detection of only one antibiotic, ofloxacin, at Vista del Rio Assisted Living (Figure 2). Also, in comparison to the concentrations found at hospital sites, the concentration contributed from Vista del Rio is nominal.

3.4 Genotoxicity in Hospital Effluent

Genotoxicity refers to the amount of damage a toxin can do to DNA molecules. Genotoxic substances are also often mutagens and carcinogens (Hartmann et al., 1998). Fluoroquinolone antibiotics, particularly ciprofloxacin, have been shown to display genotoxic effects in hospital effluent where concentrations were in the 3000ng/l to 87,000 ng/l range (Hartmann et al., 1998). While ciprofloxacin was only found at a maximum concentration of 2000 ng/l in this study, temporal and spatial variability in effluent concentrations are likely to exist and could result in concentrations within the genotoxic range at times. Additionally, ofloxacin, which is also a fluoroquinolone but was not specifically addressed in the Hartmann et al. study, was found at very high concentrations in all three hospital samples and is therefore also of concern for its potential contribution to genotoxic effects.

At concentrations found in hospital effluent, genotoxic effects from ciprofloxacin most significantly impair prokaryotic rather than eukaryotic organisms and do not appear to pose an acute human genotoxic risk (Hartmann et al., 1998). Still, prokaryotic organisms can be found in the activated sludge of sewage treatment plants where they could come

into contact with significant concentrations of fluoroquinolone antibiotics (Hartmann et al., 1998). While not well understood, there is concern that this type of exposure could result in the disruption of microbial ecology or perhaps facilitate the proliferation of antibiotic-resistant organisms.

3.5 Differences in Occurrence and Concentration of PhACs from Source to SWRP Influent

While hospital effluent samples contained six different antibiotics and caffeine, the wastewater sample collected at the SWRP influent site contained only three antibiotics (Figure 4). Four antibiotics and caffeine dropped below detection levels between the primary source and SWRP. This difference in concentrations of antibiotics between the source samples 1-5 (Table 3) and the SWRP influent can likely be attributed to: 1) dilution by other wastewater sources that do not contain PhACs, and /or 2) processes affecting the fate and transport of the PhAC such as sorption, biotic, and abiotic transformations (Huang et al., 2001). However, since the study design did not allow for hospital and residential effluent to be tracked temporally from source to SWRP influent, it is possible that the sample of influent collected at SWRP did not contain any of the originally sampled hospital or residential effluent but instead contained effluent that never had detectable concentrations of the PhAC. While it is likely the case that the drop in concentrations of PhACs in wastewater is primarily due to dilution and/or one of the processes affecting fate and transport, it is important to understand that temporal variations in concentration of PhACs in hospital or residential discharges may also

contribute. Determination of exact processes affecting concentrations and fate of PhACs from source to river is an important area for further research.

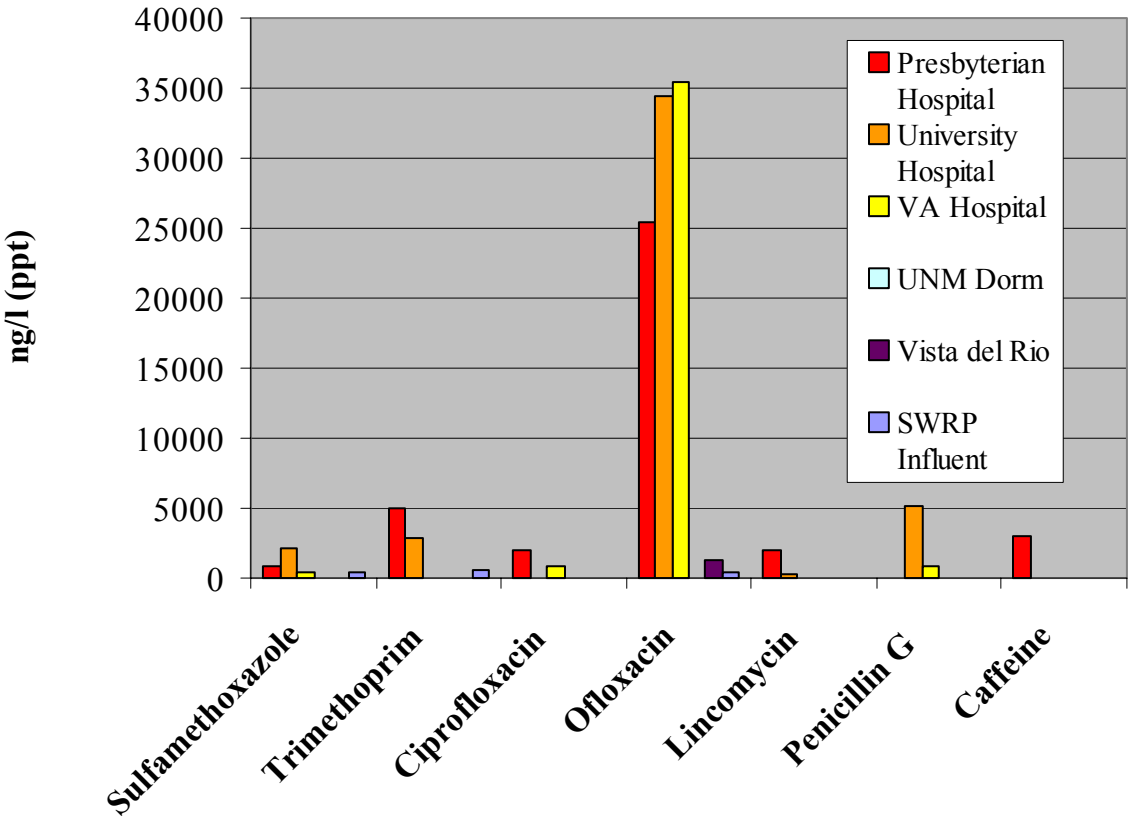

Figure 4: Differences in concentrations of PhACs between their sources and the SWRP influent. The reduction in concentrations of PhACs between their various point sources and the SWRP influent ranges from 2-81% for sulfamethoxazole, 80-88% for trimethoprim, and 64-99% for ofloxacin.

3.6 Concentrations of PhACs Before and After Wastewater Treatment

The second objective of this study was to assess removal of PhACsby the SWRP. Three antibiotics (sulfamethoxazole, trimethoprim, and ofloxacin) were present both in the SWRP influent and effluent samples. Interestingly, these PhACs appear to have experienced between 20 and 77 percent removal (Figure 5). While the experimental design of this study makes it imprudent to definitively claim that SWRP removed these

PhACs, the fact that SWRP influent and effluent samples were 48-hour composites does lend some confidence to the results. Consequently, it is likely that one of the SWRP

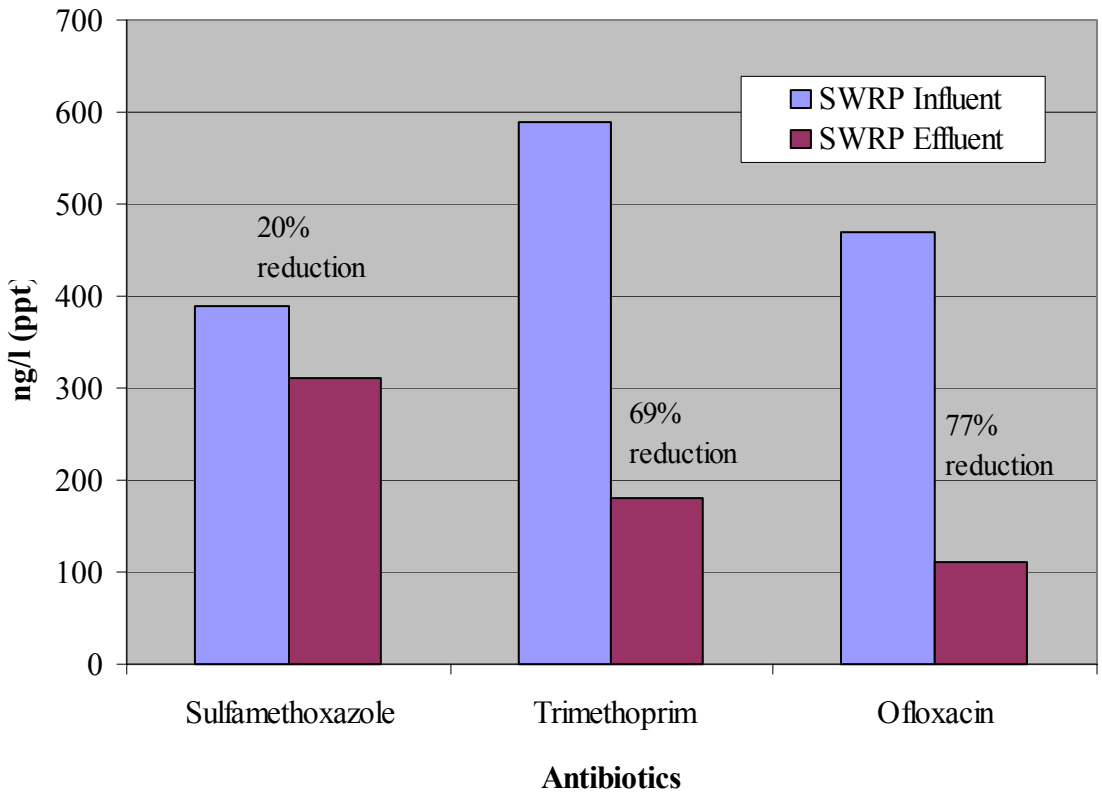

Figure 5: Removal efficiency of SWRP for the three antibiotics detected in the SWRP influent

treatment processes (activated sludge or chlorination) was responsible for the observed reductions. It is also notable that the removal efficiency by SWRP varies for the three antibiotics. This variability is likely due to differences in chemical properties and structure of the PhACs that make them more or less sensitive to SWRP treatment processes and consequently result in different removal efficiencies. Interestingly, all three PhACs present in SWRP samples were from different drug classes and therefore, as predicted by Huang et al. (2001), were expected to behave differently, and in fact, did. Sulfamethoxazole, (a sulfonamide) demonstrated poor removal, whereas, trimethoprim

(classified as 'other') and ofloxacin (a fluoroquinolone) were both more efficiently removed, though to differing degrees (Huang et al., 2001). Again, the exact processes (sorption, biotic or abiotic transformation) responsible for the removal are not known and are beyond the scope of this study. However, it would be interesting to collect samples between different treatment phases within SWRP to determine which phase and processes are responsible for the removal or transformation of each PhAC.

Following treatment at the SWRP, three antibiotics were detected in the SWRP effluent. This effluent is thus continually infusing antibiotics into the Rio Grande, though at relatively low concentrations. The effects of this discharge are not known. In fact, little is known at all about the acute or long-term effects to aquatic species or, more generally, about safe allowable limits of PhACs in the environment. Consequently, the inability of SWRP to fully remove PhACs is disconcerting. Advanced wastewater treatment techniques such as reverse osmosis, activated carbon, and ozonation have been shown to significantly reduce or eliminate antibiotics – including sulfamethoxazole – from wastewater effluents; however, most wastewater treatment facilities do not employ these techniques (Huang et al., 2001; Sedlak and Pinkston, 2001). Furthermore, even if these advanced techniques were widely employed, these processes have not been shown to fully remove all PhACs and, consequently, issues surrounding potential long term effects at low concentrations of PhACs could continue to be a concern (Daughton and Ternes, 1999; Sedlak and Pinkston, 2001).

3.7 Occurrence and Fate of PhACs in the Rio Grande

The final objective of this study was to investigate the occurrence and fate of PhACs in the Rio Grande by collecting samples both upstream and downstream of SWRP. With regard to occurrence, no PhACs were detected at Rio Grande 1, upstream of SWRP, and only one antibiotic, sulfamethoxazole, was detected at the two sampling sites below SWRP (Figure 6). The lack of detection of PhACs at Rio Grande 1 is consistent with two prior NMED studies in which PhACs were undetected in samples from this location (McQuillan, 2001, 2002). This is good news since this is near the planned diversion site for the City of Albuquerque's Drinking Water Program.

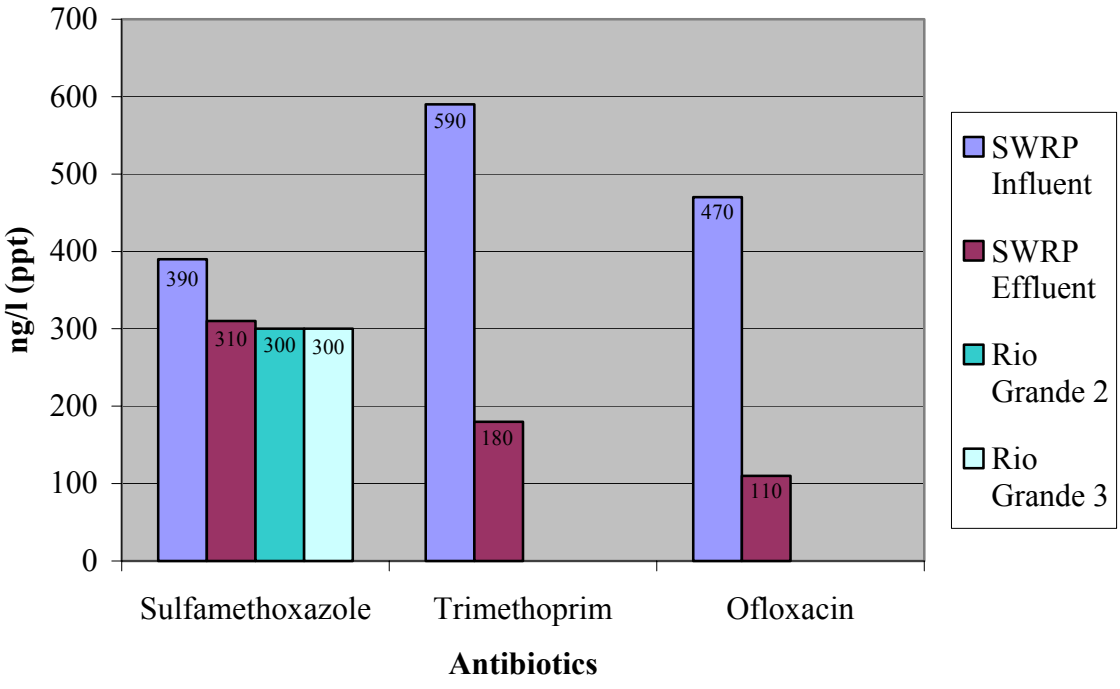

Figure 6: Concentration of antibiotics at SWRP and in the Rio Grande

Although three PhACs were detected in the SWRP effluent, the trimethoprim and ofloxacin were present at very low concentrations. It is reasonable to assume that dilution by the river caused these two antibiotics to drop below detection limits in the Rio Grande since the Rio Grande flow rate was 5.5 times that of the SWRP effluent (See Appendix A). However, it is possible that photolysis or some other transformative process might also have played a role. Fluoroquinolones are especially susceptible to photodegradation (Huang et al., 2001) for which the wide and shallow river morphology of the Rio Grande offers ample opportunity. Consequently, photodegradation must be considered a possible explanation for the absence of ofloxacin from the Rio Grande samples.

Similarly, the fact that the sulfamethoxazole concentration remains relatively stable in the SWRP effluent and in Rio Grande samples 2 and 3, seems to support the predictions made by Huang et al., (2001), that sulfamethoxazole is not particularly sensitive to photolysis or other transformation processes and tends to persist and transport readily in the environment. Alternatively, it is unclear why the concentrations of sulfamethoxazole in the SWRP effluent and Rio Grande samples 2 and 3 remain virtually unchanged when dilution alone should have resulted in a 5.5 fold reduction (Appendix A). Possible explanations for this result might include: 1) the SWRP effluent contained conjugates or metabolites of sulfamethoxazole that were not accounted for in analysis and were not in pharmaceutically-active forms in the SWRP effluent but were later converted back to the detectable parent form of the drug after reaching the river, or 2) temporal variations in sulfamethoxazole concentrations exist in the SWRP effluent from day to day.

Since study design did not temporally track samples from the SWRP into the Rio Grande, temporal variations could potentially explain this result. In fact, the Rio Grande samples were collected about a week before the SWRP effluent samples. Consequently, if the SWRP effluent entering the Rio Grande on the day of collection of the Rio Grande 2 and 3 samples had concentrations of sulfamethoxazole 5.5 times greater than those detected in the SWRP effluent in this study, the concentration of sulfamethoxazole found in this study in Rio Grande 2 and 3 samples would be consistent with dilution effects. However, since temporal fluctuations of this magnitude are unlikely, it is possible that some combination of factors was responsible for the results obtained.

Maintaining adequate flow in the Rio Grande is important for the preservation of water quality because it allows for the dilution of contaminant loads entering the river. With the City of Albuquerque Drinking Water Program, additional water will be diverted from the Rio Grande. The City of Albuquerque will be diverting 94,000 af/y but predicts the effective loss of flow through Albuquerque to be minimal, at 34,000 af/y. At present, on the collection date of 3/31/03, the SWRP effluent was 15.4% of the Rio Grande flow. This would increase to 16.9% if 34,000 af/y were effectively lost as predicted (Appendix A). While not a significant change, this could potentially raise PhAC concentrations as well as other chemical pollutant concentrations to levels of concern.

3.8 Comparisons with Prior Studies

The finding of sulfamethoxazole in the Rio Grande is consistent with results obtained by the USGS in their surveillance of US streams in 1999 and 2000 where sulfamethoxazole and trimethoprim were both detected in 12.5 percent of 104 streams with a median

concentration of 150 ng/l (Kolpin et al., 2002). It is curious, however, that trimethoprim was not detected in the Rio Grande since these two drugs frequently appeared to be detected together and in similar concentrations by the USGS (Kolpin et al., 2002) (Table 5). Perhaps the answer lies in the differences of removal by SWRP where trimethoprim is reduced by approximately 69 percent and sulfamethoxazole by only 20 percent (Figure 5). This may indicate that treatment processes within SWRP are affecting the trimethoprim more readily than the sulfamethoxazole. Table 5 is included to allow for further comparison of results from USGS, NMED, and this study (Kolpin et al., 2002).

Similarly, it is also interesting that in previous NMED studies involving Rio Grande samples, other PhACs, such as estrone, amitriptyline, and caffeine were detected. In light of these findings, it is somewhat surprising that none of these PhACs were detected in this study, particularly since the Rio Grande sample sites in this study focused on Albuquerque, the most populated region in New Mexico. Analyses were performed by SLD for both this study and the prior NMED studies when these other PhACs were detected (McQuillan, 2000, 2001). However, new instrumentation not previously used by SLD was utilized for this study and therefore, might explain the different findings.

However, a recent study conducted by the U. S. Fish and Wildlife Service and SLD (using the older instrumentation) investigated the same 29 non-antibioitic PhACs tested for in this study, and detected only 17β-estradiol at the analytical detection limit of 10 communication, unreferenced). None of the 29 non-antibiotic PhACs were detected in

Table 5: Comparison of PhACs detected in three different studies:
1) U.S. Streams by the USGS (Kolpin et al., 2002), 2) the Rio Grande in prior NMED studies (McQuillan, 2001), 3) the Rio Grande in this study.

PhAC	USGS* frequency of detection (%)	USGS median concentration (ng/l)	Concentrations found in Prior NMED studies (ng/l)	Concentration detected in this study (ng/l)
sulfamethoxazole	12.5	150	0	300
trimethoprim	12.5	150	0	0
norfloxacin	0.9	120	0	0
lincomycin	19.2	60	0	0
oxytetracycline	1.2	340	0	Not tested
sulfamethazine	4.8	20	0	0
sulfamethizole	1	130	0	0
tylosin	13.5	40	0	0
fluoxetine	1.2	120	0	0
caffeine	61.9	81	200 and 1500	0
cholesterol	84.3	830	0	0
equiline	1.4	147	0	0
17α-ethynl estradiol	15.7	73	0	0
17β-Estradiol	10.6	160	0	0
mestranol	10	74	0	0
estrone	7.1	27	140	0
amitriptyline	Not tested	Not tested	30	0

*The USGS study detected additional compounds but only those also tested for in the other studies are included here for comparison

Albuquerque reaches of the Rio Grande despite use of the older analytical instrumentation. This indicates that the difference in instrumentation is unlikely to be responsible for the differences in results.

A second possible reason that NMED may have detected PhACs that were not detected by this study or the U. S. Fish and Wildlife Service study, might include differences in dilution of wastewater effluents due to differences in Rio Grande flow rates at time of collection. However, it is unlikely that flow was less during the NMED study than during

this study as collections for this study were performed during a very low flow period (446 cfs).

Alternatively, it is possible that differences are due to spatial variability between the Rio Grande sample locations selected in each study despite relatively close proximity. Specifically, in the NMED study, estrone and caffeine were found “in the South Valley”. However, the exact location as it compares to the Rio Grande sample locations from this study is not known but could be miles away.

A final possible explanation might be differences in photodegradation effects due to differences in sunlight during or preceding collection of Rio Grande samples, although, it is known that both the NMED and this study collected Rio Grande samples on sunny days. The differences found between all of these studies and the proposed explanations clearly reflect the inherent difficulties in studying PhACs and offer a glimpse of the myriad variables involved in fully understanding this issue.

4.0 CONCLUSION

This study establishes a preliminary inventory of PhACs in effluent from hospital and residential sources, raw influent and treated effluent at the City of Albuquerque municipal wastewater treatment plant, and the Rio Grande in Albuquerque, NM. As anticipated, hospitals were found to be a significant source of antibiotics with concentrations ranging from 300 ng/l to 35,000 ng/l. On the other hand, sampling of residential wastewater resulted in detection of only one antibiotic. However, it is important to remember that while concentrations from individual residential sources may be low or below detection levels, they can be numerous and, when combined, may contribute a relatively significant load of PhACs to wastewater.

While antibiotics were detected in all hospital samples, it is surprising and not well understood why none of the non-antibiotic PhACs were detected, or why caffeine was only detected at one site. One explanation might be due to differences in chemical properties/structures that limit the persistence and transport of the non-antibiotic PhACs more readily than the antibiotics. It is also possible that interferences associated with the high concentrations of solids and organics in raw wastewater limited the ability to detect these compounds at trace levels.

Three antibiotics (sulfamethoxazole, trimethoprim, and ofloxacin) were detected in the SWRP influent and effluent at levels ranging from 470 ng/l in the influent to 110 ng/l in the effluent. Specifically, concentrations of these PhACs in the effluent sample are

reduced between 20 and 77 percent by the SWRP treatment processes. This difference in response to the treatment processes at SWRP is believed to be attributable to differences in the chemical properties and structures affecting their fate and persistence in the treatment environment.

With regard to occurrence of PhACs in the Rio Grande, none were detected at the sampling site upstream of the SWRP, and only one antibiotic, sulfamethoxazole, was detected at the two sampling sites below the SWRP (300 ng/l). The trimethoprim and ofloxacin, present at relatively low concentrations in the SWRP effluent, but absent in the river, are assumed to have dropped below detection limits due to dilution by the river. However, the possibility that photolysis or some other transformative process might also have played a role cannot be ruled out. With respect to the sulfamethoxazole, it appears to be resistant to transformation and persists in the river over a distance of approximately five miles with no change in concentration.

Overall, the results of this study are not alarming. Despite prior NMED detection in the Rio Grande, no estrogenic hormones were found. This data may ease the concern regarding possible environmental problems due to the presence of estrogenic hormones. In addition, although antibiotic concentrations in hospital effluent were relatively high, detection and concentration in the Rio Grande was minimal with only sulfamethoxazole being detected.

Still, issues of concern do arise. With relatively high levels of two fluoroquinolone antibiotics detected in hospital effluent and one fluoroquinolone present in SWRP influent and effluent, the issue of genotoxicity and its resultant impairment of prokaryotic organisms is of concern for its potential to disrupt microbial ecology (Hartmann et al., 1998). Also, with multiple antibiotics detected in all three hospital effluents, the research by Guardabassi et al, (1998) is of particular interest. This study lends credence to the concern that bacteria may develop antibiotic resistance through exposure to antibiotics in hospital or pharmaceutical plant wastewater effluents. Presently, little is known regarding environmentally safe levels for antibiotics in wastewater or surface waters. Clearly more research is needed to quantify the risk such that appropriate action can be taken to mitigate harmful effects or alternately, redirect efforts and limited resources. However, complicating factors such as the temporal and spatial variability in PhAC detections make it difficult to compare studies, assess risk, or institute policy.

While the relatively low concentrations of sulfamethoxazole detected in the Rio Grande are not known to cause any human or ecological health risks, it is still wise to employ the precautionary principle and focus on reducing or eliminating the occurrence of PhACs whenever possible. To this end, the quantification of PhAC contributions from hospitals provides valuable information that should be used to educate and motivate the medical community to improve clinical practice standards regarding the dispensing and disposal of medications as discussed in the USGS concept of "Green Pharmacy" (Daughton, 2003). In addition to reducing the load of PhACs entering wastewater, improvement of wastewater treatment technology and wider use of existing technology (reverse osmosis,

activated carbon, and ozonation) is warranted. Ultimately, it is my hope that the results of this study can be used as a foundation for future management decisions affecting water quality and its consequences for aquatic and human species.

5.0 SUGGESTIONS FOR FUTURE WORK

In the past decade, concern regarding chemical pollution has expanded beyond the traditional priority pollutants to include micro-contaminants such as PhACs. Research on this topic has been increasing worldwide, particularly in Europe and in the United States, where several instrumental studies have been conducted by U.S. governmental agencies. Although significant advances have been made, many questions remain. More research is needed in all areas; but, areas of particular importance might include identification of: 1) source contributions, 2) fate and transport characteristics, 3) wastewater treatment removal efficiencies, 4) effects on aquatic and other species, and 5) optimization of analytical techniques. While future research opportunities are seemingly limitless, several topics have been identified during the course of this project. Furthermore, many of the suggestions stated here would specifically benefit New Mexico and could potentially be conducted on relatively limited budgets.

Generally speaking, investigation into issues of temporal variability is important. Clarification or illumination of temporal trends might explain some of the observed differences between studies and help to direct future sampling protocols. For instance, results might help illuminate the relative importance of composite vs. grab sampling techniques or help determine appropriate composite collection schedules. Investigation of temporal variability could be addressed for source contributions, wastewaters, surface waters or any sample of concern. Specifically, this might include sampling hourly over a 24-hour period to determine how hospital effluent, wastewater, or surface water concentrations vary. Temporal sampling could also be done daily at the same time of day

to determine changes not associated with diurnal patterns but rather fluctuations from day to day. Seasonal collections might also be of interest due to potential seasonal variability in PhAC usage.

Another general consideration in study design might involve evaluation of analytical techniques. Samples could be sent to two or more labs to evaluate the reliability and validity of results. For instance, results could be compared between labs analyzing the same sample with different techniques or between labs utilizing different techniques to analyze the same sample.

With regard to source contributions, it is worth considering determination of the total load of PhACs contributed by a given source. To do this, it is necessary to know the flow rate during sample collection. Total load is important when trying to perform a mass balance approach to tracking PhACs throughout their course to determine fate and transport in the environment. While this is an increasingly popular approach, it does add another level of complexity to the study design. Additionally, it is not necessarily an essential component for inventory studies since the concentration of PhAC is generally the issue of concern in regard to effects on aquatic species.

In light of the relatively high concentrations of antibiotics found in hospital effluents in this study, contacts have been made at University Hospital to educate and motivate the medical community to improve clinical practice standards regarding the dispensing and disposal of medications as discussed in the USGS concept of "Green Pharmacy"

(Daughton, 2003). As an employee of University hospital it is the author's intention to encourage and participate in the implementation of this process. Additionally, however, further research is needed to assess the environmental risks associated with these genotoxic substances. In general, the potential for antibiotic resistance to develop in organisms exposed to very low concentrations of antibiotics in the aquatic environment needs to be addressed. Although this pathway for the development of antibiotic resistance is widely discussed in the literature as an emerging threat, little documentation is available to validate the concern (Guardabassi et al., 1998). Further research is urgently needed to quantify the risk such that appropriate action can be taken to mitigate harmful effects or alternately, redirect efforts and limited resources.

Another major topic for further investigation involves wastewater treatment techniques and their PhAC removal efficiencies. There are numerous studies that have documented the removal of PhACs by various wastewater treatment facilities. However, more clarity is needed in determining the exact processes responsible for the removal. To assess this, samples could be collected at the SWRP influent, between each distinct treatment process, and at the effluent. Another interesting project might be to compare removal efficiencies at SWRP with those at the Santa Fe wastewater treatment plant since these facilities utilize different techniques (UV radiation vs. chlorination specifically). Also, with the planned implementation of the Albuquerque Drinking Water Program and its associated additional Rio Grande diversion, the SWRP will likely become a slightly greater percentage of the Rio Grande flow, consequently minimizing dilution by the river. If the impact on flow is significant, it might be interesting to resample the Rio Grande

sites investigated in this study to see if additional PhACs are detected or if concentrations are elevated.

Since some PhACs tend to adsorb to soils and clay, it would be interesting to investigate the presence of PhACs in riverbed sediments in the Rio Grande, downstream of the SWRP. Similarly, it might be interesting to sample soils near landfills, particularly those that receive wastewater treatment sludge. Soils from city parks or golf courses that are irrigated with surface water might also be of interest. Furthermore, groundwater associated with each of these soil samples could be sampled to assess for leaching of PhACs into groundwater.

Recent literature reflects a trend away from simply quantifying aqueous concentrations and instead, is moving toward the tracking of PhACs utilizing a mass balance approach that addresses the ultimate fate of the PhAC. To address these issues of fate, it is important to determine the transformation and degradation processes involved. For instance, some PhACs tend to adsorb to sludge during the treatment process, others may biodegrade or form transformation products due to alterations in their chemical structures. A clearer understanding of the fate of PhACs in wastewater treatment plants could be achieved by analyzing the mass of PhACs in the aqueous phase and in wastewater sludge (to account for sorption processes). Additionally, attempts could be made to track other transformation/degradation products when the chemical structures of the products are known.

In addition to these specific areas of focus, there are many other research opportunities that might best be addressed in a laboratory. For instance, the effects of photodegradation could be evaluated for different PhACs and drug classes to help determine sensitivity to this degradation process. Another project would be to investigate tendencies of PhACs to adsorb to sludge, soils, clay, or minerals. This project would help to advance our understanding of the fate and persistence of PhACs in the environment

Research pertaining to effects on aquatic species is another area where laboratory research is indicated and more research is essential. This is particularly true in regard to estrogenic compounds and as noted previously, antibiotics. Research investigating long-term low dose exposure to PhACs is an area of particular concern. Similarly, there is much interest in the potential risk to aquatic organisms associated with concurrent exposure to combinations of PhACs, particularly when the drugs in combination are from the same drug class or tend to act similarly on the target organism.

In conclusion, this issue of PhACs in the environment is an area of much concern for a wide variety of environmental disciplines. Input from diverse fields of study is essential to gain a clear and thorough understanding of this complex topic. While a few suggestions have been made here, there are myriad other opportunities available for further research in this fast-growing and interesting area of study.

"Not everything that can be counted counts, and not everything that counts can be counted"

- Albert Einstein

GLOSSARY OF TERMS

Abiotic transformation: A non-biologically induced change in the PhAC. Hydrolysis and photolysis are common degradation pathways for PhACs whereas little is know about other types of abiotic transformation such as oxidation and reduction processes as they apply to PhACs in the environment (Huang et al., 2001)

Antibiotic: A drug class. Antibiotics are a special class of drug. Antibiotics are drugs that are used to fight infections. In this study they were categorized separately from the other PhAC because they required application of a different analytical detection technique and because as a class they are of particular concern in the environment due to their potential to facilitate the proliferation of antibiotic-resistant organisms.

Antibiotic resistance: When bacteria develop this, antibiotics are no longer effective at stopping their growth and infections can flourish. Illnesses caused by such bacteria are consequently difficult to control and can spread rapidly. Strains of bacteria that display antibiotic resistance seem to be on the rise.

Anti-convulsants: A drug class; a drug used to treat or control convulsions such as in epilepsy.

Anti-depressants: A drug class; a drug used to treat depression (these often have undesirable side effects

Anti-inflammatories: A drug class; a drug used to treat or control inflammation

Analgesic: A drug class; a drug used to decrease pain.

Biochemical processes: Reactions of chemical compounds such as sorption, biotic transformation, and abiotic transformation (Huang et al., 2001)

Biotic transformation: Changes in PhACs due to biological processes; biodegradation

Class: See Drug class

Drug: The active ingredient in a PhAC; a substance other than food intended to affect the structure or function of the body (http://www.m-w.com/cgi-bin/dictionary); In this study drug and PhAC are interchangeable

Drug class: A categorization or grouping of drugs based on commonalities regarding their effects on target organs or organisms. Drugs in the same class tend to behave similarly and often have similar chemical and physical properties.

Effluent: Flowing out

Fate: What happens to a PhAC throughout its existence in the environment; i.e. is it in the aqueous phase, adsorbed to a solid, or transformed or degraded into a non-PhAC.

Fluoroquinolone: A type or sub-classification of antibiotics

Genotoxicity: The amount of damage a genotoxic substance can cause to a DNA molecule. Genotoxicity also relates to mutagenicity and carcinogenicity.

Genotoxic effects: DNA damage

Hormones: A drug class; a chemical substances created by the body or synthetically produced that control numerous body functions; examples include birth control pills and hormones used for hormone replacement therapy in menopausal women.

Hospital source: A location that contributes PhACs from a hospital to the wastewater system. In this study there are three sampling sites that are hospital sources: Presbyterian, UNM, and the VA Hospitals.

Influent: Flowing in

Lab reagent blank: Whatever solvent is used for analysis. In this study it is de-ionized water for the antibiotics and dichloromethane for the non-antibiotic PhACs.

Lab fortified blank: The analytical solvent (de-ionized water or dichloromethane) spiked with standards of all the PhACs to be investigated.

Lab fortified matrixes: An actual field sample spiked with standards of all the PhACs to be investigated.

Macrolide: A type or sub-classification of antibiotics

Microgram/liter (µg/l): A concentration measurement. A microgram is 10^{-6} grams. Although not technically correct for fluid measurements, this is sometimes referred to as ppb (parts per billion)

Nanogram/liter (ng/l): A concentration measurement. A nanogram is 10^{-9} grams. Although not technically correct for fluid measurements, this is sometimes referred to as ppt (parts per trillion).

NMED: New Mexico Environment Department, collaborating agency for this study

Persistence: A PhACs ability to remain in a detectable pharmaceutically active form in the environment; a PhAC has high persistence in the aquatic environment if it remains pharmaceutically active over for a long period of time or through a long course of travel.

PhAC: Pharmaceutically active compound. A compound with pharmaceutical properties such that it behaves and acts upon target organisms in a manner similar to a pharmaceutical.

Pharmaceutical: A medicinal drug (http://www.m-w.com/cgi-bin/dictionary)

Photodegradation: See photolysis

Photolysis: The chemical breakdown of a compound or in this case, a PhAC, caused by sunlight; photodegradation.

Point source: Sources of PhAC contributions to wastewater or surface water that can be localized as a specific point. In this study there are five investigated potential point sources that could contribute PhACs into the wastewater system: the three hospitals and the two residential sites. The only point source contributor to the Rio Grande is the SWRP effluent. Non-point source contributors include sources that cannot be localized such as runoff from an agricultural field. Non-point sources were not addressed by this study.

Precautionary principle: This is based on the idea that people "must acknowledge uncertainty is inherent in managing natural resources, recognize it is usually easier to prevent environmental damage than to repair it later, and shift the burden of proof away from those advocating protection toward those proposing an action that may be harmful." (http://www.biotech-info.net/ctw_quote.html).

QAPP: Quality Assurance Project Plan drafted by the NMED for EPA-funded projects that involve sample collection and analyses. It requires approval by the EPA.

Residential source: A location that contributes PhACs from domestic locations (where people live, not from industrial, commercial or hospital locations) to wastewater system. In this study there are two sampling sites that are residential sources: UNM Alvarado dormitory and Vista del Rio Assisted Living/Retirement Community.

Sexual disruption: In the case of wild fish exposed to PhACs, this refers to fish developing characteristics/morphology of the opposite sex (male to female and female to male). In addition to physical characteristics, studies have shown changes in sexual function such as an inability to reproduce.

SLD: Scientific Laboratory Division, New Mexico Department of Health. Contract agency for PhAC laboratory analysis.

Sorption: A binding of one compound to another. In the case of PhACs this would be a PhAC binding to another compound such as clay material or minerals, soil, or activated sludge. (Huang et al., 2001)

Sulfonamide: A type or sub-classification of antibiotics

Tetracycline: A type or sub-classification of antibiotics.

Transformation: A breakdown of the PhAC structure such that it is no longer pharmaceutically active.

Transport: the act of remaining mobile within the environment; a PhAC has high mobility if it remains mobile and is able to move from one environment to another or along a course of travel (i.e. from hospital effluent through the wastewater treatment plant and into the river)

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APPENDIX A:

FLOW RATE AND DILUTION CALCULATIONS FOR THE RIO GRANDE AND SWRP EFFLUENT AT PRESENT AND AFTER CITY OF ALBUQUERQUE SAN JUAN-CHAMA DIVERSION

Present Flow Rates and Dilution Percentages for SWRP Effluent and the Rio Grande in Albuquerque, NM

SWRP effluent average flow rate for collection dates 4/8/03-4/10/03	= 52.5 mg/d
(52.5 mg/d x 1 cfs / .6464 mg/d)	= 81 cfs
Rio Grande at Albuquerque flow rate for collection date 3/31/03 (USGS, 2003) (USGS Albuquerque gage is upstream of SWRP)	= 446 cfs
Flow rate of the Rio Grande after the SWRP effluent addition (446 cfs + 81 cfs)	= 527 cfs
Percentage of flow rate contributed by SWRP effluent (81 cfs /527 cfs x 100)	= 15.4%
Dilution of SWRP effluent by the Rio Grande (81 cfs:446 cfs)	= 1**:**5.5

Predicted Flow Rates and Dilution Percentages for SWRP Effluent and the Rio Grande in Albuquerque, NM After City of Albuquerque San Juan-Chama Diversion

The City of Albuquerque is planning to switch from a dependence on ground water to the predominant use of surface water. To do this, the City of Albuquerque will decrease ground water pumping and divert 94,000 af/y from the Rio Grande, north of Paseo del Norte Blvd. in Albuquerque. Although the diversion from the river will be 94,000 af/y, the City has predicted that, due to hydrologic connections between groundwater and the Rio Grande, the end result of this 94,000 af/y diversion will actually be a loss of only

34,000 af/yr in the Rio Grande through the City of Albuquerque. (City of Albuquerque, 2003). Calculations below show 1) the effect of the full 94,000 af/y to show the maximum potential effect of the diversion if no replacement was gained through aquifer-enhanced flow and, 2) the effective diversion of 34,000 af/y as predicted by the City, based on aquifer-enhanced flow in the Rio Grande due to reduced groundwater pumping.

Calculations are based on the 3/31/03 Rio Grande at Albuquerque flow rate of 446 cfs (USGS, 2003) and the 4/8/03-4/10/03 average SWRP effluent flow rate of 81 cfs.

Maximum Effect of City of Albuquerque Diversion	**= 94,000 af/y**
(94,000 af/y x 43,560 cf/af)	= 4.1×10^9 cf/y
(4.1×10^9 cf/y x 1 yr. / 31,536,000 sec)	= 128 cfs
Percentage of Rio Grande flow that will be diverted (128 / 446 x 100)	= 28.9%
Rio Grande at Albuquerque post diversion flow rate (446 cfs – 128 cfs)	= 318 cfs
Flow rate of the post-diversion Rio Grande after addition of SWRP effluent (318 cfs + 81 cfs)	= 399 cfs
Percentage of post-diversion flow rate contributed by SWRP effluent (81 cfs / 399 cfs)	= 20.3%
Maximum dilution of SWRP effluent by the Rio Grande, post diversion (81 cfs : 318 cfs)	= 1**:**3.9

City Predicted Effect of City of Albuquerque Diversion	**= 34,000 af/y**
(34,000 af/y x 43,560 cf/af)	=1.5×10^9 cf/y
(1.5×10^9 cf/y x 1 yr. / 31,536,000 sec)	= 47 cfs
Percentage of Rio Grande flow that will be diverted (47/446 x 100)	= 10.5%

Rio Grande at Albuquerque post diversion flow rate
(446 cfs – 47 cfs) = 399 cfs

Flow rate of the post-diversion Rio Grande after addition of SWRP effluent
(399 cfs + 81.2 cfs) = 480 cfs

Percentage of post-diversion flow rate contributed by SWRP effluent
(81.2 cfs / 480 cfs) = 16.9%

Maximum dilution of SWRP effluent by the Rio Grande, post diversion = 1**:**4.9
(81cfs:399 cfs)

It should be noted, that these calculations are based on the 3/31/03 flow of 446 cfs. This is a relatively low flow. The calculations of percent of flow contribution by SWRP of 15.4%, 20.3 % and 16.9% are only accurate for the Rio Grande flow of 446 cfs. Much of the year, the flow is greater than this and the percent contribution of the SWRP would be less. At times, however, the Rio Grande does have even lower flows with a mean low flow or 4Q3 of approximately 250 cfs. This level was reached several times in 2003. To address this, during periods of extremely low flow, the City of Albuquerque plans to stop diversions from the Rio Grande to keep water in the river to maximize dilution of the SWRP effluent. None the less, the change from ground water pumping to Rio Grande diversion may reduce Rio Grande flow and consequently, the ability of the Rio Grande to dilute the SWRP effluent. This could result in the increase of concentrations of PhACs in the Rio Grande downstream of the SWRP to levels of concern.

APPENDIX B:

SAMPLE SITE COLLECTION DETAILS AND GENERAL CHEMICAL MEASUREMENTS

Sample Site Location	Collection Date 2003	Time of Collection	Weather	Sample Temp. (Celsius) [c]	Electrical Conductance (µ S/cm)	pH	Total Dissolved Solids (ppt). [a]	Time of Chemical Measurements
Presbyterian Hospital	04/30	6:00a - 10:00a	sunny clear	9.5°	725	8.6		11:15a
University Hospital	03/31	6:00a - 10:00a	sunny clear	21.1°[b]	850	7.38	0.43	10:00a
VA Hospital	05/07	6:00a - 10:00a	sunny clear	9.2°	709	7.7		2:30p
UNM Dorm	05/01	6:00a - 10:00a	sunny clear	13.0°	878			12:00p
Vista Del Rio	04/07	6:00a - 10:00a	cloudy		535	7.6		8:30a on 4/8[d]
SWRP Influent	04/08 – 04/10	6:00a – 6:00a (48 hr)	varied	3.0° - 4.0°	1127 and 1076	6.96-7.28		[e]
SWRP Effluent	04/08 – 04/10	6:00a – 6:00a (48 hr)	varied		813 and 835	7.61-7.83		[e]
Rio Grande 1 [f]	03/30	11:50a-12:35p	sunny clear	5.6°	330	8.6	.17	12:00p on 3/31
Rio Grande 2 [f]	03/30	2:15p-2:45p	sunny clear	3.0°	360	8.41	.18	12:00p on 3/31
Rio Grande 3 [f]	03/30	4:30p-5:00p	sunny clear	2.7°	570	8.42	.29	12:00p on 3/31

[a] when this box is blank = instrumentation not available on this date
[b] temperature collected at sample site at 10 am along with chemical measurements using a portable instrument that was lost and inaccessible for later testing. No ice in ISCO sampler during collection of this sample.
[c] when this box is blank = not collected due to investigator/equipment error. Here, ppt is parts per thousand
[d] these chemical measurements were taken at SLD the day after the sample had been delivered, not by the portable unit, as with the UNM Hospital and not at the Biology Annex Lab as is the case with the other samples
[e] The City of Albuquerque Lab collected the pH and EC measurements around 10 am each day
[f] Rio Grande flow as of 4:30 pm on 3/30/03 was 446 cfs (USGS, 2003)

APPENDIX C:

CHEMICAL PROPERTIES AND PHARMACOKINETICS FOR COMMONLY DETECTED ANTIBIOTICS

Trimethoprim/Sulfamethoxazole

http://www.aegis.com/factshts/network/access/drugs/sulfame.html

http://www.aegis.com/factshts/network/access/drugs/tmp.html

Brand Names: Bactrim, Septra. When administered alone, sulfamethoxazole brand names include Gantanol and Urobak

Excretion Percentage: The free forms of sulfamethoxazole/trimethoprim are considered to be the therapeutically active forms. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose of sulfamethoxazole/trimethoprim is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N4-acetylated metabolite. When administered together as sulfamethoxazole/trimethoprim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Applications: To treat common respiratory infections, and is also prescribed to people who have sinusitis. Bactrim is used for prevention and treatment of PCP pneumonia, particularly in patients with HIV. As a single drug product, sulfamethoxazole is most commonly used to treat urinary tract infections.

Pharmacokinetics: Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound and metabolized forms; sulfamethoxazole also exists as the conjugated form. The metabolism of sulfamethoxazole occurs predominately by N4-acetylation, although the glucuronide conjugate has been identified. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives. The free forms of sulfamethoxazole/trimethoprim are considered to be the therapeutically active forms.

Ciprofloxacin

http://www.rxlist.com/cgi/generic/cipro_cp.htm

Excretion Percentage: Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged. After intravenous administration, approximately 50% to 70% of the dose is excreted in the urine as unchanged drug.

Molecular Weight: 331.4

Chemical Formula: C(17)H(18)FN(3)O(3)
Ciprofloxacin is 1-cyclopropyl-6-fluoro-1, 4-drhydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid
Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

Pharmacokinetics: It is soluble in dilute (0 1N) hydrochloric acid and is practically insoluble in water and ethanol. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. After a 250-mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 mg/ml during the first two hours and are approximately 30 mg/ml at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing.

Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. Following a 200-mg I.V. dose, concentrations in the urine usually exceed 200 mcg/ml 0-2 hours after dosing and are generally greater than 16 mcg/ml 8-12 hours after dosing. Following a 400-mg I.V. dose, urine concentrations generally exceed 400 mcg/ml 0-2 hours after dosing and are usually greater than 30 mcg/ml 8-12 hours after dosing. The renal clearance is approximately 22 L/hr. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing. After I.V. administration, three metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10% of the intravenous dose.

The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

Ofloxacin

http://www.rxlist.com/cgi/generic/oflox.htm

http://www.rxlist.com/cgi/generic/oflox_cp.htm

Brand Names: Floxin

Excretion Percentages: Ofloxacin has a pyridobenzoxazine ring that appears to decrease the extent of parent compound metabolism. Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Studies indicate that <5% of an administered dose is recovered in the urine as the desmethyl or N- oxide metabolites. Four to eight percent of an ofloxacin dose is excreted in the feces.

Molecular Weight: 361.4.

Chemical Formula: C(18)H(20)FN(3)O(4)

Clinical Pharmacology:
Chemically, ofloxacin, a fluorinated carboxyquinolone, is the racemate, (±)-9- fluoro-2,3-dihydro-3-methyl-10- (4-methyl-1-piperazinyl)-7-oxo-7H- pyrido[1,2,3-de]-1,4-benzoxazine -6- carboxylic acid. Ofloxacin is an off-white to pale yellow crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine. The relative solubility characteristics of ofloxacin at room temperature, as defined by USP nomenclature, indicate that ofloxacin is considered to be soluble in aqueous solutions with pH between 2 and 5. It is sparingly to slightly soluble in aqueous solutions with pH 7 and freely soluble in aqueous solutions with pH above 9. Ofloxacin has the potential to form stable coordination compounds with many metal ions. This in vitro chelation potential has the following formation order: Fe+3 > Al+3 > Cu+2 > Ni+2> Pb+2 > Zn+2 > Mg+2> Ca+2 > Ba+2.

Applications: Floxin Tablets and IV are synthetic broad-spectrum antimicrobial agents for oral or intravenous administration.

Pharmacokinetics: Following oral administration, the bioavailability of ofloxacin in the tablet formulation is approximately 98%. Maximum serum concentrations are achieved one to two hours after an oral dose. Absorption of ofloxacin after single or multiple doses of 200 to 400 mg is predictable, and the amount of drug absorbed increases proportionately with the dose.
Ofloxacin has biphasic elimination. Following multiple oral doses at steady-state administration, the half-lives are approximately 4-5 hours and 20-25 hours. However, the longer half-life represents less than 5% of the total. Accumulation at steady-state can be estimated using a half-life of 9 hours. The total clearance and volume of distribution are approximately similar after single or multiple doses. Elimination is mainly by renal excretion.

APPENDIX D:

FATE, TRANSPORT, AND PERSISTENCE OF PHARMACEUTICALLY ACTIVE COMPOUNDS

Antibiotic Class	Persistence	Factors Affecting Fate and Transport
Sulfonamide	High [1]	Moderate to weak adsorption to soils [1]
Fluoroquinolone	High if sunlight absent [1]	Moderate adsorption to soils [1] Substantial adsorption to sewage sludge [2] With 15-20 hours residence time in river, concentrations of ciprofloxacin and norfloxacin were reduced by 66% and 28% respectively [2]
Macrolide	Moderate [1]	Moderate adsorption to soils [1]
Tetracycline	High if sunlight absent [1]	High adsorption to soils; generally low transport [1] Oxytetracycline strongly interacts with clay affecting its mobility and bioavailability; However, when competing solutes are present, this binding will be reduced and the bioavailability and mobility of oxytetracycline will be affected [3] Sensitive to transformation via photolysis [1] Resists degradation via conventional wastewater treatment [4] Complexes with metals making Solid Phase Extraction (SPE) difficult [5]
B-Lactam	Low [1]	Weak adsorption to soils [1]
Trimethoprim-other		Trimethoprim reduced to below detection limits by conventional drinking water treatment plant [6]
Penicillin		Penicillin G requires acidic condition for optimum SPE recovery [5] Easily degrade in the environment [2]

1 = Huang et al., 2003
2 = Alder et al., 2003
3 = McKay et al., 2003
4 = Kulis, personal communication, unreferenced, 2003
5 = Chapman, personal communication, unreferenced, 2003
6 = Stackelberg et al., 2003