

OCCURRENCE AND FATE OF PHARMACEUTICALS IN THE POMPERAUG RIVER

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STATEMENT OF CRITICAL REGIONAL OR WATER PROBLEM:

Pharmaceuticals and other compounds of wastewater origin have been observed throughout the US in surface waters impacted by urban activities. The presence of pharmaceuticals in aquatic environments is of concern because, even at ng/L levels, these molecules are biologically active and can affect critical development stages and endocrine systems of aquatic organisms. Current pharmaceutical fate studies have been survey-oriented, only documenting occurrence in a variety of environmental systems. Few data regarding temporal and spatial distributions, or environmental degradation rates of pharmaceuticals in surface waters have been collected. No such studies have been conducted to date in the US.

Environmental occurrence of pharmaceuticals is of particular concern in the Pomperaug River watershed. Here the primary source of pharmaceutical inputs is a wastewater treatment plant that serves a retirement community of 5000 with an average of 6 medications per person. The treatment plant provides up to 20% of river flow and thus pharmaceutical impacts are expected to be greater in this watershed than the national average.

STATEMENT OF RESULTS AND BENEFITS:

A study will be conducted in the Pomperaug River to assess inputs and fates of high-use pharmaceuticals to this aquatic environment. Samples will be obtained quarterly at the influent and effluent of the wastewater treatment plant and at 5 locations downstream between the treatment plant and the outlet of the watershed at the Housotonic River. Results of this research will include: (1) seasonal ambient concentrations of pharmaceuticals, and (2) seasonal measurements of pharmaceutical fluxes through the study reach. Concentration levels are of importance for ecotoxicologic exposure assessments. Flux measurements will be used to calculate environmental degradation rate constants, or half lives, for the non-conserved pharmaceuticals.

This study will expand the understanding of water quality in the Pomperaug River and complement on-going research activities in this watershed. On a broader scale, the rate observations made in this study will provide a context within which to interpret point observations

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of pharmaceuticals obtained in ongoing national surveys (*e.g.*, USGS NAWQA study of Pharmaceuticals and Organic Compounds of Wastewater Origin).

NATURE, SCOPE AND OBJECTIVES OF RESEARCH:

Pharmaceuticals have been identified recently as an important class of aquatic contaminants that have the potential to degrade ecosystem health [1-5]. Important sources of pharmaceutical compounds in aquatic environments are discharges from municipal wastewater treatment plants (MWTP) or septic systems. The pharmaceutical compounds in these wastewater streams derive from human usage with only a small contribution from manufacturing activities. Unmetabolized and partially metabolized drugs that are excreted in human wastes are poorly removed in conventional MWTP and septic systems [6]. The bacterial consortia that are the basis of these treatment systems lack suitable enzyme systems for fast degradation of pharmaceuticals with complex chemical structures. Further, the polar nature of most pharmaceuticals inhibits their removal by passive sorption to bacterial biomass. With these poor removals in treatment plants and the growth of human populations, discharges of pharmaceuticals from MWTP and septic systems to aquatic environments are expected to increase with continued elevations in drug use.

The risk posed to aquatic organisms and humans by increasing exposures to pharmaceuticals in the environment are unknown. Pharmaceutical compounds are developed to induce specific biological responses in humans; however, these bioactive compounds may induce detrimental effects in non-target organisms upon release to the environment [*e.g.*, binding of flux-inhibiting drugs to critical protein transporters, 7, 8]. The potential for such actions caused Daughton and Ternes to posit that pharmaceuticals may be acting as subtle agents of change by which small, barely perceptible effects will ultimately result in profound changes to nontarget species populations [see review by Daughton and Ternes, 1]. Such broad ecological effects may be analogous to those experienced in the 1960s shortly after the introduction of organochlorine pesticides such as DDT [as immortalized by R. Carson in *Silent Spring*, 9], but little research currently exists on the environmental fate of pharmaceutical compounds. Specific health effects of concern include the development and spread of antibiotic resistance in native bacterial populations [10-13] and the extent to which pharmaceuticals can act as endocrine disruptors [1]. At present, these exposure scenarios cannot be evaluated accurately because little is known about the environmental behavior of pharmaceutical compounds.

Current understanding of pharmaceutical fates in the environment is being constructed from survey studies of a variety of environmental systems. A study by Ternes [6] gives a feeling for environmental inputs of pharmaceuticals from typical municipal wastewater treatment plants. The median concentrations of 32 drugs and metabolites ranged from 0.1 to 2.2 $\mu\text{g/L}$, although maximum concentrations were up to ten times greater at the 49 plants sampled. These concentrations are reduced by dilution upon mixing with surface waters at the wastewater plant discharge point; however, pharmaceutical concentrations of 0.02 to 2 $\mu\text{g/L}$ have been reported in surface waters far from discharge sites [2 and references therein, 3, 14-17]. Although the majority of these cited studies have reported on observations in European waters, the recently completed USGS national water quality survey has demonstrated the ubiquity of pharmaceutical compounds in US aquatic environments as well [17]. Unfortunately, little insight into controlling processes that attenuate pharmaceutical concentrations in the environment can be derived from

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these studies because temporal and spatial (*e.g.*, discrete locations downstream from MWTP discharge) monitoring were not undertaken.

Objectives

The objectives of this proposed study are to monitor the temporal and spatial distributions of pharmaceutical compounds introduced to the environment from a well-defined wastewater treatment plant discharge to a river. The specific tasks will include quarterly sample collection from the treatment plant influent and effluent, and at discrete locations downstream in the river channel. Observed concentrations in the river will be compared to predicted concentrations using a conservative transport model to: (1) identify pharmaceutical compounds with potential for ecotoxicological risk in this watershed, and (2) to estimate the magnitude of sink mechanisms for unconserved compounds.

This study will be conducted in the Pomperaug River, a tributary of the Housatonic River, located in western Connecticut near the town of Southbury. This study site was chosen because it offers several unique advantages over other study sites. First, the only point source discharge of pharmaceutical compounds to the Pomperaug River is the Heritage Water Treatment Plant (HWTP) (Figure 1). This plant collects and treats wastewater from the residential retirement community of Heritage Village (population 5000) and a small amount of wastewater from a palliative care facility. Given that each of the Heritage Village residents takes an average of 6 medications (Marc Taylor, M.D., personal communication) and that there are no industrial inputs to HWTP, pharmaceutical concentrations from this source are expected to be greater than would be observed for a typical municipal wastewater treatment plant. Further, the dilution ratio of effluent into the river channel is low (*c.f.*, HWTP – 4.6 cfs (0.4 MGD) and Pomperaug River 10 – 30 cfs) and thus, the pharmaceutical signal in this environment is expected to easily be detected by current analytical methods [18].

A second reason for choosing the Pomperaug River study site is the availability of supporting data from this watershed. The Pomperaug River Watershed Coalition is working to establish a water balance for the main river channel as part of its mission to protect the quality and quantity of the Pomperaug River's surface and subsurface waters. The members of this coalition have taken a strong science-based approach to this work and have established a clearing house of data, including land use, flow volumes and water quality throughout this watershed. The Coalition has also established a strong network of stakeholders within the watershed community, including the HWTP plant owners who have granted sampling permission for this study. In addition, 70 years of historical flow data is available from a USGS gauging station located 900 m downstream from HWTP.

Finally, pharmaceutical data obtained in this study will support on-going investigations of water quality within the Pomperaug River watershed. For example, USGS has identified 15 drinking water supply wells in this watershed as sampling points for the National Water Quality (NAWQA) survey. Target analytes in this survey include 75 pharmaceutical and other organic compounds of wastewater origin (Craig Brown, USGS, personal communication). Several of the USGS study wells are located adjacent to the HWTP (Figure 1) and identification of pharmaceutical compounds in these wells and in the Pomperaug River may suggest surface water influences on the aquifer.

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METHODS, PROCEDURES AND FACILITIES:

Pharmaceutical Compounds

The choice of pharmaceutical compounds to monitor must take into consideration usage and metabolism rates, the potential for toxicological impacts on non-target organisms and availability of analytical methods suitable to environmental samples. Nation-wide, the top 25 most prescribed drugs include lipid regulators, antihypertensives, hormone replacement therapies, beta-blocker and calcium channel blocker medications and anti-inflammatories [19]. All of these medications are typical of those expected to be used in a senior population.

Of the most widely prescribed drugs, the classes that are known, or strongly suspected, to have ecotoxicological risk are serotonin reuptake inhibitors (*e.g.*, fluoxetine) and beta-blockers (*e.g.*, fenfluramine). Direct toxicological evidence for induced spawning behavior in clams and feminization of crabs has been documented for fenfluramine and fluoxetine (Prozac), respectively, at environmentally relevant concentrations [1]. These induced behaviors arise because of common modes of drug action between humans and these non-target organisms [1].

Finally, the combined analytical advances in solid phase extraction techniques and mass spectrometry detection have pushed detection limits of over 125 pharmaceutical compounds below 0.05 µg/L in environmental samples [17, 18].

On the basis of usage, toxicity and our expertise with GC/MS techniques (see Analysis below), we will monitor estrogens, neutral pharmaceuticals (includes common lipid regulators clofibrate and fenofibrate, psychiatric drug diazepam, β-blockers metoprolol and terbutalin), and acidic drugs (includes anti-inflammatoryies naproxen, diclofenac). Additional pharmaceuticals that will also be isolated with the target analytes can be found in methods of Koplín *et al.* [17] and Ternes [18], and are omitted here for brevity. Usage information that is specific to the Southbury community, including Heritage Village, will be obtained from dispensing records from the local pharmacy and used to tune the final list of analytes.

Sampling Locations and Protocol

Quarterly sample collection will be conducted at the Heritage Water Treatment Plant and through the downstream reach of the Pomperaug River. The proposed sample dates are May, August, November 2003 and February 2004 to encompass relevant seasonal variations.

Heritage Water Treatment Plant: HWTP operates as a conventional activated sludge plant. Influent is coarsely screened, metered and then flows into one of four extended aeration tanks for removal of organic matter and nitrogen. Aeration is followed by clarification to remove biological solids. The clarified water is next chlorinated to deactivate pathogens. This step signifies the end of engineered treatments. The post-chlorination effluent is directed to one of two man-made ponds for dechlorination. These ponds operate as natural systems with no engineered controls. Finally, flow from these ponds discharges by open channel to the Pomperaug River. Average daily capacity of this plant is 0.4 MGPD.

Three sample points have been identified at the Heritage Water Treatment Plant: (1) influent, (2) post-chlorination, and (3) entry to the Pomperaug River. The intermediate sample location between the chlorination treatment and the dechlorination ponds was included to compare pharmaceutical removals in the engineered system with the natural pond system, and

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ultimately, with losses in the river system. Oral agreement to sample at this facility has been obtained at the time of this proposal submission (Ray Adamaitis, CT Water Company, personal communication).

Pomperaug River: The Pomperaug River is a third-order stream with typical median flows that range from 10 – 30 cfs, as measured at a USGS gauging station 890 m (0.56 mi) downstream of the HWTP discharge. The river reach between HWTP and the Housatonic River is 9700 m (6.1 mi) with only 2 minor brook inputs. Throughout this reach, the river channel is wadeable with a rocky bottom and steep banks, as is characteristic of Connecticut rift geology.

Samples will be collected for pharmaceutical analysis at 5 locations downstream from the HWTP discharge point (Figure 1). One sampling point will be coincident with the USGS gauging station where the most accurate calculations of relative wastewater and channel flow contributions to the Pomperaug River can be made. The other sample points are spaced approximately to a logarithmic scale to improve estimates of environmental degradation rates for the monitored analytes. All of the sample locations are bordered by properties that are town- or land trust-owned, and thus are accessible by the public. Sample locations may be modified to better capture dynamics of pharmaceutical concentrations based upon results of the May 2003 sampling event.

The HWTP has been identified as the sole point source of pharmaceutical compounds in the Pomperaug River. However, the high use of septic treatment systems throughout the watershed indicate that non-point sources of pharmaceuticals may also be introduced to the Pomperaug River through groundwater flows. Thus, a sixth river water sample will be collected 500 m upstream of the HWTP discharge point to assess background concentrations of pharmaceuticals that are transported into the study area by Pomperaug River flow.

Samples will be collected on a flow-corrected time schedule so that a single ‘packet’ of water is followed from the HWTP discharge. This technique will enable conversion of spatial variations in pharmaceutical concentrations to reaction time equivalents in a batch reactor, and hence meaningful estimates of pharmaceutical attenuation rates will be possible. Standard stream tracer techniques will be employed to delineate the fluid ‘packet’ using fluorescent rhodamine tracer [20]. To further verify channel dilution effects due to infiltration of groundwater, boron and chloride concentrations will be measured at the sample points. Boron is a common tracer of wastewater effluents [21]. Chloride concentrations in wastewater [50 – 90 mg/L, 21] are greater than in freshwater streams [\sim 2 mg/L, 22], although other sources (*e.g.*, manure leachate) may contribute chloride to the Pomperaug River.

Samples for pharmaceutical analyses will be collected in clean 1-L polypropylene sample bottles. A total of 4 samples will be collected by immersion at each location. An additional 250 mL sample will be collected for analysis of conserved wastewater tracers in the Pomperaug River. Samples will be stored in a cooler for transport back to Storrs. Samples will be preserved by refrigeration at 4°C and extracted within 72 hours. A unique sample ID number will be assigned to each sample. All treatments will be documented in a bound log-book.

Where possible, river sediment grab samples will also be collected at the sample points during the November 2003 sampling trip. These samples will be extracted to give qualitative verification of whether sediments are important sinks for pharmaceuticals in this watershed.

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Sediment samples will be collected with a clean metal trowel, transferred to a polypropylene sample bottle and preserved by freezing (-20°C) until analysis.

Analytical

Pharmaceutical analyses in water samples will be conducted using published methods [17, 18]. The four 1-L samples from each location will be composited and then split to quantify estrogenic pharmaceuticals, neutral pharmaceuticals and acidic pharmaceuticals. Appropriate recovery standards will be added to each sample to account for compound losses in sample analysis methods. Briefly, the method for each of the compound classes entails: (1) pharmaceutical extraction by passage through a solid-phase extraction column; (2) elution with appropriate solvent, and (3) addition of a derivatizing agent to increase pharmaceutical volatility. Slight differences in water pre-treatments, solvent types and derivatization conditions necessitate the use of 3 parallel analyses. Derivatized products will be quantified by gas chromatography (GC) with mass spectrometry (MS) detection (Shimadzu QP5050A GC/MS system available in PI's lab). If interferences from wastewater constituents limit GC/MS detection for certain key samples, liquid chromatography (LC) with MS detection will be applied for quantification. LC/MS analysis is available from the Chemistry Department at UConn on a fee-per-sample basis.

A number of quality assurance/quality control (QA/QC) checks will be incorporated into the sample design. First, each sample trip will include trip blanks consisting of high purity water that is transferred to a sample container and transported to the sample site. Method blanks consisting of high purity water will be carried through all of the sample preparation and analysis steps. Method spikes will be prepared by adding pharmaceutical compounds to high purity water or samples of wastewater effluent and analyzed to assess compound recoveries. QA/QC checks will account for 10% of sample analyses with a minimum of one trip blank, one method blank and one method spike included in each sampling round. Prior to each sample trip, 2 of the 9 sample locations will be chosen randomly for obtaining duplicate samples.

Boron analyses will be conducted by inductively coupled plasma (ICP) spectrometry (for fee service available from Environmental Research Institute, UConn) and chloride concentrations will be quantified using an ion selective electrode.

Sediment samples will be analyzed using extraction techniques that are currently under development in our lab as part of a USDA-funded investigation of antibiotic fates in agricultural soils. Present sediment extraction techniques (*e.g.* EPA Method 3550) yield inadequate recoveries of polar pharmaceutical compounds; however, competitive displacement, pH and ionic strength adjustments are promising alternate approaches (MacKay, unpublished results).

In all sample analysis techniques, instruments will be calibrated with a 6-point calibration curve. Calibration standards will be run as unknowns every 8 analyses with acceptance criteria of $\pm 15\%$, or as determined in method development.

Conceptual Modeling

Ultimately, the results obtained in this study will be used to assess environmental degradation rates of pharmaceutical compounds. First, observed pharmaceutical concentrations in the Pomperaug River will be compared to expected concentrations given dilution effects of inflowing groundwater and minor stream contributions to the river channel. Dilution effects will be calculated from the stream tracer measurements using the added fluorescent tracer (dispersive

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mixing of sample packet) and the wastewater-derived boron and chloride tracers (fractional contribution of wastewater to total flow) using standard techniques [20]. Insignificant differences on a compound-by-compound basis between observed fluxes and calculated dilution-corrected pharmaceutical fluxes at each downstream sampling point indicate pharmaceutical compounds that undergo no transformations or have no significant loss mechanisms within this ecosystem. On the other hand, observed pharmaceutical fluxes that are lower than obtained solely by dilution will indicate that sinks for these compounds are important within the study reach.

Characteristic environmental degradation rates will be estimated for unconserved pharmaceutical compounds using a simple first-order loss model [20]. This quantitative approach will yield the first reported environmental degradation rate constants for compounds in the pharmaceutical class. However, this approach gives little insight into the exact mechanisms of loss since it quantifies the summative effect of multiple processes (*e.g.*, photodegradation, microbial degradation, sorptive uptake by sediments).

Work Plan and Time Line

PI Dr Allison MacKay will oversee this research project, providing guidance for analytical methods and QA/QC protocols. Sample collection and analysis, including method validation, will be conducted by graduate research assistant Ms. Raquel Figueroa. The following timeline marks milestones in project completion:

March 2003 – Method assessment and validation with genuine standards, preliminary dilution ratio characterization in river channel.

May 2003 – Spring sample collection and data analysis.

August 2003 – Summer sample collection and data analysis.

November 2003 – Fall sample collection and data analysis.

February 2004 – Winter sample collection and data analysis.

March 2004 – Presentation of results to Pomperaug River Watershed Coalition and manuscript preparation.

RELATED RESEARCH:

The results from this research will give important insights into the temporal variability of pharmaceutical fates in engineered and natural systems. For example, comparison of pharmaceutical inputs to the Heritage Water Treatment Facility at the four sample dates will indicate annual source variability of pharmaceutical compounds. The fluxes of individual pharmaceuticals to the Pomperaug River are expected to be lower than the fluxes into the plant. Comparisons of influent and post-chlorination fluxes will indicate the seasonal variability of engineered treatments. For example, bacterial metabolism is higher in summer months and may lead to increased within-plant pharmaceutical removals than during winter months. Comparisons of pharmaceutical fluxes at the post-chlorination and treatment plant discharge points will indicate removal effectiveness in the non-engineering detention pond system. Again, seasonal differences may be apparent, such as decreased photolysis due to algal mat covers in summer, relative to

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winter. Such effects would be indicated by examination of photosensitive pharmaceuticals [e.g., dichlofenac, 23].

Examination of pharmaceutical concentrations in the Pomperaug River will indicate seasonal changes in compound fates over longer residence times. First, seasonal variations in wastewater-to-channel flow ratios will affect pharmaceutical concentrations, and hence, aquatic organism exposures in the river ecosystem. During high streamflow periods such as spring, the annually more constant wastewater flows will form a smaller proportion of channel flow at the discharge site. In addition pharmaceutical concentrations may be more quickly attenuated as a function of distance from the HWTP in spring due to increase groundwater contributions and overland flow throughout the watershed. In addition to apparent changes in pharmaceutical concentrations, environmental loss rates of pharmaceutical compounds may also vary seasonally, reflecting changes in the relative importance of loss mechanisms (e.g., decreased microbial activity in winter, decreased sunlight intensity in winter). Given the modeling approach taken, we will only be able to see summative effects of changes in rates of individual loss mechanisms.

The conclusions drawn from this investigation will broaden the understanding of pharmaceutical fates in the environment. As noted previously, “fates” of pharmaceuticals have been characterized solely on the basis that pharmaceutical compounds have been observed in a variety of environmental studies. Thus, the proposed work is complementary to ongoing survey investigations (e.g., USGS NAWQA survey) because environmental reaction rates for key pharmaceuticals in a river environment will be quantified. Such rates will provide some context within in which to interpret point observations of pharmaceuticals obtained in these surveys (e.g., how far downstream from MWTP discharge point would pharmaceutical exposure risks be important?).

Only two other published investigations have systematically conducted mass balance modeling of a pharmaceutical compound in an environmental system. Poiger’s research group investigated the sources and sinks of diclofenac and triclosan in a Swiss lake [23, 24]. Analyte concentrations were measured at lake inputs and outlet, as well as depth profiling at various locations in the lake. Well-controlled laboratory studies were conducted to quantify the characteristic rate constants of the hypothesized degradation processes of photolysis and microbial degradation. These rate constants, along with turbulence parameters and inlet concentrations were input to a mixing model of the lake to predict the observed. Predictions were consistent with observations, indicating that the key removal processes were captured with modeling effort. A key difference between the Swiss work and the study proposed here is the inclusion of pharmaceutical compounds with known toxicological activities in non-target organisms at environmentally relevant concentrations (e.g., beta-blockers).

Observations made in the study outlined in this proposal will also direct future mechanistic studies into the fate and risks posed by pharmaceuticals in the environment. For example, controlled laboratory investigations can be designed to identify mechanisms for compound removal for pharmaceutical compounds that are not conserved in the Pomperaug River ecosystem. On the other hand, pharmaceutical compounds that show little decrease in concentration, beyond dilution effects, warrant ecotoxicological investigations as these represent chronic contaminants. Evidence for detrimental effects could be obtained through examination of biomarkers of pharmaceutical exposure in aquatic organisms. Such investigations are beyond the

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scope of the work proposed here, but will be pursued in future through other funding opportunities.

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TRAINING POTENTIAL:

This project will provide half-time support to a Level II graduate research assistant who will be responsible for coordinating the sampling trips, conducting sample analyses, and interpreting data. Additional involvement of volunteer graduate or undergraduate researchers from PI MacKay's research group will occur on sample days, thus exposing these students to field sampling techniques. Results from this study will also be incorporated into Dr. MacKay's courses in Water Quality Engineering (CE260) and Environmental Engineering Chemistry (CE390, CE490) to expose undergraduate and graduate students to current topics in environmental contamination and data analysis.

INFORMATION TRANSFER PLAN:

Results from this 1-year study of temporal and spatial distributions of pharmaceuticals in the Pomperaug River will be published in the peer-reviewed journal *Environmental Science and Technology*. This publication will contain some of the first reported environmental degradation rate constants for compounds in the pharmaceutical class. An oral presentation of the results will be made to the Pomperaug River Watershed Coalition to foster integration of this water quality investigation with on-going activities in the study watershed. Identification of this study site was undertaken in collaboration with the Chairman and co-founder, Dr. Marc Taylor.

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