POPULATION DYNAMICS AND PHARMACEUTICAL CONTAMINATION IN STREAMS AND RIVERS ACROSS THE UNITED STATES

by

Stephanie Gordon

A Thesis
Submitted to the
Graduate Faculty
of
George Mason University
in Partial Fulfillment of
The Requirements for the Degree
of
Master of Science
Environmental Science and Policy

Committee:

_____ Dr. Gregory Foster, Thesis Director

_____ Dr. Thomas Huff, Committee Member

_____ Dr. Enrique Montano, Committee Member

_____ Dr. Ingrid Visseren-Hamakers,
Graduate Program Director

_____ Dr. A. Alonso Aguirre,
Department Chairperson

_____ Dr. Donna Fox, Associate Dean,
Student Affairs & Special Programs,
College of Science

_____ Dr. Peggy Agouris, Dean,
College of Science

Date: _____ Spring 2019
George Mason University
Fairfax, VA

Population Dynamics and Pharmaceutical Contamination in Streams and Rivers Across the United States

A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at George Mason University

By

Stephanie Gordon
Bachelor of Arts
James Madison University, 2013

Director: Gregory D. Foster, Professor
Department of Chemistry and Biochemistry

Spring Semester 2019
George Mason University
Fairfax, VA

ACKNOWLEDGEMENTS

I would like to acknowledge the effort and support of my family and friends who have been extraordinarily supportive, thoughtful, and patient as this degree process and writing dragged on. Particular recognition goes to my older sister/editor/cheerleader who has read my writing more times than any person should have to, and to my husband, who has always supported me in everything.

I would also like to thank my thesis committee members, Dr. Huff and Dr. Montano, for hanging in there through many delays, and a special thanks to Dr. Foster and Arion Leahigh who put in an extraordinary amount of effort trying to pull together a heap of data to make this thesis complete.

Finally, I'd like to thank the team at Fairfax County Government for helping pull together all the local population data for this effort.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ACS.....American Community Survey
API.....Active Pharmaceutical Ingredient
CART.....Classification and Regression Trees
CDC.....Centers for Disease Control
CSO.....Combined Sewer Overflow
DMR.....Discharge Monitoring Report
EPA .....Environmental Protection Agency
GCMS.....Gas Chromatography–Mass Spectrometry
GMU.....George Mason University
HUD.....Department of Housing and Urban Development
LC-MS/MS.....Liquid Chromatography-Tandem Mass Spectrometry
LRL.....Lab Reporting Limit
MDL.....Method Detection Limit
NHD.....National Hydrography Dataset
PPCP.....Pharmaceutical and Personal Care Products
UA.....Urbanized Area
UC.....Urbanized Cluster
USCB.....United States Census Bureau
WWTP.....Wastewater Treatment Plant

ABSTRACT

POPULATION DYNAMICS AND PHARMACEUTICAL CONTAMINATION IN STREAMS AND RIVERS ACROSS THE UNITED STATES

Stephanie Gordon, M.S.

George Mason University, 2019

Thesis Director: Dr. Gregory D. Foster

Pharmaceutical contamination of surface waters across the United States has become an issue of increasing concern and study. These compounds can negatively impact the health of aquatic species and present an exposure risk to other species and humans who interact with contaminated water or use them as a source of drinking water. Pharmaceutical compounds and metabolites can enter streams from multiple sources including leaky sewer pipes, septic tanks, sewer overflow, and wastewater treatment plant effluent. Although human use is undoubtedly the main source of pharmaceutical loading to streams, stream contamination studies often focus on landscape point and non-point sources as it is difficult to geographically define populations affecting contamination in surface waters. This study develops a method to identify and define human populations contributing to environmental water contamination and additionally uses previous sampling efforts to apply this method at three scales: national, regional, and local. The

method developed is also used to understand the relationships between population demographics and socioeconomic factors with type and concentration of pharmaceuticals at each scale using Classification and Regression Tree (CART) analysis. Results indicate that at the national scale, income is an important variable in determining presence of a variety of pharmaceutical groups while at the regional scale age and gender variables were most important. Results at the local scale were not able to be generated with the data available. The method presented and subsequent results may be useful in future study efforts to tailor sampling locations and lab efforts to pharmaceuticals of interest based on contributing populations.

INTRODUCTION AND BACKGROUND

Contamination of surface waters across the United States has been an increasingly important issue and the focus of studies at multiple scales (Barnes et al., 2008; Batt, Kincaid, Kostich, Lazorchak, & Olsen, 2016; Focazio et al., 2008). A national reconnaissance of pharmaceuticals and other anthropogenically sourced compounds in streams found that more than 80% of streams tested positive for contamination (Kolpin et al., 2002). In particular, pharmaceuticals in streams and rivers have been a target of interest as they have been observed to negatively impact aquatic species (Ramirez et al., 2009), present a risk of exposure to species interacting with contaminated water and have even been detected in drinking water sources and tap water in households (Benotti et al., 2009).

Pharmaceutical compounds can enter surface waters through a variety of pathways, the most well-known being discharge form wastewater treatment plants (WWTPs) that treat human waste and release pharmaceuticals and other organic waste compounds to stream water (Stackelberg et al., 2004). Suites of these compounds have been shown to persist downstream from sources (Barber et al., 2013), and can have negative effects on the downstream aquatic ecosystems (Sanchez et al., 2011). Not all releases of waste have undergone treatment and sewer systems can release untreated

water back into streams and river via combined sewer overflows (CSOs), which are a known source of wastewater pollutants and hormones (P. Phillips & Chalmers, 2009; P. J. Phillips et al., 2012). Additionally, leaking underground pipes can release untreated wastewater into the ground, allowing contaminant to flow back to streams through groundwater, and leaking or discharging septic tanks have been shown to be a source of contaminants far downgradient from their location (Carrara et al., 2008; Conn, Lowe, Drewes, Hoppe-Jones, & Tucholke, 2010; P. J. Phillips et al., 2015; Swartz et al., 2006).

An important factor in the influence of sewer systems on water quality is the question of whether the underground sewer pipes are releasing contaminants and compounds into the groundwater. CSO outlets, WWTP effluents, and flooded retention ponds are an obvious source of contamination to surface waters. However, groundwater seepage is responsible for providing baseflow of streams (water flow that is not influenced by rainfall or overland flow after a precipitation event), and associated contaminants in the groundwater, particularly water-soluble contaminants, can be released into the surface waters (Fitzgerald, Roy, & Smith, 2015). Sewer pipes are one potential source as pipes deteriorate and leak with age. A study of groundwater in Germany found severe groundwater infiltration into the sewer pipes during high-pumping times as well as increased levels of contaminants in the groundwater under the sewer system, indicating that the leaky pipes were the dominant source of groundwater contamination in that area, despite the fact that the sewer system was only 30 years old (Eiswirth & Hötzl, 1997). In California, sites with a high probability of underground pipe failure based on a model including age and pipe material had high similarity score

between analysis of sewerage and surrounding groundwater samples, indicating that exfiltrating sewers were the likely source (Lee et al., 2015). Although an exact age for determining a leaky or potentially faulty sewer system is hard to pin-down, in the United States many major sewer systems were built following the end of World War II, and some of the oldest sewer systems dating back to the 1800s are still in use (Burian, Nix, Pitt, & Durrans, 2000; Evans, 2015). The US Department of Housing and Urban Development recommends inspecting and replacing home sewer pipes made of steel if they are anywhere from 20-50 years old, replacing copper piping, which came into widespread use in the 1930s, when they are about 50 years old (translating to the 1980s for most of the country), and replacing yellow brass around 40 years old (HUD, 2000). Other than the obvious outputs of pharmaceutical-laden water from combined sewer overflows, leaky sewer pipes and WWTP effluent, pharmaceuticals find a path to surface water and drinking water sources from leaking underground septic tanks. Bradley et al. (2016) found no significant difference in the pharmaceutical concentrations between sites with small WWTP discharges and no WWTP discharges, suggesting that sources other than direct WWTP effluent are responsible for the presence of pharmaceuticals in surface water. Further, anoxic zones around large septic tanks have been found to harbor similar levels of anthropogenic compounds to those inside the septic tanks, and some of these compounds have been found at elevated levels far downgradient of the septic system (Swartz et al., 2006).

Although not every compound found in surface waters has been assessed for its potential to negatively impact human or aquatic populations, Sanderson et al. (2004) used

chemical modeling techniques and various physical activity factors of pharmaceutical compounds found in surface waters to rank pharmaceutical groups by potential environmental hazard level. From this study, cardiovascular, gastrointestinal, antiviral, anxiolytic sedatives, hypnotics and antipsychotics, corticosteroids, and thyroid pharmaceuticals were ranked as the most hazardous pharmaceutical classes. These pharmaceutical groups all exhibit high potential for ecotoxicity, bioaccumulation, and persistence in sewage sludge. In the aquatic environment, the presence of pharmaceuticals has been directly linked to a variety of negative impacts on benthic communities, aquatic vegetation and fish populations. These range from altered species dynamics stemming from altered endocrine system function in fish (Blazer et al., 2014; Blazer et al., 2011; Iwanowicz et al., 2016), to acute toxicity affecting survival or growth of benthic invertebrate populations (Dussault, Balakrishnan, Sverko, Solomon, & Sibley, 2008). Some pharmaceutical compounds are shown to directly bioaccumulate through the aquatic food chain (Lagesson et al., 2016), which can affect other species including humans through the ingestion of contaminated food. However, the more important exposure factor to humans is the mere presence of pharmaceuticals in surface waters, to which they are directly exposed or use as drinking water (Deo & Halden, 2013; Furlong et al., 2017).

Efforts to link human population presence and dynamics have generally focused on quantifying illicit drug use in an upstream population (Burgard, Banta-Green, & Field, 2014), known as sewer or wastewater-based drug epidemiology. This method relies on using sewage influent (just before treatment at a WWTP) to assess drug use in upstream

communities. Studies often employ census data or a wastewater facility's design capacity to assess the population size for a given sewer treatment area and draw conclusions about the use of certain substances within the population (O'Brien et al., 2014; Rico, Andrés-Costa, & Picó, 2017). However, these studies usually estimate a proportion of population use, do not address a range of pharmaceutical types, and don't seek to understand the demographic factors like age of the population, gender, race, or socioeconomic status, that could be influencing the presence of certain substances.

Alternatively, stream contamination studies have generally focused on point and non-point landscape sources to understand the relationships between water quality endpoints and those sources (Ciparis, Iwanowicz, & Voshell, 2012; Osorio, Larrañaga, Aceña, Pérez, & Barceló, 2016; Veach & Bernot, 2011; Young, Iwanowicz, Sperry, & Blazer, 2014). Many of those studies also contain source data that links back to human waste presence, for example WWTPs or CSOs in a watershed. However, few studies address the influence of human populations on stream contamination in areas where a WWTP is not present.

Previous reports have indicated that a potentially large source of pharmaceuticals found in septic and sewer effluent are the result of dumping or flushing of pharmaceuticals down the drain (Tong, Peake, & Braund, 2011). However, the studies reported in that review detailing this practice in the US were all conducted prior to 2007, when the first federal guidance to dispose of pharmaceutical in the trash was passed (Glassmeyer et al., 2009). Vatovec et al. (2016), in a study designed to understand pharmaceutical disposal practices and how shifting population dynamics alter

pharmaceutical contamination, concluded that the practice of flushing or dumping medications is uncommon, and unused medications were most likely to be disposed of in the trash as solid waste. The study expected to find a spike in pharmaceutical loads during move out, when students are assumed to dispose of any unwanted or unused medication, but the relatively unchanged overall concentration of total pharmaceuticals in the effluent over the 10-day period confirmed that flushing was not a regular disposal method. This study also found that during the move-out period, the concentrations of diabetes/ulcer medications, cardiovascular medications and anti-histamines all increased as the younger population left, and the older population became more prevalent. Thus, the other important finding in this study was that the age of population was most important factor in type of pharmaceuticals found in effluent, but not total loads.

Additionally, it may seem obvious to simply use prescription rates as an indicator of potential environmental contamination. However, non-adherence to prescribed medications is widespread in the United States and is generally seen in people under-using, rather over-using, prescribed medications (Nieuwlaat et al., 2014). According to Viswanathan et al., (2012), "Studies have consistently shown that 20 percent to 30 percent of medication prescriptions are never filled, and that approximately 50 percent of medications for chronic disease are not taken as prescribed." On top of that, people who do fill and take their medications usually only take half the prescribed amount (Nieuwlaat et al., 2014).

While there is evidence that many of the landscape sources are tied back to human presence (the main sources being WWTPs, CSOs, impervious surface density, asphalt

and coal tar sealant (Bryer, Scoggins, & McClintock, 2010; Sackett et al., 2015), very few studies address the influence of population dynamics of people living in these areas on the concentration and range of contaminants found in water downstream. Wastewater treatment facilities discharging treated human waste are a proven source of anthropogenic contaminants in streams, however septic tanks, leaking pipes and other sewer outfalls have also been established as a source of organic wastewater contaminants to groundwater and surface waters (Swartz et al., 2006). As such, the inputs from people to all these systems should be assessed.

This study will leverage the previous field work carried out by the Environmental Protection Agency (EPA), United States Geological Survey (USGS) and George Mason University (GMU) as part of larger water quality assessments. These studies represent sampling and pharmaceutical analysis at national, regional, and local scales and provide an avenue to develop methods to identify and analyze population dynamics in relation to surface water contamination. These studies were conducted to assess pharmaceutical concentration in surface waters and address a lack of data for pharmaceutical occurrences in streams and rivers across the United States. Similarly, this study seeks to address a lack of knowledge concerning the influence of population dynamics on pharmaceutical occurrences in rivers and streams. Specifically, answers to the question of what influence human population demographics (including age, gender and socioeconomic dynamics) have on pharmaceutical chemical presence and concentrations in streams are addressed. Therefore, this study creates a method to define the contributions of human populations to surface waters at three scales using different levels of data resolution. Additionally,

using this method and non-parametric statistics, this study also explores the relationships between demographic factors and pharmaceutical types and concentrations at each scale.

MATERIALS AND METHODS

Study Areas and Pharmaceutical Data

To understand human population-pharmaceutical contamination relationships at different scales, data were obtained from three different studies including a large, national scale study (Batt et al., 2016), regional headwater stream survey (Bradley et al., 2016), and detailed local sampling above and below three different wastewater treatment facilities (Foster et al., 2019; Arion Lehigh, personal communication) (Figure 1). Pharmaceutical and study area data for the National scale analysis were acquired from previously published work by Batt et al. (2016) which measured pharmaceutical concentrations at 182 sites selected from the Environmental Protection Agency's (EPA) 2008 and 2009 National Rivers and Stream Assessment (EPA, 2016). These sites were sampled one time each, between June 2008 and January 2010, and are primarily urban locations on larger order (>5th order) streams and rivers, about half of which were sampled downstream from a wastewater treatment plant. Samples were analyzed for a suite of 54 active pharmaceutical ingredients (APIs) using LC-MS/MS. Details of the study design and sampling methods are provided in Batt et al. (2016). Following the steps taken for statistical analysis in the original study, records marked as "non-detect" were replaced with ½ times the method detection limit value for each compound (Batt et al., 2016).

For the regional analysis, data was obtained for 59 study sites in the southeastern United States from Bradley et al. (2016). The sites cover a range of urban and rural landscapes, extending through high density urban areas in Atlanta Georgia, Greenville, South Carolina, Charlotte, North Carolina and Washington, DC. Each site was sampled five times from Spring to early Summer of 2014. The mean value of the five samples was then calculated by compound for each site. Stream samples were analyzed for 108 anthropogenic marker compounds using GCMS. A detailed description of sampling and analysis methods employed are available in Bradley et al. (2016). Many of the samples were recovered below the lab reporting limit (LRL) and were therefore reported at a censored value. In those cases, the new value was calculated as half the censored value reported, following previous guidelines wherein lab reporting levels are set at two times the long-term method detection level by the lab reporting the values (Childress et al., 1999).

At the local scale, George Mason University conducts annual sampling in conjunction with the Alexandria Renew Wastewater Treatment Facility in Alexandria, Virginia. Water samples were collected from Hunting Creek (Alexandria, VA) three to five times, with sampling occurring in spring, summer, and fall of 2018, and analyzed for 91 pharmaceuticals and personal care products (PPCPs). Additionally in 2018, sites adjacent to two other wastewater treatment facilities, Arlington County WWTP and Noman Cole Jr. Pollution Control Plant, were also sampled and analyzed for PPCPs (Arion Leahigh, personal communication). Although samples in the above local scale studies were taken from the mainstem Potomac River, these sites were not used in this

study because detailed sewersheds were not available for all WWTPs upstream of the mainstem Potomac sites. The samples were analyzed using LC-MS/MS and censored values were replaced with ½ the method detection limit (MDL). Details on sampling and laboratory analytical methods are provided in Foster et al. (2019). The average value of PPCP compounds across samples above and below the outfall pipe were summed by pharmaceutical use group to be used for statistical analysis.

For all studies, pharmaceutical compounds and metabolites were classified into broader use and type categories. Compounds identified as not representative of pharmaceutical use (aspartame, triclocarban, perfluorooctanoic acid), whose primary purpose was veterinary use (sulfadimethoxine, sulfamethazine, sulfaquinoxaline, sulfathiazole, enrofloxacin), identified as an herbicide or insecticide (DEET, atrazine, periponyl butoxide), or compounds with multiple primary treatment applications (clonidine) were removed. Remaining compounds were categorized based on their primary use, or if the compound was identified as a metabolite, that metabolite was categorized into the same group as the parent compound. Carisoprodol, a primary metabolite of meprobamate, is also separately prescribed as a muscle relaxant. Given the decline in meprobamate prescriptions since the 2010s (James, Nicholson, Hill, & Bearn, 2016), carisoprodol was placed in the muscle relaxants category. The final groups for analysis were: antibiotics, anticholinergics, anticonvulsants, antidepressants, antidiabetics, antidiarrheals, antifungals, antihelmintics, antihistamines, antilipemics, antimetabolics, antivirals, anxiolytics, aromatase inhibitors, benzodiazepines, blood thinners, bronchodilators, cardiovasculars, corticosteroids, cough suppressants, diuretics,

hormones, illicit, muscle relaxants, opioids, opioid antagonists, pain relievers (non-opioid), selective estrogen receptor modulators (SERM), stimulants, and stomach acid reducers (Appendix A).

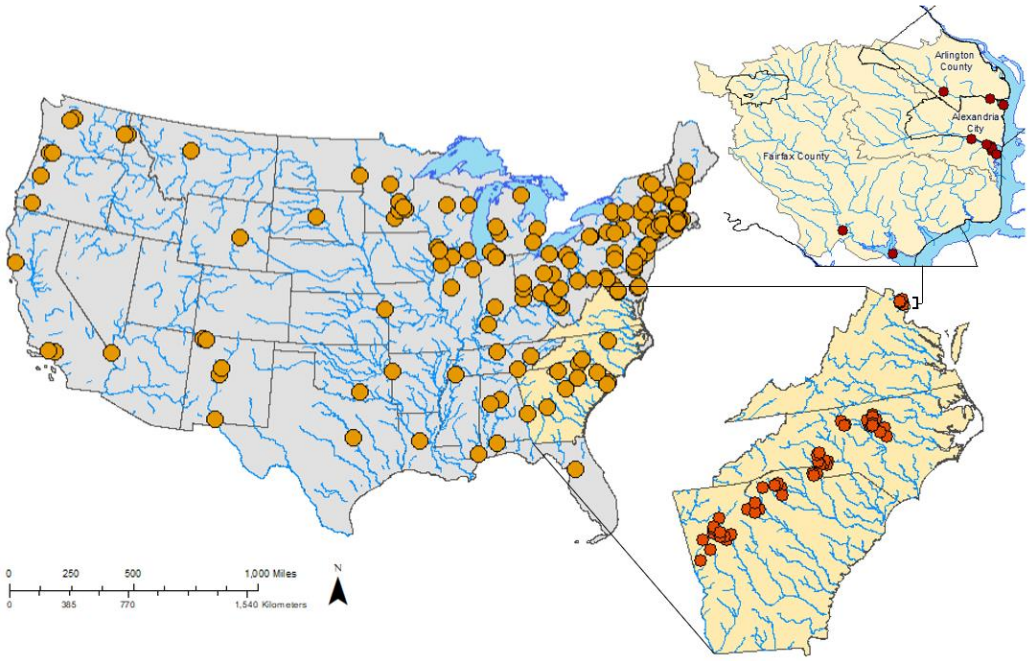


Figure 1. Map of study areas at the national (left), regional (bottom right), and local (top right) scale.

Watersheds

At the national scale, watersheds were available as part of the larger EPA effort to provide site and landscape data for aquatic surveys. Watersheds were downloaded for all sites included in the 2008-2009 EPA Rivers and Streams Assessment from the EPA National Aquatic Resources Survey data download page (https://www.epa.gov/national-aquatic-resource-surveys/data-national-aquatic-resource-surveys), and were matched to

the sites used by Batt et al. (2016) using the unique identifier "SiteID". Any watersheds whose boundaries extended beyond the political boundaries of the conterminous United States were removed, leaving 151 sites for further analysis (see Figure 1).

At the regional scale, the latitude and longitude of each site was used as input into USGS StreamStats V4 web application (https://streamstatsags.cr.usgs.gov/streamstats/). The StreamStats application delineates watershed boundaries using digital elevation data from the USGS 3D elevation program processed to match high-resolution National Hydrography Dataset (NHD) streamlines (Ries et al., 2017). Watershed boundaries for regionals sites were downloaded as individual polygon shapefiles for each site.

Watersheds for all sites at the local scale were also delineated and downloaded using the coordinates of the sampling location as input to the StreamStats application.

Sewersheds

At the national scale, sewersheds for individual wastewater treatment facilities were not available and contacting all WWTPs present in the 151 national watersheds was beyond the scope of this study. Instead, a surrogate sewer treatment area was developed using Tigerline shapefiles from the US Census Bureau (USCB). The Tigerline geographies representing urban areas, defined as "all territory, population, and housing units located within urbanized areas (UAs) and urban clusters (UCs)" (USCB, 2014) and the places boundary dataset which contain areas identified as "a city, town, village, or borough, [among] other legal descriptions" (USCB, 2014) were downloaded from the Tigerline FTP site to serve as areas likely treated by sewer, rather than septic, infrastructure. These

were downloaded from the 2009 geographies to coincide with the sampling time frame of the study.

Sewer treatment areas for the regional scale (Figure 2) were available from a variety of sources. For Virginia, direct sewer treatment areas were obtained from USGS, (Peter Claggett, personal communication) and for North Carolina from the North Carolina OneMap Geospatial Portal (http://data.nconemap.gov/). Data for sewer treatment areas for South Carolina and Georgia was unavailable at the time of the study. Instead, for South Carolina, boundaries of municipal areas obtained from South Carolina Department of Transportation download portal (http://info.scdot.org) and were combined with the Tigerline urban areas boundary dataset and the places boundary dataset downloaded for 2014 from the Tigerline FTP site. For the state of Georgia, very few datasets were available and sewer treatment areas were estimated using only the urban and place area boundaries. Together the urban, place, and municipal areas serve as a surrogate for potentially sewered areas throughout the states of Georgia and South Carolina.

Sewer treatment areas for Alexandria Renew and Noman Cole Jr. WWTPs are available from the Fairfax County Government public works webpage (https://www.fairfaxcounty.gov/publicworks/wastewater/wastewater-treatment). Images were georeferenced to county boundaries using ArcMap 10.6.1 (ESRI, 2011) and sewer treatment areas were hand-delineated. Arlington County WWTP treatment area was also hand-delineated using maps from the Blue Plains WWTP (DC Water, 2016) along with the Fairfax County maps.

Wastewater Treatment Plants

Wastewater treatment facilities were downloaded for the United states using the EPA Discharge Monitoring Report (DMR) pollutant loading tool (https://echo.epa.gov/tools/web-services/loading-tool). The EPA DMR includes annual reports from Clean Water Act permitted dischargers and includes a variety of facility types (EPA, n.d.). This was used so that the monitoring period could be specified to coincide with the sampling time frame. Because all the USCB data used for the national scale study is 2009, this was chosen as the monitoring period for the DMR pollutant loading tool as well. Points were downloaded as CSVs (comma-separated-value files) for each EPA region for the time period January 1 – December 31, 2009, using the search criteria 2-digit SIC code = 49 (electrical, oil and sanitary facilities). The files were joined and cleaned in R (R Core Team, 2017) to remove duplicate permit features and duplicate facilities. DMR facilities and DMR outfalls were displayed in ArcGIS using the facility latitude and longitude for facility locations, or for outfalls using the permit feature latitude and longitude. These points were clipped to the surrogate sewer areas and were cleaned using keywords to flag and remove records that were not related to water treatment services.[1] At this point, the cleaned DMR facilities representing wastewater treatment (which here includes lagoons, CSOs, and various types of water pollution treatment facilities) were used to subdivide the surrogate sewer areas into individual areas of influence, roughly approximating the sewer treatment area for each facility. This was

[1] Keywords: Oil, power, gas, electric, hydroelectric, nuclear, generat, energy, manufacture, manufacturing, asphalt, development, steam, LNG, landfill, desalination, FWSD, supply, TMDL, offshore, energy, well, zuni plant, disposal, recycling, dominion, station, pump

done using Thiessen Polygon function in ArcMap. Thiessen polygons can be used to apportion point coverage into a polygon layer where each polygon only contains one point. The polygons are created so that all location within a polygon are closer to the point within that polygon than any other point from the original point file (ESRI, 2019). In this case, the Thiessen polygons function as individual sewer treatment areas for individual WWTPs (Figure 2).

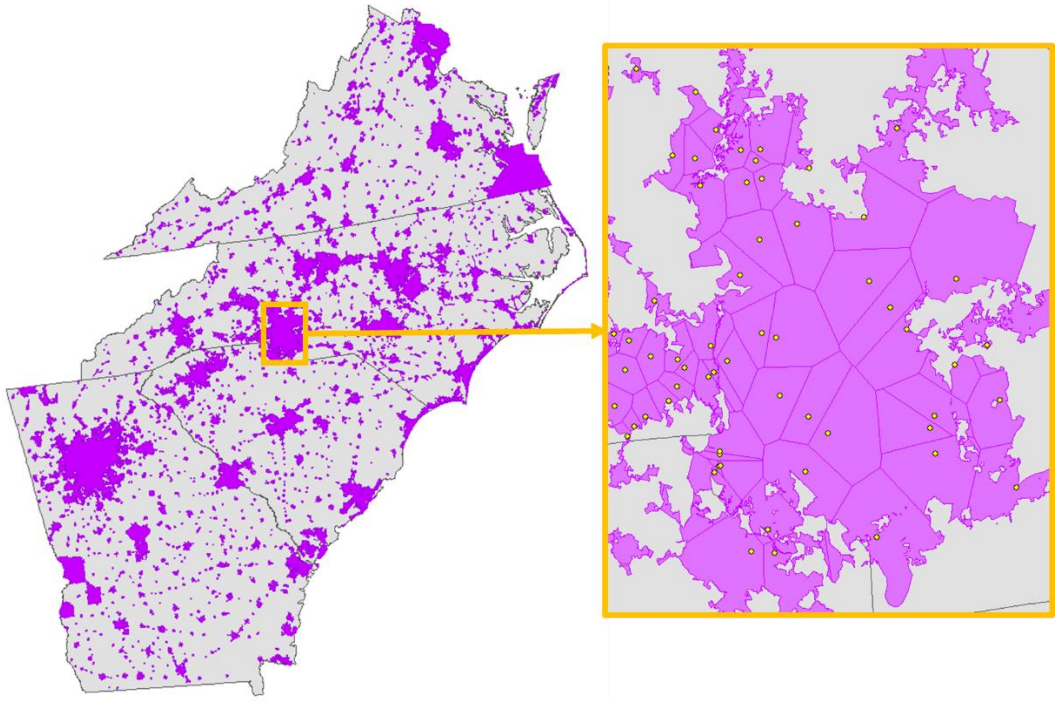


Figure 2. Example of using surrogate sewer treatment areas at the regional scale (left) and the EPA DMR facilities (yellow points, right) to define individual sewer treatment areas for each facility (right).

Final Treatment Areas

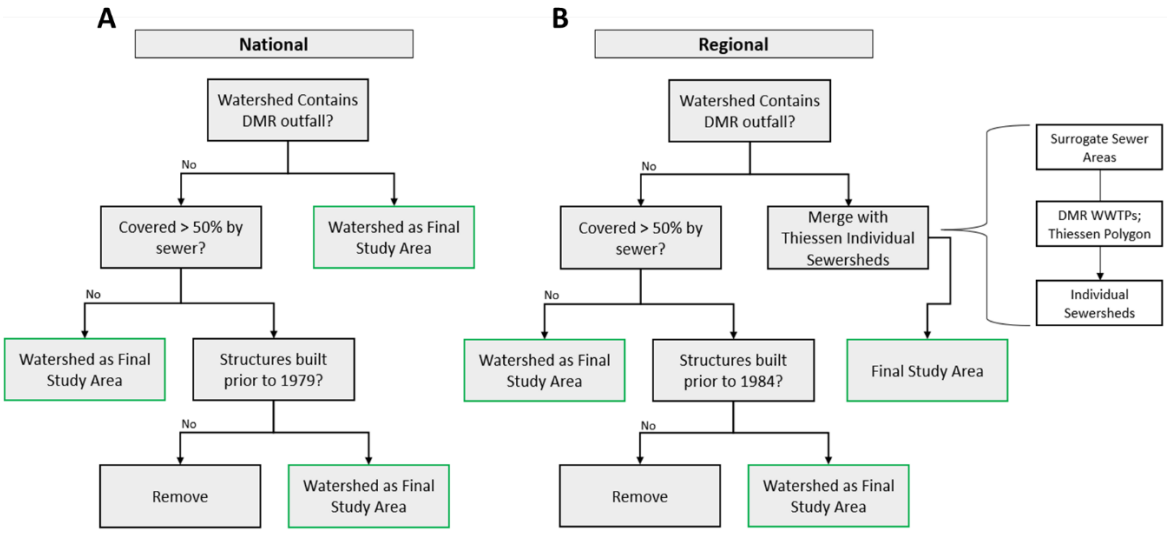


Figure 3. Flow chart describing how final study areas are determined for the A. national and B. regional scales. At the local scale, all study sites not on the mainstem of the Potomac River were kept.

To define the total population and sources contributing to the sample sites, final treatment areas had to be created that capture both the sewersheds and watersheds upstream of each site.

At the national and regional scales, a set of decisions were made to refine the final treatment areas based on sewer treatment areas and watersheds (Figure 3). At the national scale, the watersheds attributed to the study sites were large, on average encompassing about 297,000 square kilometers, with only one watershed below 500 square kilometers. As a result, the watersheds generally encompassed the entirety of the upstream urban/place areas that would include sewer populations. Watersheds identified as having

DMR outfalls were kept for final analysis. Any watersheds that had no DMR outfalls were only kept for further analysis if the watersheds encompassed an area that was less than 50% sewered, or, if they were 50% sewered but had no outfalls, the watershed was kept if the average median age of structures by census tract meant the structures were built before 1979. This follows the HUD guidelines and a previous study finding that infrastructure over ~ 30 years old is potentially leaking contaminants into groundwater and surface waters (Eisworth & Hötzl, 1997; HUD, 2000). Therefore, these final study areas represent watersheds where at least 50% of the population within it is contributing compounds to the sampled water. Following these rules (Figure 3A), only one site was removed from final analysis, leaving 150 sites for final statistical analysis.

The regional scale analysis followed a similar set of rules for defining final treatment areas, with the exception that watersheds which contained a sewer outfall were merged with the sewershed for the associated facility to create a new final treatment area that encompasses the population contributing to stream contamination at that point from septic and sewer influences (Figure 3B, Figure 4). Otherwise if a watershed had no DMR outfalls, was less than 50% sewered or had structures more than 30 years old, the watershed was kept as the final treatment area. Following these rules, 11 watersheds were identified as containing a DMR outfall. Of these, two watersheds that contained DMR outfalls didn't have any sewer treatment areas to associate with it as the sewer facilities were outside the municipal/urban/place boundaries. In total, nine watersheds have additional sewer treatment areas merged with the watershed for the final treatment area. Thirteen watersheds had no DMR outfall and an average median build date before 1984,

and were removed prior to statistical analysis, leaving 46 final treatment areas to define the upstream contributing populations.

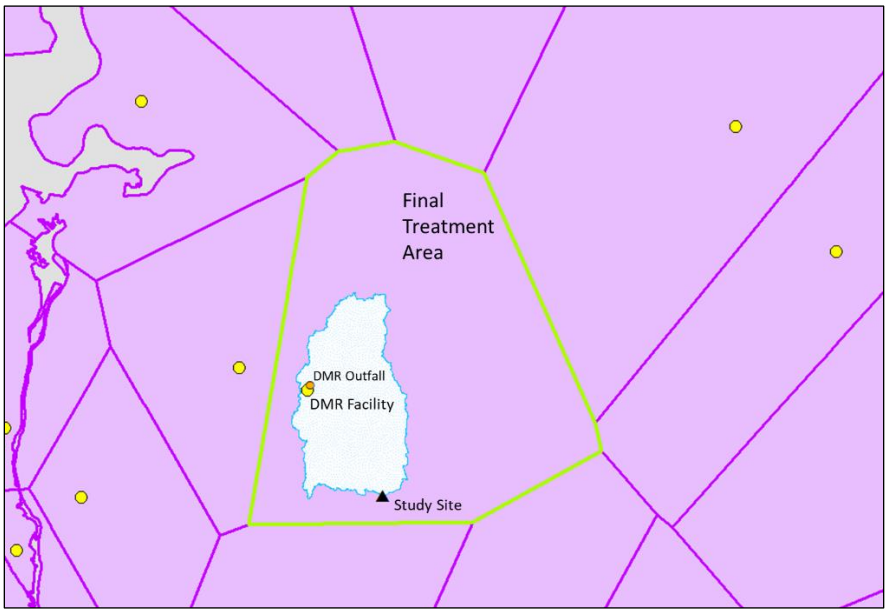


Figure 4. Example of merging the watershed (outlined in blue) and sewer treatment area to define a final treatment area (green) at the regional scale. The site shown is in Charlotte, North Carolina.

At the local scale, watersheds for the sites above the WWTP outfalls were used to define the final populations, while sites below the outfalls were merged with the hand-delineated sewersheds. If sites below the outfalls had almost identical final treatment areas, the sites were joined as the upstream contributing population were also almost identical. Upon closer inspection there are several DMR facilities within the boundary of each sewershed, however these are bus or rail terminals, auto shops or other types of regulated facilities and the only regularly discharging population treatment plants are the Noman Cole Jr. facility, Alexandra Renew, and Arlington County WWTP. Build date of

structures ranged from before 1939 to 2007, with the average build date being 1965, so all watersheds were kept for statistical analysis.

Census Data

Data for the census block groups was obtained from the Tigerline FTP download site (https://www.census.gov/cgi-bin/geo/shapefiles/index.php). Census block groups were downloaded as ESRI shapefiles for 2014. Population data was downloaded from the American Community Survey (ACS) download center (https://factfinder.census.gov/faces/nav/jsf/pages/download_center.xhtml) for four community characteristics which were thought to be potentially influential factors on the presence of pharmaceuticals in streams: total population, sex by age, race, and income for the past 12 months. Median age of structures was also downloaded for use in defining and selecting final study areas for statistical analysis. All ACS data was downloaded from either the 2009 or 2014 5-year ACS[2] estimates, to coincide with the stream sampling dates, and joined to the Tigerline blockgroup shapefiles in ArcMap by the GEOID field. Given the large number of census groups (n = 72), age groups and income brackets were simplified into 5 age ranges by male and female, representing percent of the total population, and 5 income ranges representing percent of total houses earning incomes within that range (Table 1). Race categories were also simplified into 6 categories; population estimates for people identified as Hispanic were not provided in ACS table B02001 and were not included in this study. Percent coverages of each census block that

[2] ACS tables used: B01001 "Sex by Age", B02001 "Race", B19001 "Household Income in the Past 12 Months", and B25035 "Median Year Structure Built"

fell into watersheds or sewer treatment area were calculated in ArcMap and used to determine total population, sex by age of residents (percent by age group), race (percent by race), average median income and average median age of housing structures for the study area.

ACS data for 2018 was not released at the time of the study for use at the local scale. However, population estimates for similar demographic categories were provided by Fairfax County GIS services (Katherine Miga, personal communication) using ESRI Business Analyst demographic estimates to provide annual estimates per block group. These estimates utilize the ACS census data in addition to postal records and other sources to estimate more precise populations at similar geographies (ESRI white paper). Categories were aggregated into groups resembling the ACS groups used at the larger scales (Table 1).

Table 1. Final population categories for analysis. *Indicates values used only at the local scale.

Final Population Categories	
Total Population (count)	Percent Male Age 0 - 19
Percent White	Percent Male Age 20 - 49
Percent Black	Percent Male Age 50 - 79
Percent Native American	Percent Male over 80
Percent Asian	Percent Female Age 0 - 19
Percent Hawaiian or Pacific Islander	Percent Female Age 20 - 49
Percent Other Race	Percent Female Age 50 - 79
Percent Male	Percent Female over 80
Percent Female	Percent of Households Earning under 35k*
Percent of Households Earning under 30k	Percent of Households Earning 35k - 49k*
Percent of Households Earning 30k - 60k	Percent of Households Earning 50k - 99k*
Percent of Households Earning 60k - 99k	

Percent of Households Earning 100k to 150k	
Percent of Households Earning over 150k	

Statistical Methods

Although the primary purpose of this paper is to establish a method by which aquatic contaminants can be attributed to upstream population demographics, an additional step was taken to understand the nature of these relationships with pharmaceutical types and concentrations at all three levels. Classification and Regression Trees (CART) analysis was used to develop models for each scale and response combination using the rpart package in R (Therneau, Atkinson, & Ripley, 2017). CART is a method of analysis that's particularly useful in the study of environmental data as it is designed to handle non-linear and missing values, which are often present in environmental data (De'ath & Fabricius, 2000). The output of a single tree is represented graphically by building down from the current mean value of the response data, with splits at significant explanatory variables. The primary split is the most important explanatory variable and subsequent data splits aim to partition the response variable into homogenous groups based on the mean value of the response variable (De'ath and Fabricius, 2000). Given the presence of outliers in the datasets (see Appendix A), an attempt was made to select variables to input into the CART models using the randomForest package in R (Liaw and Wiener, 2002) to build 1000 trees and select important features; however, this process did not change the variables selected by the CART trees and this method was deemed unnecessary for this study. The trees identify a threshold in the independent variable above and below which

you can expect a new higher or lower mean value of the response variable. CART trees can produce results with many levels and interior branches, allowing for a more nuanced understanding of the relationships with different values in the response variables. However, for this study only the relationships leading to the highest mean value of each pharmaceutical category are reported.

RESULTS

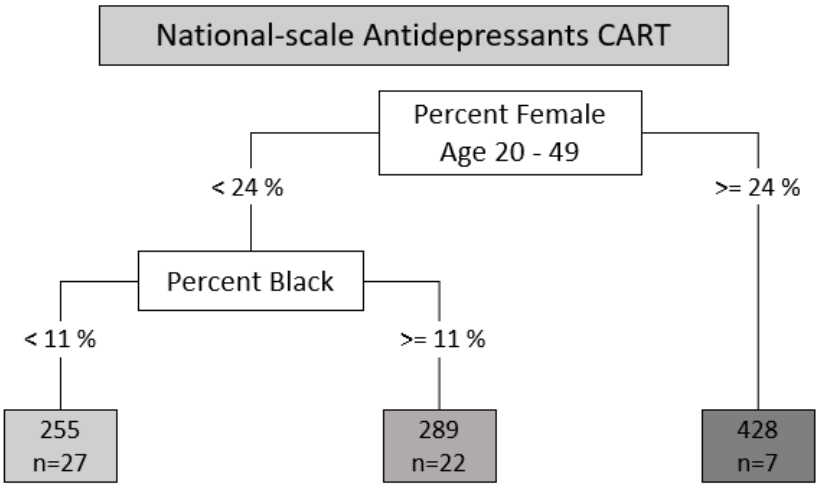


Figure 5. Example of results from CART at the national scale with concentration (ng/L) of compounds identified as cardiovascular use as the response variable. The first variables at the top of the tree is the most important variable for splitting the response into a higher and lower mean value. The box on the bottom right (dark gray) indicates the highest mean concentration based on the threshold identified in the independent variable. The highest concentrations of cardiovasculars occur when percent of the population that is female age 20 – 49 is greater than 24%. The box on the bottom left (light gray) is the lowest mean concentration identified by following the splits back up to the primary split. Here the lowest mean value of cardiovascular compounds occurs when the population is comprised of < 24% females age 20 - 49 and percent of the population identified as Black is less than 11%.

An example of the CART model results for national-scale antidepressants can be seen in Figure 5. The first variable indicated at the top of the tree is considered the most important in determining the relationship between demographics and concentration. The highest mean concentration of antidepressants is indicated along the outermost branch to

the right of the tree, while the lowest mean concentration is to the left. The highest concentrations are the focus of these results.

Table 2. A) national and B) regional CART results for pharmaceutical groups and relationships with population demographics. The primary split is most important variable, additional splits that lead along branches to highest concentration of that pharmaceutical group are indicated in the fourth column after the direction and value of the primary split. Local results are not reported as there were too few samples to generate CART results.

Pharmaceutical Group	**Number Unique Values**	**Primary Split**	**Relationship to Highest Concentration**
A. National			
Antibiotics	109	Percent Male age 50 - 79	< 14%
Anticholinergics	2	Percent American Indian	>= 6.9%
Anticonvulsants	61	Percent of households making 30k - 59k	< 21%
Antidepressants	14	Percent Female age 20 - 49	>= 21%
Antihistamines	2	Percent of households making 60k - 99k	>= 29%
Antilipemics	29	Percent of households making 100k - 150k	>= 21%
Benzodiazepines	4	Percent Black	< 0.16%
Blood Thinners	3	Percent Female	>= 51%
Bronchodilators	3	Percent Black	< 0.16%
Cardiovasculars	105	Percent of households making below 30k	< 18%; Percent Male < 50%
Corticosteroids	3	Percent Female	>= 51%
Diuretics	57	Percent of households making 100k - 150k	>= 19%; Percent of households making 100k - 150k <20%
Hormone	4	Total Population	>= 6682
Opioids	18	Percent of households making 100k - 150k	>= 19%; Percent Asian < 1.5%
Pain Relievers	18	Percent Other race	< 2.3%; Percent Female age 20 - 49>= 19%
Stimulants	15	Percent White	>= 96%; Percent Male >= 50%
Stomach Acid Reducers	7	Percent of households making 100k - 150k	>= 19%; Percent Hawaiian or Pacific Islander > 0.016%
Total Pharmaceuticals	129	Percent of households making below 30k	< 18%; Percent of households making below 30k >= 14%
B. Regional			
Antibiotics	19	Percent Female age 20 - 49	>= 24%
Anticholinergics	1	NA	NA

Anticonvulsants	26	Percent Female age 20 - 49	>= 24%
Antidepressants	28	Percent Female age 20 - 49	>= 24%
Antidiabetic	45	Percent of households making over 150k	>= 14%
Antidiarrheals	1	NA	NA
Antifungals	15	Percent Female age 20 - 49	>= 24%
Antihelmintics	17	Percent of households making over 150k	>= 19%
Antihistamines	26	Percent Female age 20 - 49	>= 24%
Antilipemics	14	Percent of households making over 150k	>= 10%
Antimetabolics	9	Percent Black	>= 35%
Antivirals	25	Percent Female age 20 - 49	>= 24%
Anxiolytics	10	Percent of households making 100k - 150k	< 16%; Percent Male < 48%
Aromatase Inhibitors	1	Removed	Removed
Benzodiazepines	25	Percent Black	>= 35%
Blood Thinners	3	Total Population	< 2535; Total Population >= 2105
Bronchodilators	10	Percent Male	< 50%; Percent Other race < 4.7%
Cardiovasculars	34	Percent Female age 20 - 49	>= 24%
Corticosteroids	9	Total Population	>= 2040
Cough Suppressants	8	Percent Female age 20 - 49	>= 24%
Diuretics	10	Percent Female age 20 - 49	>= 24%
Hormones	4	Percent Other race	>= 7.2%; Percent Asian < 5.9%
Muscle Relaxants	25	Percent Female age 20 - 49	>= 24%
Opioids	31	Percent Female age 20 - 49	>= 24%
Pain Relievers	41	Percent Asian	>= 8.5%
Selective Estrogen Receptor Modulator	4	Percent Male	< 49%; Percent Female over 80 >= 1.2%; Percent of households making 30k - 59k >= 27
Stimulants	46	Percent American Indian	>= 0.47%
Stomach Acid Reducers	24	Percent Black	>= 50 %
Total Pharmaceuticals	46	Percent Female age 20 - 49	>= 24%

At the national scale, 18 regression tree models were produced, one for each pharmaceutical group and one for the total concentration of all pharmaceutical

compounds (Table 2A). Concentrations and ranges for each pharmaceutical category are shown in Figure 6. For eight of these trees, income factors were the most important variables. High concentrations of pharmaceuticals in the groups antihistamines, antilipemics, diuretics, opioids and stomach acid reducers were related to higher percentages of households earning higher incomes. Conversely, lower incomes brackets (below $60,000) showed a negative relationship with higher concentrations of anticonvulsants, cardiovasculars and total pharmaceutical concentration. Cardiovasculars, diuretics and opioids also exhibited a secondary split on the right side of the trees. The highest concentrations of cardiovascular compounds were seen when less than 18% of households were earning below 30k and less than 50% of the population was male. Diuretic concentrations exhibited a second split on the same variable, where the highest concentrations were found when that metric is between 19% and 20% of households making $100,000 – $150,000. The total concentration of all pharmaceutical compounds similarly showed two splits on the same variable, percent of households making below $30,000. The highest total pharmaceutical concentrations were between 14% and 18% of households earning below $30,000. Opioid concentration was highest when percent of households earning $100,000 and $150,000 was greater than 19% and percent of the population identified as Asian is below 1.5%. For six of the trees, race was the most important factor, although there was no clear pattern among those results. A higher percent in the American Indian population (> ~7%) was related to higher concentrations of anticholinergics, while a lower percent of the population identified as Black or Other race was related to higher concentrations of benzodiazepines, bronchodilators and non-

opioid pain relievers. Non-opioid pain relievers were additionally split on percent of the population that is female age 20 – 49, where the highest concentrations were present when more than 19% of the population fell into that category. Stimulant concentrations were positively related to percent of the population identified as White (>96%) and percent of the population classified as male (50%). Antibiotics and antidepressants were the only two pharmaceutical categories where sex by age was the most important variable. Higher concentrations of antibiotics were inversely related to percent of the population that was male between 50 and 79 years old (< 14%). Antidepressants showed the opposite relationship, where higher concentrations of antidepressants were related to higher percent of females age 20 – 49 (>= 21%). Gender by itself was identified as the most important variable for blood thinners and corticosteroids, where the highest concentrations for both were seen when more than 51% of the population is female. Finally, only one pharmaceutical group was split on the total population in a study area: hormones. Higher hormone concentrations are related to population counts greater than 6,682 people per treatment area.

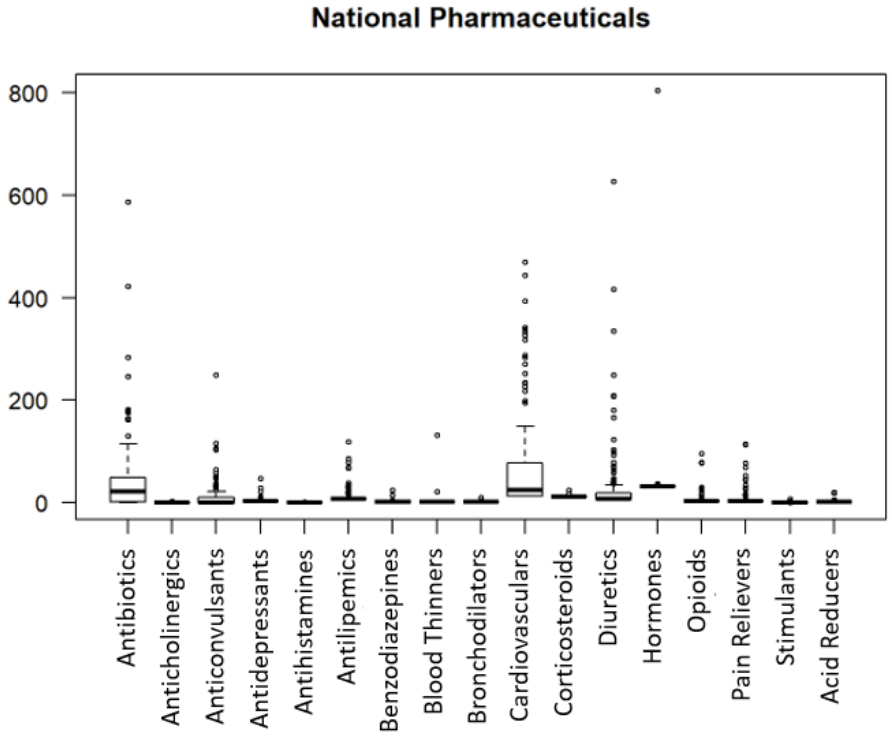


Figure 6. Boxplots of pharmaceutical categories for the national scale showing range and potential outliers for each pharmaceutical category.

At the regional scale, 27 regression trees were produced – concentrations of anticholinergics and antidiarrheals lacked variation in the recovered concentrations and no trees were able to be constructed for these two pharmaceutical groups (Table 2B; Figure 7). Percent of the population in the sex by age group 'female age 20 – 49' was the primary split for 12 of the CART models (antibiotics, anticonvulsants, antidepressants, antifungals, antihistamines, antivirals, cardiovasculars, cough suppressants, diuretics, muscle relaxants, opioids, and total pharmaceutical concentration), all of which exhibited

the same single split where more than 24% of the population in this age/gender bracket was related to higher concentrations.

Income was the primary split for antidiabetics, antihelmintics, antilipemics, and anxiolytics. The first three exhibited a positive relationship with percent of households earning over $150,000, where higher concentrations were seen above 14%, 19% and 10%, respectively. Anxiolytics showed the opposite relationship with percent of households earning between $100,000 - $150,000; the highest concentrations were seen below 16% and were additionally split on percent male, where less than 48% of the population was male resulted in the highest concentration of anxiolytics. Race was the primary predictor for six of the pharmaceutical groups: antimetabolics, benzodiazepines, hormones, pain relievers, stimulants and stomach acid reducers. Higher concentrations of benzodiazepines, antimetabolics and stomach acid reducers were related to percent black above 35%, 35% and 50%, respectively. The highest concentrations of hormones were reported at percent of the population identified as Other race greater than 7.2% and percent of the population identified as Asian below 5.9%. Pain relievers were highest when percent of the population identified as Asian was greater than 8.5%, and stimulant concentrations were highest when percent of the population identified as American Indian was greater than about half of a percent. For bronchodilators and selective estrogen receptor modulators (SERM), higher concentrations were identified when below about 50% of the population was male. Bronchodilators additionally were highest at low percent Other race (< 4.7%) and SERM was split on percent female over 80 years old (>= 1.2%) and percent of households making $30,00 - $50,000 (>= 27%). Total population

was the most important variables for concentrations of blood thinners and corticosteroids, albeit showing the opposite relationships. The highest concentrations of blood thinners were indicated between 2,105 and 2,535 people per treatment area, while the highest concentrations of corticosteroids were related to populations greater than 2,040 people. Although a tree was generated for aromatase inhibitors, this category was like anticholinergics and antidiarrheals in that all reported recoveries were censored values and once replaced with ½ the lab reporting limit, there was no variation in the response variable. Because of this, these tree results removed from the results table (Table 2).

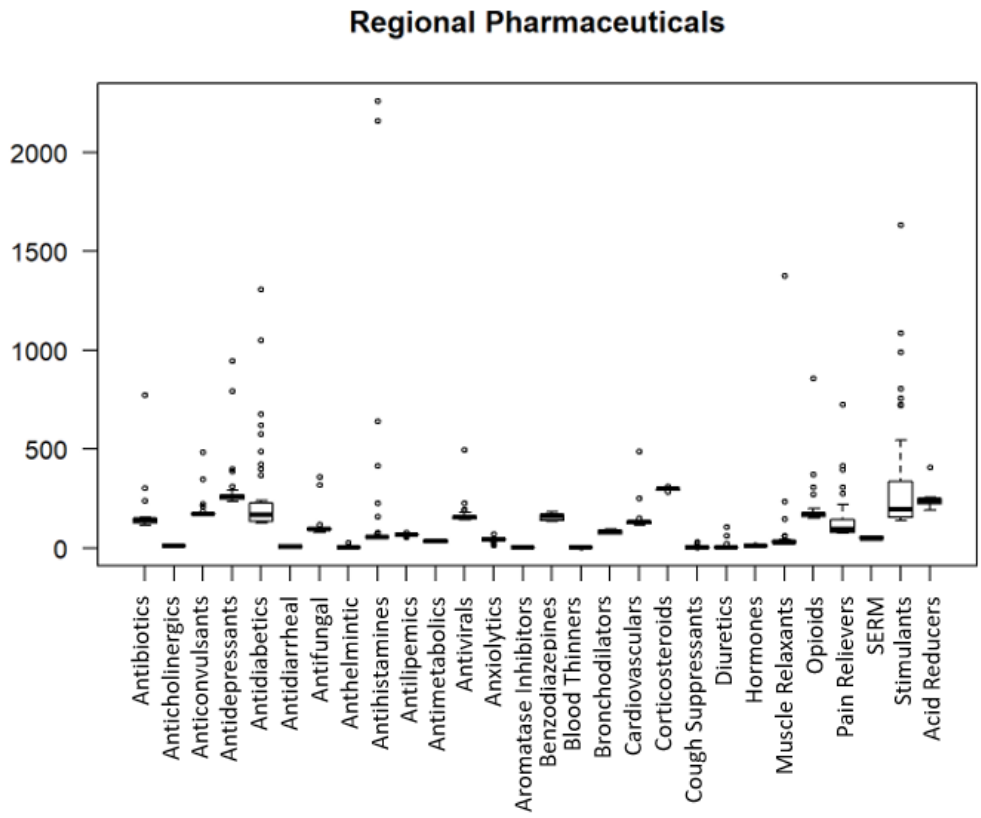


Figure 7. Boxplots of pharmaceutical categories for the regional scale showing range and potential outliers for each pharmaceutical category.

There were not enough observations at the local scale to generate any CART results. Results for concentrations of the pharmaceutical categories used can be seen in Figure 8.

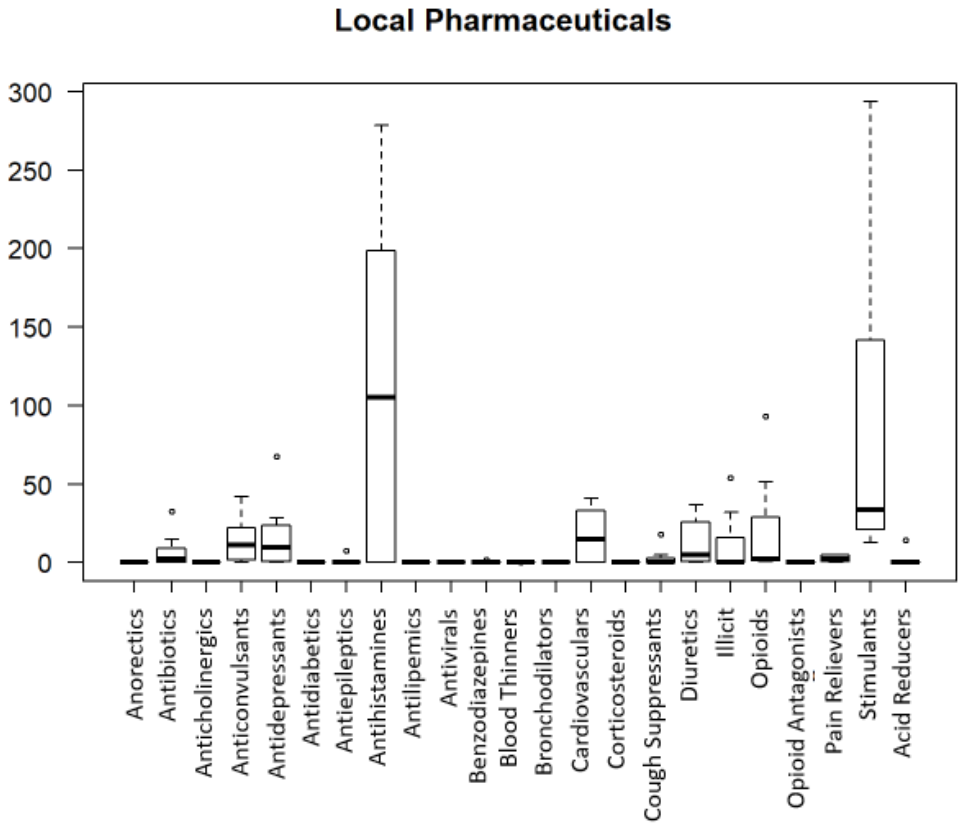


Figure 8. Boxplots of pharmaceutical categories for the local scale showing range and potential outliers for each pharmaceutical category.

DISCUSSION

The CART analyses yielded an understanding of the relationships between demographic factors such as age, gender, race and income with environmental pharmaceutical contamination and revealed interesting trends in demographic relationships. At the national scale, results indicated that income was the most important variable for almost half of the pharmaceutical categories measured. Considering cost of pharmaceuticals and affordability is an important deciding factor in whether people pick up or use prescriptions (Viswanathan et al., 2012), relationships indicating higher pharmaceutical concentrations in higher income brackets, where medication is likely easier to acquire, is not surprising. At the regional scale, three of the four categories where household income over $150,000/year was the most important variable showed the same positive relationship with higher concentrations. Following that, the highest total pharmaceutical concentrations were observed when a small percentage of people in the treatment area (between 14% and 18% of households) earn less than $30,000, putting the rest of households in a study area above that income threshold. Only anxiolytics, medicines used to reduce feelings of anxiety, showed the opposite relationship with higher income. For this study, this category is comprised of a single non-benzodiazepine anxiolytic, meprobamate, whose use has been largely replaced by benzodiazepines (James et al.,

2016). However, the cost of this compound over time has increased, and this relationship is puzzling compared to the other income-related outcomes.

Other similarities between the national and regional scale results are limited to benzodiazepines, where percent Black was the most important variable. However, the relationships were contradictory. At the national scale, higher concentrations of benzodiazepines are found when a very small part of the population is Black. Previous studies support this, founding that minority groups are prescribed and use (African-American women in particular) far fewer benzodiazepines than White populations (Cook et al., 2018; Hall et al., 2010). These results and studies are contradictory to the results at the regional scale which show the opposite relationship, where higher percent of the population that is Black is related to higher concentration of benzodiazepines. These results may be indicative of regional use patterns differencing in the southeast United States in this study versus previous studies conducted in New England (Cook et al., 2018; Hall et al., 2010).

At the regional scale, percent of the population identified as Black was also the dominant predictor of antimetabolics and stomach acid reducers. Both showed a positive relationship with higher values. Antimetabolics here is comprised of a single compound, methotrexate, which is used to treat various types of cancer as well as rheumatoid arthritis (Jolivet, Cowan, Curt, Clendeninn, & Chabner, 1983). According to the American Cancer Society (2019), “black males overall have the highest cancer incidence (549 per 100,000) and death (240) rates of the major racial/ethnic groups,” which may account for higher concentrations of cancer treatment drug in populations comprised of

higher percentages of black people. Stomach acid reducers in this study include several over the counter medications not tracked through prescriptions.

Antibiotic concentrations at the national level were predicted by the percent of the population that was male aged 50 – 79. According to the CDC, the highest number of antibiotic prescriptions are written for children under two and people 65 and older (CDC, 2017), but prescription rates for adults are extremely high, totaling 198 million antibiotic prescription in 2014 (CDC, 2017). These results may be indicative of a subset of the adult population ingesting more of these prescribed antibiotics than others.

Anticholinergics serve the primary function of blocking acetylcholine activity in the brain. At the national scale, the only anticholinergic in this category is Benztropine, which is specifically used to treat Parkinson's disease. However little information on prescription profiles are available for Benztropine, so the relationship with percent of the population that is Native American is difficult to clarify further.

Four pharmaceutical groups were predicted by percent of the population either male or female: national scale blood thinners and corticosteroids, both higher in higher percent female populations, and regional scale bronchodilators and SERM, both lower in lower percent male populations. Corticosteroids here are comprised of both over the counter topical anti-inflammatory creams and nasal sprays as well as prescriptions and are difficult to relate to prescription rates as they can be used to treat a wide array of maladies. Blood thinners in this study is limited to Warfarin, which is prescribed to prevent or reduce blood clots. The relationship observed with bronchodilators follows the national statistics on asthma sufferers. According to the CDC, women make up 60% of

people with asthma (CDC, 2019) and people identified as non-Hispanic "Other" race make up only 8% of asthma sufferers. Bronchodilators exhibited a second split on Other race, where lower values are related to the highest concentrations of bronchodilators. The selective estrogen receptor modulators (SERM) group is comprised of Raloxifene and Tamoxifen, which are used to treat and prevent osteoporosis and to treat certain forms of breast cancer, respectively. This also follows the additional splits on the highest concentrations of SERMs, where higher percent of the population that is female over age 80 is related to higher SERM concentrations, as older women are more likely to need treatment for osteoporosis and related issues.

Finally, although percent of the population that is female between the age of 20 and 49 was the most frequently selected variable across the regional pharmaceutical category models (n = 12), this was only shared as the primary predictor at the national level for the antidepressant category. Women overall are more likely to take antidepressants than men and according to the CDC, this number is highest for women between 40 and 59 years old (Pratt, Brody and Gu, 2011), an age group which is partially captured in the aggregated ACS age groups used in this study. Therefore, it is unsurprising that if more than about a quarter of the population falls in this age range, higher concentrations of antidepressants are found downstream. The repeated presence of the percent female age 20 – 49 variable at the regional scale may suggest that this group is related to use of a wide range of pharmaceutical types, or there may be some underlying bias in the data. However, at the regional scale, this group was not strongly correlated (Pearson's $|r > 0.7|$) with any other demographic group except percent of the

population that is male between the age of 50 and 79, and no obvious distribution bias exists to support that idea. It is more likely that these repeat relationships are a result of the sampling locations in the regional scale study. A recent study analyzing prescription data for female patients over the course of 10 years (Melamed & Rzhetsky, 2018) found that the use of prescribed drugs is significantly more similar for counties located close together and for counties with similar demographics. In the same study, similar prescription patterns were observed in the southeast specifically for allergy and cold medicines, drugs for obesity related illnesses, and diabetes. Given the smaller geographic range and clustering of sampling in central North Carolina, western South Carolina and northern Georgia at the regionals scale, the similarities in relationships may be due to the similarity in geographic factors. Melamed and Rzhetsky (2018) additionally reported that state-level influences, like healthcare plans, could impact drug use. The majority of final regional study sites were in Georgia (n = 17) and North Carolina (n = 19). This may also account for the differences in CART models seen when compared to the national scale study, which had several sites where the final treatment area encompassed parts of multiple states.

Caution should be used in interpreting the results of some of the CART models in this study. The values chosen at each split along a regression tree can be influenced by outliers in the response variable, and the generally low occurrences of pharmaceutical compounds at each scale resulted in a large number of values replaced with ½ the LRL or MDL for the national and regional studies. As such, sites where high pharmaceutical concentrations were able to be quantitated are in stark contrast to sites where the values

are ½ the LDL or MRL, and therefore may be controlling the relationships seen in the trees. The number of unique values per response variable is also reported (Table 2) as well as boxplots of pharmaceutical concentrations by type (Figure x). Because regression CART results can be influenced by outliers in the response variable, results with a low number of responses and large number of outliers, like hormones or blood thinners at the national scale, may not be as interpretable as the results seen in categories with fewer outliers.

There are several ways that this study could be improved. First, there is a temporal offset between sampling time and census data available. The ACS 5-year estimates, although more precise than other annual census population summaries, are an aggregate of 60 months of values and may not accurately represent the population at the time of sampling. Additionally, transient populations in areas with large universities, hospitals or tourist attractions can alter the chemical profile of the sampled waters. For example, Washington DC saw over 22 million visitors in 2018 (Destination DC, 2018), and this visiting population, although it undoubtedly affects water quality, is not captured in the ACS estimates. Sites at the national scale had large upstream treatment areas, and as such could encompass a wide variety of influential locations like these. One way to potentially account for this population shift is to incorporate economic, tourism, commuter, work location, and institutional data from universities, tourist centers, high density corporate areas and specialist hospitals to refine estimates of populations present around and up to the time of sampling.

At the local scale, sites were sampled repeatedly over the course of the year, capturing spring, summer and fall. Therefore, the average of these values is a better approximation of the annual pharmaceutical presence at these locations and can be more justifiably attached to the ACS estimates than the national or regional scale results which were sampled one time, or over the course of a few weeks. Repeat sampling for the local sites and pharmaceutical compounds is planned for future years. Given additional years of population and pharmaceutical data, these sites should be used to refine the relationships at this scale and observe changes over time. Future studies aiming to understand population demographics and pharmaceutical contamination relationships should focus on repeat sampling, similar to the local study, or should focus on an easily monitored and quantifiable upstream population (e.g. Vatovec et al., 2016).

Another potential way to improve the methods in this study is to address the accuracy of the individual sewer treatment areas at the national and regional scale. Although these were not used to develop final treatment areas at the national scale, it was observed that the sewer treatment areas were more realistic in some areas than others, particularly in the eastern versus western states. In states like Texas, Arizona, and New Mexico, the sewer treatment areas were unrealistically large, sometimes encompassing entire large cities for a single registered facility, whereas the same area in Maryland, Virginia, or North Carolina would be divided among dozens of facilities. The sewered areas that were available for Virginia at the local scale were irregular and did not follow any political, census, or geographic boundaries, therefore the thiessen polygons may be as a good an approximation as any to delineate facility treatment areas, however, the

facility size or design capacity could be taken into account to weight larger facilities more heavily, so they are given larger treatment areas.

The ability and efficiency of a facility in removing contaminants from wastewater varies based on types and levels of treatment. Facilities with advanced treatment methods are most likely removing pharmaceutical contaminates in different amounts than facilities with fewer or less advanced treatment methods. It was beyond the scope of this study to compile information on treatment type, removal efficiencies and pharmaceutical degradation related to various removal practices, however this is a large missing piece in this and other stream contamination studies.

Another factor that should be considered when interpreting these results is other potential sources of pharmaceuticals to streams. In cultivated areas, biosolids can be applied to the landscape to introduce nutrients into soils (Evanylo, 2009.). However, some pharmaceutical compounds are known to persist though biosolid preparation from sewage sludge (Chenxi, Spongberg, & Witter, 2008) and can therefore be an unintentional source of pharmaceuticals in streams (Ding, Zhang, Gu, Xagoraraki, & Li, 2011). Animal agriculture is also a known source of pharmaceuticals as animal operations often administer hormones and antibiotics to large numbers of animals (Burkholder et al., 2007) and animal pharmaceuticals have been observed in streams adjacent to confined animal feeding operations (Bernot, Smith, & Frey, 2013).

Finally, there are two major sources of pharmaceuticals that were not considered in this study that may not reflect human use: pharmaceutical formulation facilities and hospitals. The first is an obvious source as facilities that manufacture pharmaceutical

compounds generate waste in the process. Wastewater treatment plant effluent from facilities treating pharmaceutical manufacturing outflows showed 10 to 1000 times higher concentrations of some pharmaceutical compounds when compared to WWTPs not influenced by pharmaceutical manufacturing facilities(Phillips et al., 2010). Additionally, reporting on hospital methods indicates they these are in fact major sources of pharmaceuticals through disposal practices of flushing unused or overprescribed medicines, even those that are expired or spoiled (Mone, 2008; Scutti, 2018).

CONCLUSION

The development of a method to identify populations contributing to environmental contamination is an important step in understanding the complex relationships between human presence and their impact on the environment. This study developed and implemented such a method to understand the relationships in terms of pharmaceutical contamination at three different scales, additionally illustrating how it could be adjusted based on scale and resolution of available data.

Given what is known about the potential toxicity and negative effects pharmaceuticals can have on aquatic environments and species, these results add an important element in understanding the pipeline from human activity and pharmaceutical use to environmental endpoints.

Additionally, the method and results revealed in this study can be used to improve future efforts. Laboratory analysis of samples for pharmaceutical compounds relies on prior selection of which compounds to analyze. By identifying the demographics of the population in a treatment area influencing surface water, a more refined targeted set of pharmaceutical compounds cane be identified prior to analysis. However, the results here may indicate that there are regional differences that should be considered when addressing population-pharmaceutical relationships. Given the tendency of prescription

practices to follow patterns within states and geographic regions, geographic range of sites should be considered before implementing this method.

APPENDIX A

Table of compounds assessed in each study and their final pharmaceutical category.

Study	Compound	Category
GMU (2018)	Phentermine	Anorectic
GMU (2018)	Glipizide	Antidiabetic
Bradley et al. (2014)	Glipizide	Antidiabetic
GMU (2018)	Azithromycin	Antibiotic
GMU (2018)	Ciprofloxacin	Antibiotic
GMU (2018)	Penicillin G	Antibiotic
GMU (2018)	Sulfamethoxazole	Antibiotic
GMU (2018)	Tetracycline	Antibiotic
Bradley et al. (2014)	Erythromycin	Antibiotic
Bradley et al. (2014)	Sulfamethizoleate	Antibiotic
Bradley et al. (2014)	Sulfamethoxazole	Antibiotic
Bradley et al. (2014)	Trimethoprim	Antibiotic
Batt et al. (2016)	sulfamethoxazole	Antibiotic
Batt et al. (2016)	trimethoprim	Antibiotic
GMU (2018)	Benztropine	Anticholinergic
Bradley et al. (2014)	Benztropine	Anticholinergic
Batt et al. (2016)	benztropine	Anticholinergic
GMU (2018)	10_11-Carbamazepine epoxide	Anticonvulsant
GMU (2018)	Carbamazepine	Anticonvulsant
Bradley et al. (2014)	Carbamazepine	Anticonvulsant
Bradley et al. (2014)	Iminostilbene	Anticonvulsant
Bradley et al. (2014)	Phenytoin	Anticonvulsant
Batt et al. (2016)	carbamazepine	Anticonvulsant
GMU (2018)	Amitriptyline	Antidepressant
GMU (2018)	Bupropion	Antidepressant
GMU (2018)	Desvenlafaxine	Antidepressant
GMU (2018)	Escitalopram	Antidepressant
GMU (2018)	Fluoxetine	Antidepressant
GMU (2018)	Nortriptyline	Antidepressant
GMU (2018)	Paroxetine	Antidepressant

GMU (2018)	Sertraline	Antidepressant
GMU (2018)	Venlafaxine	Antidepressant
Bradley et al. (2014)	Amitriptyline	Antidepressant
Bradley et al. (2014)	Amitriptyline-10-Hydroxy	Antidepressant
Bradley et al. (2014)	Bupropion	Antidepressant
Bradley et al. (2014)	Citalopram	Antidepressant
Bradley et al. (2014)	Desvenlafaxine	Antidepressant
Bradley et al. (2014)	Duloxetine	Antidepressant
Bradley et al. (2014)	Fluoxetine	Antidepressant
Bradley et al. (2014)	Fluvoxamine	Antidepressant
Bradley et al. (2014)	Norfluoxetine	Antidepressant
Bradley et al. (2014)	Norsertraline	Antidepressant
Bradley et al. (2014)	Paroxetine	Antidepressant
Bradley et al. (2014)	Sertraline	Antidepressant
Batt et al. (2016)	10-hydroxy-amitriptyline	Antidepressant
Batt et al. (2016)	amitriptyline	Antidepressant
Batt et al. (2016)	desmethylsertraline	Antidepressant
Batt et al. (2016)	fluoxetine	Antidepressant
Batt et al. (2016)	norfluoxetine	Antidepressant
Batt et al. (2016)	norverapamil	Antidepressant
Batt et al. (2016)	paroxetine	Antidepressant
Batt et al. (2016)	sertraline	Antidepressant
GMU (2018)	Meth- amphetamine	Antidiabetic
Bradley et al. (2014)	Glyburide	Antidiabetic
Bradley et al. (2014)	Metformin	Antidiabetic
Bradley et al. (2014)	Sitagliptin	Antidiabetic
Bradley et al. (2014)	Loperamide	Anti-Diarrheal
GMU (2018)	Gabapentin	Antiepileptic
Bradley et al. (2014)	Fluconazole	Antifungal
Bradley et al. (2014)	Ketoconazole	Antifungal
Bradley et al. (2014)	Thiabendazole	Anthelmintic
GMU (2018)	Diphenhydramine hydrochloride	Antihistamine
GMU (2018)	Fexofenadine	Antihistamine
GMU (2018)	Loratadine	Antihistamine
GMU (2018)	Promethazine	Antihistamine
Bradley et al. (2014)	Chlorpheniramine	Antihistamine
Bradley et al. (2014)	Diphenhydramine	Antihistamine
Bradley et al. (2014)	Fexofenadine	Antihistamine
Bradley et al. (2014)	Hydroxyzine	Antihistamine
Bradley et al. (2014)	Loratadine	Antihistamine

Bradley et al. (2014)	Promethazine	Antihistamine
Batt et al. (2016)	promethazine	Antihistamine
GMU (2018)	Bezafibrate	Antilipemic
Bradley et al. (2014)	Ezetimibe	Antilipemic
Bradley et al. (2014)	Fenofibrate	Antilipemic
Batt et al. (2016)	gemfibrozil	Antilipemic
Batt et al. (2016)	simvastatin	Antilipemic
Bradley et al. (2014)	Methotrexate	Antimetabolite
GMU (2018)	Acyclovir	Antiviral
Bradley et al. (2014)	Abacavir	Antiviral
Bradley et al. (2014)	Acyclovir	Antiviral
Bradley et al. (2014)	Lamivudine	Antiviral
Bradley et al. (2014)	Nevirapine	Antiviral
Bradley et al. (2014)	Oseltamivir	Antiviral
Bradley et al. (2014)	Valacyclovir	Antiviral
Bradley et al. (2014)	Penciclovir	Antiviral
Bradley et al. (2014)	Meprobamate	Anxiolytic
Bradley et al. (2014)	Fadrozole	Aromatase Inhibitor
GMU (2018)	(±)-Lorazepam	Benzodiazepine
GMU (2018)	Alprazolam	Benzodiazepine
GMU (2018)	Clonazepam	Benzodiazepine
GMU (2018)	Diazepam	Benzodiazepine
GMU (2018)	Nitrazepam	Benzodiazepine
GMU (2018)	Nordiazepam	Benzodiazepine
GMU (2018)	Oxazepam	Benzodiazepine
GMU (2018)	Temazepam	Benzodiazepine
Bradley et al. (2014)	Alprazolam	Benzodiazepine
Bradley et al. (2014)	Diazepam	Benzodiazepine
Bradley et al. (2014)	Lorazepam	Benzodiazepine
Bradley et al. (2014)	Nitrazepam	Benzodiazepine
Bradley et al. (2014)	Nordiazepam	Benzodiazepine
Bradley et al. (2014)	Oxazepam	Benzodiazepine
Bradley et al. (2014)	Temazepam	Benzodiazepine
Batt et al. (2016)	alprazolam	Benzodiazepine
GMU (2018)	Warfarin	Blood Thinner
Bradley et al. (2014)	Warfarin	Blood Thinner
Batt et al. (2016)	warfarin	Blood Thinner
GMU (2018)	Albuterol	Bronchodilator
GMU (2018)	Formoterol	Bronchodilator
Bradley et al. (2014)	Albuterol	Bronchodilator

Bradley et al. (2014)	Theophylline	Bronchodilator
Bradley et al. (2014)	Tiotropium	Bronchodilator
Batt et al. (2016)	albuterol	Bronchodilator
GMU (2018)	Atenolol	Cardiovascular
GMU (2018)	Atorvastatin	Cardiovascular
GMU (2018)	Diltiazem	Cardiovascular
GMU (2018)	Enalapril	Cardiovascular
GMU (2018)	Lisinopril	Cardiovascular
GMU (2018)	Metoprolol	Cardiovascular
GMU (2018)	Nadolol	Cardiovascular
GMU (2018)	Propranolol	Cardiovascular
GMU (2018)	Verapamil	Cardiovascular
Bradley et al. (2014)	Atenolol	Cardiovascular
Bradley et al. (2014)	Dehydronifedipine	Cardiovascular
Bradley et al. (2014)	Desmethyldiltiazem	Cardiovascular
Bradley et al. (2014)	Diltiazem	Cardiovascular
Bradley et al. (2014)	Metoprolol	Cardiovascular
Bradley et al. (2014)	Nadolol	Cardiovascular
Bradley et al. (2014)	Norverapamil	Cardiovascular
Bradley et al. (2014)	Pentoxifyllineate	Cardiovascular
Bradley et al. (2014)	Propranolol	Cardiovascular
Bradley et al. (2014)	Verapamil	Cardiovascular
Batt et al. (2016)	amlodipine	Cardiovascular
Batt et al. (2016)	atenolol	Cardiovascular
Batt et al. (2016)	atorvastatin	Cardiovascular
Batt et al. (2016)	diltiazem	Cardiovascular
Batt et al. (2016)	diltiazem-desmethyl	Cardiovascular
Batt et al. (2016)	enalipril	Cardiovascular
Batt et al. (2016)	metoprolol	Cardiovascular
Batt et al. (2016)	propanolol	Cardiovascular
Batt et al. (2016)	valsartan	Cardiovascular
Batt et al. (2016)	verapamil	Cardiovascular
GMU (2018)	Budesonide	Corticosteroid
Bradley et al. (2014)	Betamethasone	Corticosteroid
Bradley et al. (2014)	Fluticasone propionate	Corticosteroid
Bradley et al. (2014)	Hydrocortisone	Corticosteroid
Bradley et al. (2014)	Prednisolone	Corticosteroid
Bradley et al. (2014)	Prednisone	Corticosteroid
Batt et al. (2016)	fluocinonide	Corticosteroid
Batt et al. (2016)	fluticasone	Corticosteroid

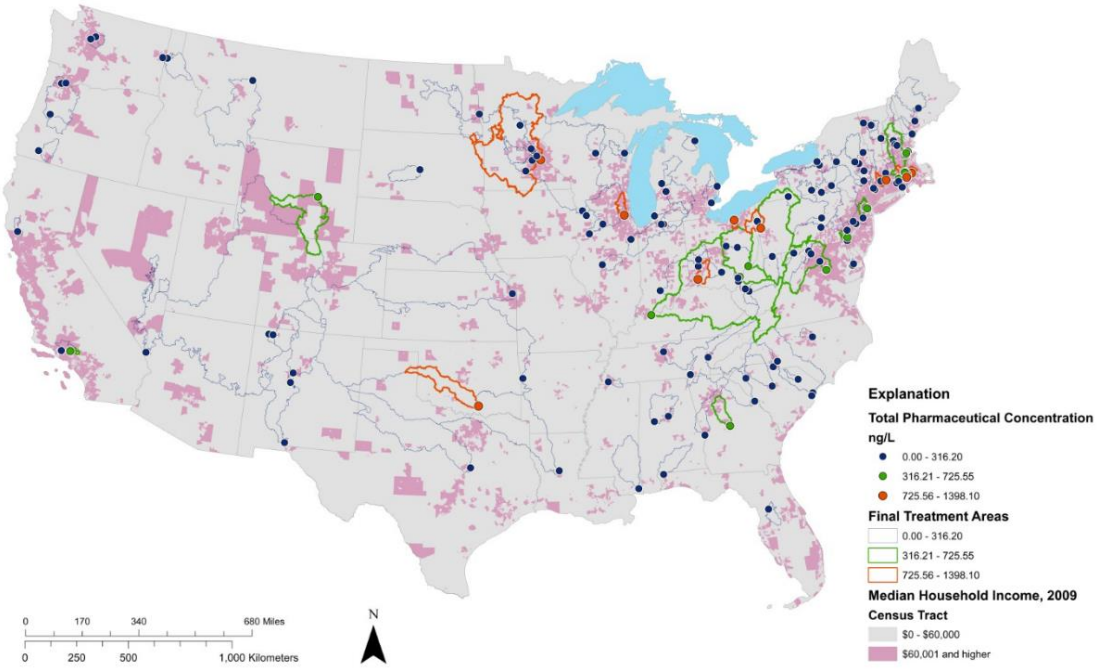
Batt et al. (2016)	hydrocodone	Corticosteroid
Batt et al. (2016)	hydrocortisone	Corticosteroid
Batt et al. (2016)	prednisone	Corticosteroid
GMU (2018)	Dextromethorphanan	Cough Suppressant
Bradley et al. (2014)	Dextromethorphanan	Cough Suppressant
GMU (2018)	Furosemide	Diuretic
GMU (2018)	Hydrochlorothiazide	Diuretic
GMU (2018)	Triamterene	Diuretic
Bradley et al. (2014)	Triamterene	Diuretic
Batt et al. (2016)	furosemide	Diuretic
Batt et al. (2016)	triamterene	Diuretic
Batt et al. (2016)	hydrochlorthiazide	Diuretic
Bradley et al. (2014)	Norethindrone	Hormone
Batt et al. (2016)	progesterone	Hormone
Batt et al. (2016)	testosterone	Hormone
Batt et al. (2016)	norethindrone	Hormone
GMU (2018)	Flunitrazepam	Illicit
GMU (2018)	MDA	Illicit
GMU (2018)	MDEA	Illicit
GMU (2018)	MDMA	Illicit
Bradley et al. (2014)	Carisoprodol	Muscle Relaxant
Bradley et al. (2014)	Metaxalone	Muscle Relaxant
Bradley et al. (2014)	Methocarbamol	Muscle Relaxant
GMU (2018)	Buprenorphine	Opioid
GMU (2018)	cis-Tramadol HCl	Opioid
GMU (2018)	Codeine	Opioid
GMU (2018)	Fentanyl	Opioid
GMU (2018)	Hydrocodone	Opioid
GMU (2018)	Hydromorphone	Opioid
GMU (2018)	Meperidine	Opioid
GMU (2018)	Metformin	Opioid
GMU (2018)	Methadone	Opioid
GMU (2018)	Morphine	Opioid
GMU (2018)	Oxymorphone	Opioid
GMU (2018)	Propoxyphene	Opioid
Bradley et al. (2014)	Codeine	Opioid
Bradley et al. (2014)	Hydrocodone	Opioid
Bradley et al. (2014)	Methadone	Opioid
Bradley et al. (2014)	Morphine	Opioid
Bradley et al. (2014)	Oxycodone	Opioid

Bradley et al. (2014)	Propoxyphene	Opioid
Bradley et al. (2014)	Tramadol	Opioid
Batt et al. (2016)	oxycodone	Opioid
Batt et al. (2016)	propoxyphene	Opioid
GMU (2018)	Naloxone	Opioid Antagonist
GMU (2018)	Naltrexone	Opioid Antagonist
GMU (2018)	2-Hydroxy- Ibuprofen	Pain Reliever (non-opioid)
GMU (2018)	Celecoxib	Pain Reliever (non-opioid)
GMU (2018)	Diclofenac	Pain Reliever (non-opioid)
GMU (2018)	Naproxen	Pain Reliever (non-opioid)
Bradley et al. (2014)	Acetaminophen	Pain Reliever (non-opioid)
Bradley et al. (2014)	Antipyrine	Pain Reliever (non-opioid)
Bradley et al. (2014)	Lidocaine	Pain Reliever (non-opioid)
Bradley et al. (2014)	Phenazopyridine	Pain Reliever (non-opioid)
Batt et al. (2016)	acetaminophen	Pain Reliever (non-opioid)
Batt et al. (2016)	ibuprofen	Pain Reliever (non-opioid)
GMU (2018)	Aspartame	REMOVED
GMU (2018)	Atrazine Mercapturate	REMOVED
GMU (2018)	Clonidine	REMOVED
GMU (2018)	DEET	REMOVED
GMU (2018)	Enrofloxacin	REMOVED
GMU (2018)	Perfluoro- octanoic Acid	REMOVED
GMU (2018)	Sulfadi- methoxine	REMOVED
GMU (2018)	Sulfamethazine	REMOVED
GMU (2018)	Sulfa-quinoxaline	REMOVED
GMU (2018)	Sulfathiazole	REMOVED
GMU (2018)	Triclocarban	REMOVED
Bradley et al. (2014)	Atrazine	REMOVED
Bradley et al. (2014)	Clonidine	REMOVED
Bradley et al. (2014)	Methyl-1H-benzotriazole	REMOVED
Bradley et al. (2014)	Piperonyl butoxide	REMOVED
Bradley et al. (2014)	Quinine	REMOVED
Bradley et al. (2014)	Sulfadimethoxine	REMOVED
Batt et al. (2016)	clonidine	REMOVED
Bradley et al. (2014)	Raloxifene	SERM
Bradley et al. (2014)	Tamoxifen	SERM
GMU (2018)	3’-Hydroxy cotinine	Stimulant
GMU (2018)	Caffeine	Stimulant
GMU (2018)	Cotinine	Stimulant
GMU (2018)	Nicotine	Stimulant

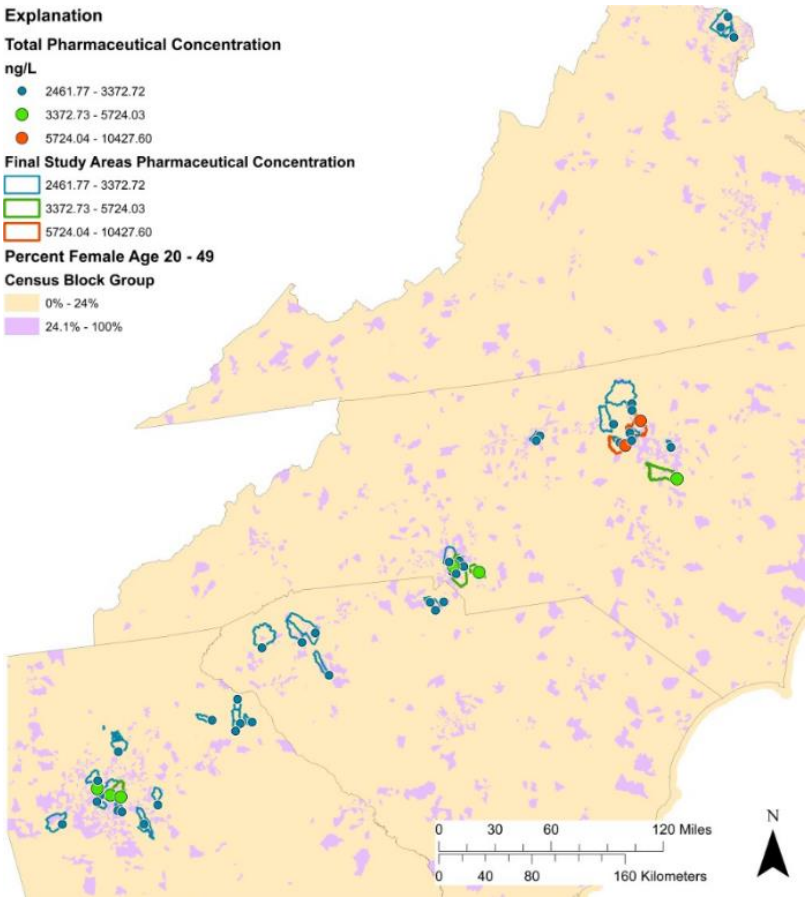
Bradley et al. (2014)	Amphetamine	Stimulant
Bradley et al. (2014)	Caffeine	Stimulant
Bradley et al. (2014)	Cotinine	Stimulant
Bradley et al. (2014)	Nicotine	Stimulant
Bradley et al. (2014)	Phendimetrazine	Stimulant
Bradley et al. (2014)	Pseudoephedrine and Ephedrine	Stimulant
Bradley et al. (2014)	Xanthine-1,7-Dimethyl	Stimulant
Batt et al. (2016)	amphetamine	Stimulant
GMU (2018)	Cimetidine	Stomach Acid Reducer
GMU (2018)	Ranitidine	Stomach Acid Reducer
Bradley et al. (2014)	Cimetidine	Stomach Acid Reducer
Bradley et al. (2014)	Famotidine	Stomach Acid Reducer
Bradley et al. (2014)	Omeprazole and Esomeprazole	Stomach Acid Reducer
Bradley et al. (2014)	Ranitidine	Stomach Acid Reducer
Batt et al. (2016)	ranitidine	Stomach Acid Reducer

APPENDIX B

A. National pharmaceutical concentrations in relation to higher income (above $60,000 median annual income) census tracts across the US.



B. Regional pharmaceutical concentrations in relation to census block groups with higher (>24%) percent of the population that is female between age 20 and 49.



REFERENCES

American Cancer Society, (2019). Cancer Facts & Figures 2019. Atlanta: American Cancer Society.*2014 TIGERLine Shapefiles Technical Documentation.pdf*. (n.d.). Retrieved from https://www2.census.gov/geo/pdfs/maps-data/data/tiger/tgrshp2014/TGRSHP2014_TechDoc.pdf

Barber, L. B., Keefe, S. H., Brown, G. K., Furlong, E. T., Gray, J. L., Kolpin, D. W., … Zaugg, S. D. (2013). Persistence and Potential Effects of Complex Organic Contaminant Mixtures in Wastewater-Impacted Streams. *Environmental Science & Technology*, *47*(5), 2177–2188. https://doi.org/10.1021/es303720g

Barnes, K. K., Kolpin, D. W., Furlong, E. T., Zaugg, S. D., Meyer, M. T., & Barber, L. B. (2008). A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States — I) Groundwater. *Science of The Total Environment*, *402*(2), 192–200. https://doi.org/10.1016/j.scitotenv.2008.04.028

Batt, A. L., Kincaid, T. M., Kostich, M. S., Lazorchak, J. M., & Olsen, A. R. (2016). Evaluating the extent of pharmaceuticals in surface waters of the United States using a National-scale Rivers and Streams Assessment survey. *Environmental Toxicology and Chemistry*, *35*(4), 874–881. https://doi.org/10.1002/etc.3161

Benotti, M. J., Trenholm, R. A., Vanderford, B. J., Holady, J. C., Stanford, B. D., & Snyder, S. A. (2009). Pharmaceuticals and Endocrine Disrupting Compounds in U.S. Drinking Water. *Environmental Science & Technology*, *43*(3), 597–603. https://doi.org/10.1021/es801845a

Bernot, M. J., Smith, L., & Frey, J. (2013). Human and veterinary pharmaceutical abundance and transport in a rural central Indiana stream influenced by confined animal feeding operations (CAFOs). *Science of The Total Environment*, *445–446*, 219–230. https://doi.org/10.1016/j.scitotenv.2012.12.039

Blazer, V., Iwanowicz, D., Walsh, H., Sperry, A., Iwanowicz, L., Alvarez, D., … Manning, R. (2014). Reproductive health indicators of fishes from Pennsylvania watersheds: association with chemicals of emerging concern. *Environmental Monitoring & Assessment*, *186*(10), 6471–6491. https://doi.org/10.1007/s10661-014-3868-5

Blazer, V. S., Iwanowicz, L. R., Henderson, H., Mazik, P. M., Jenkins, J. A., Alvarez, D. A., & Young, J. A. (2011). Reproductive endocrine disruption in smallmouth bass (Micropterus dolomieu) in the Potomac River basin: spatial and temporal comparisons of biological effects. *Environmental Monitoring and Assessment*, *184*(7), 4309–4334. https://doi.org/10.1007/s10661-011-2266-5

Bradley, P. M., Journey, C. A., Button, D. T., Carlisle, D. M., Clark, J. M., Mahler, B. J., … VanMetre, P. C. (2016). Metformin and Other Pharmaceuticals Widespread in Wadeable Streams of the Southeastern United States. *Environmental Science & Technology Letters*, *3*(6), 243–249. https://doi.org/10.1021/acs.estlett.6b00170

Bryer, P. J., Scoggins, M., & McClintock, N. L. (2010). Coal-tar based pavement sealant toxicity to freshwater macroinvertebrates. *Environmental Pollution*, *158*(5), 1932–1937. https://doi.org/10.1016/j.envpol.2009.10.038

Burgard, D. A., Banta-Green, C., & Field, J. A. (2014). Working Upstream: How Far Can You Go with Sewage-Based Drug Epidemiology? *Environmental Science & Technology*, *48*(3), 1362–1368. https://doi.org/10.1021/es4044648

Burian, S. J., Nix, S. J., Pitt, R. E., & Durrans, S. R. (2000). Urban Wastewater Management in the United States: Past, Present, and Future. *Journal of Urban Technology*, *7*(3), 33–62. https://doi.org/10.1080/713684134

Burkholder JoAnn, Libra Bob, Weyer Peter, Heathcote Susan, Kolpin Dana, Thorne Peter S., & Wichman Michael. (2007). Impacts of Waste from Concentrated Animal Feeding Operations on Water Quality. *Environmental Health Perspectives*, *115*(2), 308–312. https://doi.org/10.1289/ehp.8839

Carrara, C., Ptacek, C. J., Robertson, W. D., Blowes, D. W., Moncur, M. C., Sverko, E., & Backus, S. (2008). Fate of Pharmaceutical and Trace Organic Compounds in Three Septic System Plumes, Ontario, Canada. *Environmental Science & Technology*, *42*(8), 2805–2811. https://doi.org/10.1021/es070344q

Chenxi, W., Spongberg, A. L., & Witter, J. D. (2008). Determination of the persistence of pharmaceuticals in biosolids using liquid-chromatography tandem mass spectrometry. *Chemosphere*, *73*(4), 511–518. https://doi.org/10.1016/j.chemosphere.2008.06.026

Ciparis, S., Iwanowicz, L. R., & Voshell, J. R. (2012). Effects of watershed densities of animal feeding operations on nutrient concentrations and estrogenic activity in agricultural streams. *Science of The Total Environment*, *414*, 268–276. https://doi.org/10.1016/j.scitotenv.2011.10.017

Conn, K. E., Lowe, K. S., Drewes, J. E., Hoppe-Jones, C., & Tucholke, M. B. (2010). Occurrence of Pharmaceuticals and Consumer Product Chemicals in Raw Wastewater and Septic Tank Effluent from Single-Family Homes. *Environmental Engineering Science*, *27*(4), 347–356. https://doi.org/10.1089/ees.2009.0364

Cook, B., Creedon, T., Wang, Y., Lu, C., Carson, N., Jules, P., … Alegría, M. (2018). Examining racial/ethnic differences in patterns of benzodiazepine prescription and misuse. *Drug and Alcohol Dependence*, *187*, 29–34. https://doi.org/10.1016/j.drugalcdep.2018.02.011

De'ath, G., & Fabricius, K. E. (2000). Classification and Regression Trees: A Powerful yet Simple Technique for Ecological Data Analysis. *Ecology*, *81*(11), 3178–3192. https://doi.org/10.1890/0012-9658(2000)081[3178:CARTAP]2.0.CO;2

Deo, R. P., & Halden, R. U. (2013). Pharmaceuticals in the Built and Natural Water Environment of the United States. *Water (20734441)*, *5*(3), 1346–1365. https://doi.org/10.3390/w5031346

Ding, Y., Zhang, W., Gu, C., Xagoraraki, I., & Li, H. (2011). Determination of pharmaceuticals in biosolids using accelerated solvent extraction and liquid chromatography/tandem mass spectrometry. *Journal of Chromatography A*, *1218*(1), 10–16. https://doi.org/10.1016/j.chroma.2010.10.112

Dussault, È. B., Balakrishnan, V. K., Sverko, E., Solomon, K. R., & Sibley, P. K. (2008). Toxicity of Human Pharmaceuticals and Personal Care Products to Benthic Invertebrates. *Environmental Toxicology & Chemistry*, *27*(2), 425–432.

Eiswirth, M., & Hötzl, H. (1997). The Impact of Leaking Sewers on Urban Groundwater. In *Groundwater in the urban environment*. Retrieved from https://www.researchgate.net/publication/237699275_The_impact_of_leaking_sewers_on_urban_groundwater

Evanylo, G. K. (n.d.). *Agricultural Land Application of Biosolids in Virginia: Managing Biosolids for Agricultural Use*. 8.

Fitzgerald, A., Roy, J. W., & Smith, J. E. (2015). Calculating discharge of phosphorus and nitrogen with groundwater base flow to a small urban stream reach. *Journal of Hydrology*, *528*, 138–151. https://doi.org/10.1016/j.jhydrol.2015.06.038

Focazio, M. J., Kolpin, D. W., Barnes, K. K., Furlong, E. T., Meyer, M. T., Zaugg, S. D., … Thurman, M. E. (2008). A national reconnaissance for pharmaceuticals and other organic wastewater contaminants in the United States — II) Untreated drinking water sources. *Science of The Total Environment*, *402*(2), 201–216. https://doi.org/10.1016/j.scitotenv.2008.02.021

Furlong, E. T., Batt, A. L., Glassmeyer, S. T., Noriega, M. C., Kolpin, D. W., Mash, H., & Schenck, K. M. (2017). Nationwide reconnaissance of contaminants of emerging concern in source and treated drinking waters of the United States: Pharmaceuticals. *Science of The Total Environment*, *579*, 1629–1642. https://doi.org/10.1016/j.scitotenv.2016.03.128

Glassmeyer, S. T., Hinchey, E. K., Boehme, S. E., Daughton, C. G., Ruhoy, I. S., Conerly, O., … Thompson, V. G. (2009). Disposal practices for unwanted residential medications in the United States. *Environment International*, *35*(3), 566–572. https://doi.org/10.1016/j.envint.2008.10.007

Hall, S. A., Chiu, G. R., Kaufman, D. W., Kelly, J. P., Link, C. L., Kupelian, V., & McKinlay, J. B. (2010). General exposures to prescription medications by race/ethnicity in a population-based sample: Results from the Boston Area Community Health Survey. *Pharmacoepidemiology and Drug Safety*, *19*(4), 384–392. https://doi.org/10.1002/pds.1920

Iwanowicz, L. R., Blazer, V. S., Pinkney, A. E., Guy, C. P., Major, A. M., Munney, K., … Sperry, A. (2016). Evidence of estrogenic endocrine disruption in smallmouth and largemouth bass inhabiting Northeast U.S. national wildlife refuge waters: A reconnaissance study. *Ecotoxicology and Environmental Safety*, *124*, 50–59. https://doi.org/10.1016/j.ecoenv.2015.09.035

James, A. O., Nicholson, T. R., Hill, R., & Bearn, J. (2016). Something old, something new: a successful case of meprobamate withdrawal. *Case Reports*, *2016*, bcr2015213606. https://doi.org/10.1136/bcr-2015-213606

Jolivet, J., Cowan, K. H., Curt, G. A., Clendeninn, N. J., & Chabner, B. A. (1983). The Pharmacology and Clinical Use of Methotrexate. *New England Journal of Medicine*, *309*(18), 1094–1104. https://doi.org/10.1056/NEJM198311033091805

Kolpin, D. W., Furlong, E. T., Meyer, M. T., Thurman, E. M., Zaugg, S. D., Barber, L. B., & Buxton, H. T. (2002). Pharmaceuticals, Hormones, and Other Organic

Wastewater Contaminants in U.S. Streams, 1999−2000: A National Reconnaissance. *Environmental Science & Technology*, *36*(6), 1202–1211. https://doi.org/10.1021/es011055j

Lagesson, A., Fahlman, J., Brodin, T., Fick, J., Jonsson, M., Byström, P., & Klaminder, J. (2016). Bioaccumulation of five pharmaceuticals at multiple trophic levels in an aquatic food web - Insights from a field experiment. *Science of The Total Environment*, *568*, 208–215. https://doi.org/10.1016/j.scitotenv.2016.05.206

Lee, D. G., Roehrdanz, P. R., Feraud, M., Ervin, J., Anumol, T., Jia, A., … Holden, P. A. (2015). Wastewater compounds in urban shallow groundwater wells correspond to exfiltration probabilities of nearby sewers. *Water Research*, *85*, 467–475. https://doi.org/10.1016/j.watres.2015.08.048

Melamed, R. D., & Rzhetsky, A. (2018). Patchwork of contrasting medication cultures across the USA. *Nature Communications*, *9*(1), 4022. https://doi.org/10.1038/s41467-018-06205-1

Mone, J. (2008, September 14). Tons of drugs dumped into wastewater. Retrieved January 19, 2019, from msnbc.com website: http://www.nbcnews.com/id/26706059/ns/health-health_care/t/tons-drugs-dumped-wastewater/

O'Brien, J. W., Thai, P. K., Eaglesham, G., Ort, C., Scheidegger, A., Carter, S., … Mueller, J. F. (2014). A Model to Estimate the Population Contributing to the Wastewater Using Samples Collected on Census Day. *Environmental Science & Technology*, *48*(1), 517–525. https://doi.org/10.1021/es403251g

Osorio, V., Larrañaga, A., Aceña, J., Pérez, S., & Barceló, D. (2016). Concentration and risk of pharmaceuticals in freshwater systems are related to the population density and the livestock units in Iberian Rivers. *Science of The Total Environment*, *540*, 267–277. https://doi.org/10.1016/j.scitotenv.2015.06.143

Phillips, P., & Chalmers, A. (2009). Wastewater Effluent, Combined Sewer Overflows, and Other Sources of Organic Compounds to Lake Champlain1. *JAWRA Journal of the American Water Resources Association*, *45*(1), 45–57. https://doi.org/10.1111/j.1752-1688.2008.00288.x

Phillips, P. J., Chalmers, A. T., Gray, J. L., Kolpin, D. W., Foreman, W. T., & Wall, G. R. (2012). Combined Sewer Overflows: An Environmental Source of Hormones and Wastewater Micropollutants. *Environmental Science & Technology*, *46*(10), 5336–5343. https://doi.org/10.1021/es3001294

Phillips, P. J., Schubert, C., Argue, D., Fisher, I., Furlong, E. T., Foreman, W., … Chalmers, A. (2015). Concentrations of hormones, pharmaceuticals and other micropollutants in groundwater affected by septic systems in New England and New York. *The Science of the Total Environment*, *512–513*, 43–54. https://doi.org/10.1016/j.scitotenv.2014.12.067

Phillips, Patrick J., Smith, S. G., Kolpin, D. W., Zaugg, S. D., Buxton, H. T., Furlong, E. T., … Stinson, B. (2010, June 4). Pharmaceutical Formulation Facilities as Sources of Opioids and Other Pharmaceuticals to Wastewater Treatment Plant Effluents [Research-article]. https://doi.org/10.1021/es100356f

Ramirez, A. J., Brain, R. A., Usenko, S., Mottaleb, M. A., O'Donnell, J. G., Stahl, L. L., … Chambliss, C. K. (2009). Occurrence of pharmaceuticals and personal care products in fish: Results of a national pilot study in the united states. *Environmental Toxicology and Chemistry*, *28*(12), 2587–2597. https://doi.org/10.1897/08-561.1

Rico, M., Andrés-Costa, M. J., & Picó, Y. (2017). Estimating population size in wastewater-based epidemiology. Valencia metropolitan area as a case study. *Journal of Hazardous Materials*, *323, Part A*, 156–165. https://doi.org/10.1016/j.jhazmat.2016.05.079

Sackett, D. K., Pow, C. L., Rubino, M. J., Aday, D. D., Cope, W. G., Kullman, S., … Law, M. (2015). Sources of endocrine-disrupting compounds in North Carolina waterways: A geographic information systems approach. *Environmental Toxicology and Chemistry*, *34*(2), 437–445. https://doi.org/10.1002/etc.2797

Sanchez, W., Sremski, W., Piccini, B., Palluel, O., Maillot-Maréchal, E., Betoulle, S., … Porcher, J.-M. (2011). Adverse effects in wild fish living downstream from pharmaceutical manufacture discharges. *Environment International*, *37*(8), 1342–1348. https://doi.org/10.1016/j.envint.2011.06.002

Sanderson, H., Johnson, D. J., Reitsma, T., Brain, R. A., Wilson, C. J., & Solomon, K. R. (2004). Ranking and prioritization of environmental risks of pharmaceuticals in surface waters. *Regulatory Toxicology and Pharmacology*, *39*(2), 158–183. https://doi.org/10.1016/j.yrtph.2003.12.006

Scutti, S. (2018, December 28). Pouring drugs down the drain in hospitals. Retrieved April 22, 2019, from https://www.cnn.com/2018/12/28/health/water-pharmaceutical-contaminants-epa/index.html

Stackelberg, P. E., Furlong, E. T., Meyer, M. T., Zaugg, S. D., Henderson, A. K., & Reissman, D. B. (2004). Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking-water-treatment plant. *Science of The Total Environment*, *329*(1–3), 99–113. https://doi.org/10.1016/j.scitotenv.2004.03.015

Swartz, C. H., Reddy, S., Benotti, M. J., Yin, H., Barber, L. B., Brownawell, B. J., & Rudel, R. A. (2006). Steroid Estrogens, Nonylphenol Ethoxylate Metabolites, and Other Wastewater Contaminants in Groundwater Affected by a Residential Septic System on Cape Cod, MA. *Environmental Science & Technology*, *40*(16), 4894–4902. https://doi.org/10.1021/es052595+

Tong, A. Y. C., Peake, B. M., & Braund, R. (2011). Disposal practices for unused medications around the world. *Environment International*, *37*(1), 292–298. https://doi.org/10.1016/j.envint.2010.10.002

Vatovec, C., Phillips, P., Van Wagoner, E., Scott, T.-M., & Furlong, E. (2016). Investigating dynamic sources of pharmaceuticals: Demographic and seasonal use are more important than down-the-drain disposal in wastewater effluent in a University City setting. *Science of The Total Environment*, *572*, 906–914. https://doi.org/10.1016/j.scitotenv.2016.07.199

Veach, A. M., & Bernot, M. J. (2011). Temporal variation of pharmaceuticals in an urban and agriculturally influenced stream. *Science of The Total Environment*, *409*(21), 4553–4563. https://doi.org/10.1016/j.scitotenv.2011.07.022

Viswanathan, M., Golin, C. E., Jones, C. D., Ashok, M., Blalock, S. J., Wines, R. C. M., … Lohr, K. N. (2012). Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Annals of Internal Medicine*, *157*(11), 785–795. https://doi.org/10.7326/0003-4819-157-11-201212040-00538

Young, J., Iwanowicz, L., Sperry, A., & Blazer, V. (2014). A landscape-based reconnaissance survey of estrogenic activity in streams of the upper Potomac, upper James, and Shenandoah Rivers, USA. *Environmental Monitoring & Assessment*, *186*(9), 5531–5545. https://doi.org/10.1007/s10661-014-3801-y

BIOGRAPHY

Stephanie Gordon obtained her Bachelor of Arts form James Madison University in Modern French Language with Swahili as a secondary language, and a minor in Environmental Studies.