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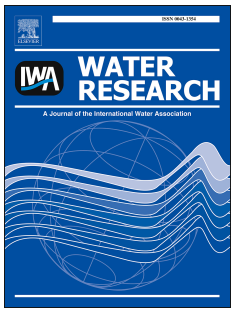

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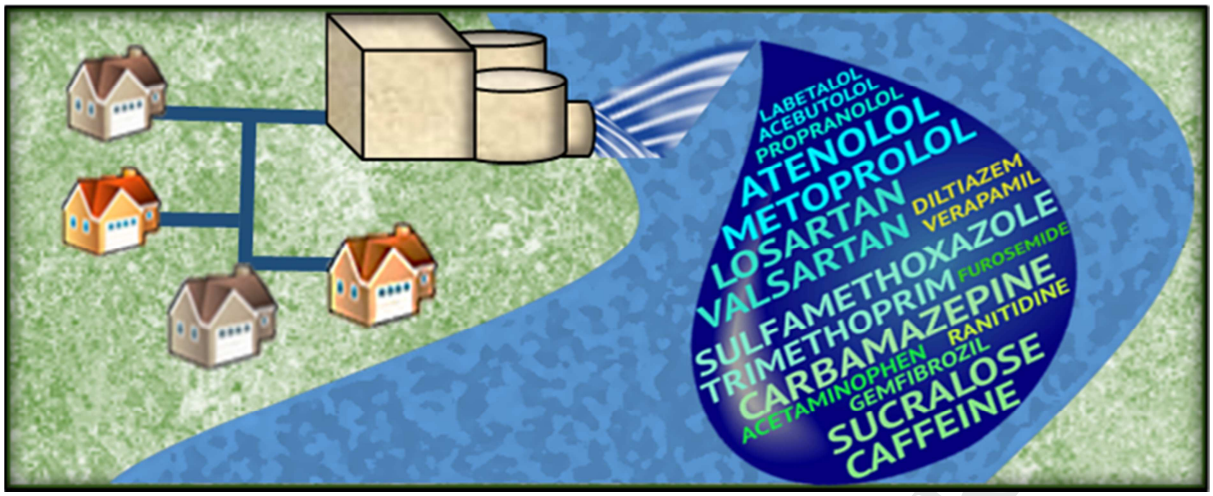

Spatial Patterns of Pharmaceuticals and Wastewater Tracers in the Hudson River Estuary

Mark G. Cantwell[a*], David R. Katz[a], Julia C. Sullivan[b], Daniel Shapley[c], John Lipscomb[c], Jennifer Epstein[c], Andrew R. Juhl[d], Carol Knudson[d], Gregory D. O'Mullan[e]

[a]U.S. Environmental Protection Agency, Office of Research and Development, 27 Tarzwell Drive, Narragansett, RI 02882, USA

[b]Oak Ridge Associated Universities, Narragansett, RI 02882 USA

[c]Riverkeeper Inc., 20 Secor Road, Ossining, NY 10562, USA

[d]Lamont Doherty Earth Observatory of Columbia University, 61 Route 9W, Palisades, NY 10964, USA

[e]School of Earth and Environmental Sciences, Queens College, City University of New York, 65-30 Kissena Blvd., Flushing, NY 11367, USA

*Corresponding author: E-mail: cantwell.mark@epa.gov

Abstract

The widespread use of pharmaceuticals by human populations results in their sustained discharge to surface waters via wastewater treatment plants (WWTPs). In this study, 16 highly prescribed pharmaceuticals were quantified along a 250 km transect of the Hudson River Estuary and New York Harbor to describe their sources and spatial patterns. Sampling was conducted over two dry weather periods in May and July 2016, at 72 sites which included mid-channel and nearshore sites, as well as locations influenced by tributaries and WWTP outfalls. The detection frequency of the study pharmaceuticals was almost identical between the May and July sampling periods at 55% and 52%, respectively. Six pharmaceuticals were measurable at 92% or more of the sites during both sampling periods, illustrating their ubiquitous presence throughout the study area. Individual pharmaceutical concentrations were highly variable spatially, ranging from non-detect to 3810 ng/L during the study. Major factors controlling concentrations were proximity and magnitude of WWTP discharges, inputs from tributaries and tidal mixing. Two compounds, sucralose and caffeine, were evaluated as tracers to identify wastewater sources and assess pharmaceutical behavior. Sucralose was useful in identifying wastewater inputs to the river and concentrations showed excellent correlations with numerous pharmaceuticals in the study. Caffeine-sucralose ratios showed potential in identifying discharges of untreated wastewater occurring during a combined sewage overflow event. Many of the study pharmaceuticals were present throughout the Hudson River Estuary as a consequence of sustained wastewater discharge. Whereas some concentrations were above published effects levels, a more complete risk assessment is needed to understand the potential for ecological impacts due to pharmaceuticals in the Hudson River Estuary.

Keywords: pharmaceuticals, wastewater tracers, Hudson River, emerging contaminants

1. Introduction

Pharmaceuticals comprise a large and growing class of chemical compounds present at elevated levels in water bodies of developed nations, primarily entering the environment following human use via wastewater treatment plant (WWTP) discharges (Gaw et al., 2016). Pharmaceutical compounds including prescription, nonprescription and illegal drugs may number in the hundreds in WWTP effluents. Many pharmaceuticals are highly prescribed and as a result enter the waste stream at high concentrations. Removal efficiency of pharmaceuticals during wastewater treatment is variable and often poor, resulting in their continuous release into the aquatic environment (Kolpin et al., 2002; Verlicchi et al., 2012). Under certain conditions, such as when combined sewage overflow (CSO) events occur, treatment systems are bypassed, resulting in the release of untreated sewage, further increasing the levels of some wastewater contaminants present (Kay et al., 2017). Consequently, many pharmaceuticals in receiving waters may be present in the ng/L to µg/L range (Roig and D'Aco, 2016).

In rivers, estuaries and coastal ecosystems that are urbanized or near densely-populated cities, the high volume and continuous discharge of WWTP effluents is a significant concern. In many such locations episodic releases of untreated wastewater via CSOs and undocumented discharges are also a factor in water quality degradation (Launay et al., 2016). It is thought that most pharmaceutical compounds remain biologically active in aquatic systems with the potential to exert adverse effects on aquatic life if present at levels above known effects thresholds (Seiler, 2002). The sustained discharge of pharmaceuticals may result in receiving waters with areas of pseudo-persistence (Daughton, 2001), resulting in chronic exposure and possible ecological effects. Pharmaceuticals are a class of pollutants that have been identified as "contaminants of emerging concern" (CECs). In the United States, there are currently no regulatory standards

associated with them and there is limited information on their occurrence and potential to impart adverse effects (USEPA, 2017). Most CECs, including pharmaceuticals, are not included in current monitoring protocols, but may be candidates for future regulation based on their toxicity and other adverse effects. To ascertain the risk of CECs such as pharmaceuticals, information on contaminant sources (e.g., domestic wastewater (WW) discharges), individual CEC loadings, and their potential for adverse effects is needed. This information can be used to inform recently developed monitoring criteria that employs a risk based framework which focuses on whether concentrations of CECs measured in the environment exceed already established thresholds for biological effects (Sengupta et al., 2014). Further, these risk based methods enable a tiered approach to monitoring and could potentially provide support for future regulation of CECs (Maruya et al., 2014).

The Hudson River Estuary (HRE) is an estuary of vital ecological and economic importance that has been understudied with regard to WW derived CECs, particularly pharmaceuticals. The HRE supports many activities, providing critical services to > 15 million residents, as well as millions of visitors annually and others who indirectly benefit from economic activity within the watershed. Major uses include transportation, commerce, industrial, and as a drinking water source. The entire length of the HRE is a receiving water for numerous WWTP discharges, along with CSO releases, of untreated WW. New York City alone discharges over 4.9×10^6 m^3/d of treated WW (NYCDEP, 2012), and over 7×10^7 m^3 of CSO discharges annually (NYCDEP, 2016). The large-scale, sustained discharge of WW results in numerous sewage-related contaminants being released to the HRE, including pharmaceuticals. Bacterial fecal indicators in the HRE show high spatial and temporal variability, though with recognizable patterns related to untreated sewage inputs and precipitation (Young et al., 2013). Although

97 long-term trends in most water quality indicators show considerable improvement in the HRE in
98 recent decades (Steinberg et al., 2004; Brosnan et al., 2006), ongoing discharges combined with
99 legacy pollutants (e.g., PCBs, PAHs) continue to present widespread water quality issues with
100 potential impacts on human health, ecosystem function and economic activity.

101 In this study, the behavior and fate of 16 high-volume-use pharmaceutical compounds, caffeine
102 and the artificial sweetener sucralose were investigated. These pharmaceuticals were selected
103 using a conceptual approach which prioritized highly prescribed drugs based on their potential to
104 cause biological effects in wastewater (Batt et al., 2016; Kostich et al., 2014). This approach is
105 similar to others used to identify CECs for monitoring and further investigation (Maruya et al.,
106 2014). The compounds were measured during dry weather along a 250-km (155-mile) transect
107 of the HRE. Sites within a heavily CSO impacted New York Harbor (NYH) embayment were
108 also sampled during both wet and dry weather conditions to begin to assess urban CSO influence
109 at the mouth of the river. The objectives were to: (1) measure the study pharmaceuticals in the
110 water column at high spatial resolution to develop an understanding of the factors controlling
111 their occurrence and spatial patterns during dry weather; and (2) evaluate two potential tracers,
112 caffeine (Benotti and Brownawell, 2009) and sucralose (Buerge et al., 2003; Oppenheimer,
113 2012), for tracking WW impacts in tidal rivers and estuaries such as the Hudson River.

114

115 **2. Materials and methods**

116 *2.1 Study location* **(HudsonMap.kml here)**

117 The morphology of the HRE is best described as a drowned river valley with little vertical rise
118 (0.006 m/km) over a 250 km distance between the Battery (NYH) and the dam at Troy, NY and

drains a watershed area of 13750 km^2 (USGS, 2017). The path of the HRE main channel runs in a relatively straight line from New York City to Albany (Figure 1). It is ~1.3 km in width at river kilometer (RK) 0 and widens, reaching its widest point of ~5.6 km at RK 63. Further north, widths taper to and remain at approximately 0.5 km from RK 188 to RK 241. River depths are highly variable, with navigable channel depths averaging 12 m and a maximum depth of 61 m. The HRE is classified as a partially mixed estuary with a moderate salinity gradient and vertical stratification (Geyer and Chant, 2006). The river is tidally influenced up to the Federal Dam at Troy (RK 245) with a tidal magnitude of approximately 1.5 m. Tidal cycles are semidiurnal, with an average tidal current of 0.7 m/s, and play an important role in salinity gradients and stratification within the river, as does the volume of fresh water (Geyer and Chant, 2006). Approximately 80% of the fresh water entering the HRE at Troy annually originates from the upper Hudson and the Mohawk Rivers, with the balance entering from tributaries (Cooper et al., 1988) (Figure 1, Table S1). Within the HRE, the position of the salinity front can be highly variable over time, with the volume of fresh water being the primary regulator (Geyer and Chant, 2006). Information on the residence time of water within the HRE is very limited, with estimates of 1 to 4 days for the haline part (Howarth et al., 2006), and from 25 to 100 days for the freshwater section (Cooper et al., 1988), varying with freshwater flows and tidal cycles.

The locations of sampling sites along the river transect are reported in RKs, starting at the New York City Battery where the Hudson enters NYH (RK 0) continuing up to RK 250. There were 65 sites along the transect, 63 of which were in the tidal estuary (Figure 1, Table S2). There were two sites at the mouths of the Mohawk and upper Hudson Rivers, just above the Troy Dam, which flow into the HRE and account for > 99% of the drainage above the dam (Wall et al.,

2008). Finally, seven sites in the interconnected waterways of upper NYH were sampled, as were CSO discharges during a wet weather event.

2.2 Sampling

Water samples were collected May 19–23 and July 12–16, 2016, off the Riverkeeper vessel *R. Ian Fletcher*. Sampling of the transect started at RK 0 and progressed to RK 249.6. Over a period of 5 days, a single grab sample was collected from 0.25 m below the water surface at each site (Table S2). Samples were kept on ice until returned to the laboratory, and stored in the dark at 4°C until processed. Extraction and analysis of samples was performed within 7 days of sample collection. Surface water conditions (e.g., salinity, temperature) were also recorded at each station during sampling with a Hydrolab data sonde. Samples from Flushing Bay within the East River were also collected from July 29 to August 6, 2016 to begin assessing urban CSO impacts on NYH.

2.3 Water extractions

Before extraction, 250 mL of water was passed through a 0.7 μm glass fiber filter (Whatman GFF) and stored in amber glass bottles. Extraction protocols followed EPA Method 1694 with slight modifications using Oasis HLB solid phase extraction (SPE) cartridges (6 cc, 500 mg, Waters Corporation). For the extractions, 250-mL samples were adjusted to pH 2 using hydrochloric acid (6N) and spiked with 100 ng of isotopically labeled internal standards (IS) (Table S3). Cartridges were conditioned with 6 mL of methanol, followed by 6 mL of pH 2 Milli-Q water, and 6 mL of pH 2 filtered artificial seawater. Samples were loaded onto SPEs using a vacuum manifold at a rate of 5 to 10 mL/min. After loading, the SPEs were rinsed with 12 mL of pH 2 Milli-Q water, dried for 15 minutes under vacuum and eluted with 12 mL of methanol. Extracts were then evaporated to dryness, reconstituted with 1 mL mobile phase

(Milli-Q:methanol, 80:20), vortexed, transferred to vials and stored at 4°C until analysis. Each set of extractions included a blank, fortified blank, duplicate, and matrix evaluation.

2.4 Analysis

The 16 pharmaceuticals in the present study were antihypertensives (acebutolol (ACB), atenolol (ATE), diltiazem (DIL), labetalol (LAB), losartan (LOS), metoprolol (MET), propranolol (PRO), valsartan (VAL), and verapamil (VER)); antibiotics (sulfamethoxazole (SUL) and trimethoprim (TRI)); an analgesic (acetaminophen (ACE)); an anticonvulsant (carbamazepine (CAR)); a diuretic (furosemide (FUR)); an antilipemic (gemfibrozil (GEM)); and an antiulcerative (ranitidine (RAN)). Caffeine (CAF) and sucralose (SUC) were measured because of their potential as WW tracers. The compounds were quantified using high purity standards (Sigma Aldrich) with isotopically enriched surrogates (deuterated and/or ^{13}C) as an IS (CDN Isotope) (Table S4). Analysis was performed on a Waters Acquity UPLC using a Waters Xevo TQD MS/MS operated in electrospray ionization (ESI) mode. Compounds were detected by MS/MS with ionization conditions of the capillary set to 0.5 kV in ESI+ and 3.5 kV in ESI- (Table S5). Compound specific settings were also used for quantification and confirmation multiple reaction monitoring (MRM) transitions (Tables S3). Compounds were calibrated using a 10-point curve ranging from 0.25 ng/mL to 300 ng/mL. Calibration curves consistently had an $r^2 = 0.99$ or better for all compounds. Calibration verification standards were also analyzed every 10 samples to confirm instrumental performance over the course of the analytical run. Recoveries for each compound were generally within 10% of reference values. Study compounds were not detected in the blanks (n=17), with the exception of CAF. One blank had a value of 3 ng/L, with all others near or below the detection limit of 0.3 ng/L. Since the minimum and mean concentrations of CAF during this study were approximately 22 ng/L and 109 ng/L,

187 respectively, this was not regarded as a substantial issue and a blank correction was not
188 performed. The method detection limits (MDLs) for the study compounds ranged from a high of
189 10 ng/L to a low of 0.01 ng/L. Because of the potential for bias in the frequency of detection
190 based on the range of individual compound MDLs, we statistically examined all data using
191 histogram frequency distribution analysis. No patterns indicating MDL bias were found for any
192 of the study compounds. Method detection limits were determined for each of the compounds
193 using instrument detection limits defined as a signal to noise ratio >10 and are reported in
194 Supplemental Data, Table S6, along with further information on quality assurance.
195
196 **3. Results and discussion**
197 *3.1 River conditions*
198 During the May and July sampling periods, average daily freshwater flows entering the HRE
199 above the dam at Troy were 1.9 x 10^7 m^3/d and 1.4 x 10^7 m^3/d, respectively (USGS, 2017) (Table
200 S1), with a 26% decline in freshwater flow to the river in July. These levels are lower than 5-
201 year monthly flow averages of 4.8 x 10^7 m^3/d and 2.9 x 10^7 m^3/d for May and July, respectively,
202 reflecting the dry conditions during this study. Currently, at least 90 municipal WWTPs
203 discharge effluent directly or into tributaries entering the HRE (Table S7). Estimates of daily
204 discharge indicate approximately 1.7 x 10^6 m^3/d of effluent entering the HRE from locations
205 above NYH (USEPA, 2016). This is approximately 7.5 and 11% of the fresh water input from
206 the Upper Hudson and major tributaries during the May and July sample periods, respectively
207 (Table S1).

208 Surface water temperatures ranged considerably between sampling periods (Figure S1). In May
209 temperatures ranged from 12.7 to 19.4°C while July temperatures ranged from 22.7 to 28.3°C.

Temperatures during both periods were coolest at the mouth of the river and rose steadily up the transect, which is mostly explained by cooler, seawater entering the river during incoming tides.

Surface salinities were highest at the river mouth (RK 0), registering values of 14.6 and 20.8 for May and July, respectively, declining with distance upriver (Figure S2). Measurable surface salinity (0.3 psu) extended as far north as RK 74 in May and RK 98 in July, with decreased freshwater flow explaining the salinity front extension in July. Strong horizontal salinity gradients have previously been reported between RK 40 and 66, with salinity fronts as far north as Poughkeepsie (RK 124). Overall, salinity and temperature observations are consistent with historical seasonal trends, which are largely driven by the variability of freshwater flow (Geyer and Chant, 2006).

3.2 Pharmaceutical occurrence and distribution

The frequency of occurrence and spatial patterns of the study pharmaceuticals were determined to provide information on their sources, distribution and behavior (Figure 2). The frequency of occurrence (expressed as %) across the whole study area were almost identical in the two months, with an average of 55% of pharmaceuticals occurring at each site during the May sampling and 52% in July. Results are presented by sites within the river and those within NYH. The absence of significant precipitation throughout the watershed resulted in low freshwater flow volumes during both sampling events and the expectation for little to no CSO input.

3.2.1 River transect

The occurrence frequencies of pharmaceuticals were somewhat variable over the length of the river, with slightly lower frequencies observed in July (Figure 2). The largest increases in occurrence were associated with sites at WWTP discharges, especially at RKs 28.2, 41.8, and

148.2 where the number of compounds present exceeded 90%. Above the Troy Dam, fresh water enters the HRE originating from the Mohawk and Upper Hudson River watersheds. Here, the percent of study pharmaceuticals present averaged between 56 and 63%, reflecting their widespread presence in these major tributaries as a result of 4.0×10^5 m^3/d of WW effluents discharged daily (Table S7). The occurrence frequencies at sites just below the dam (e.g., RKs 245.4–197.1), influenced by the cities of Troy and Albany, were similar to those above the dam ranging between 50% and 81%. The percentage of compounds present declined from RKs 188.3 through 156.1, dropping to 44–56%, due in part to dilution from major tributaries (e.g., Stockport/Kinderhook, Esopus, Catskill) entering this reach of the river. Because of the low population densities in this region, these tributaries receive smaller volumes of WW discharges (8.1×10^3 m^3/d) than those above the dam (Table S7). Combined, all of these tributaries provide significant quantities of freshwater based on recent flow data (Table S1). From RKs 141.6 through 45.1, the occurrence of pharmaceuticals ranged between 38 and 56%. One exception is at RK 84.5 (located by the WWTP outfall at the military academy at West Point), where the frequency of occurrence dropped from 81% during the May sampling to 44% in July, which likely reflects the population drop between academic sessions. Below RK 45.1, the percentage of study pharmaceuticals present increased, with well-defined spikes at RKs 41.8 and 28.2, sites with major WW inputs. The trend from RKs 43.5 through 0 is complex and suggests a number of factors influenced the percentage of pharmaceuticals present. The proximity of New York and New Jersey urban areas, with an estimated population of >12 M, along with numerous large-volume WWTP discharges clearly exerted their influence, with an average of 58% of pharmaceuticals measurable for both sampling periods. The sustained, high volume of effluent

entering the river, combined with harbor water reentering the river on incoming tides, resulted in conditions with numerous pharmaceuticals present.

During the May sampling, 7 of the 16 pharmaceuticals (ATE, CAR, LOS, MET, SUL, TRI, and VAL) were present at ≥98% of the 65 river sites. This compared closely to July, where the same compounds (excepting TRI at 77%) were present at ≥92% of the river sites (Figure 2, Table 1). The similarity in trends between compounds along the transect and between sampling periods indicates the ubiquitous nature of these compounds under similar environmental conditions (e.g., precipitation, river flow).

Concentrations of individual pharmaceuticals varied along the river transect, with many trending in a similar manner from the start of the estuary (RK 245.4) to the Battery (RK 0) (Figure 3, Table 1, Table S8). Four pharmaceuticals present throughout the river were all antihypertensive medications and can be credited for some of the highest concentrations recorded in this study. Although median concentrations for these compounds were fairly consistent between sampling periods, the maximum concentrations recorded were much higher in May, with values as high as 1070 ng/L for ATE, 1700 ng/L for LOS, 2020 ng/L for MET, and 3810 ng/L for VAL. It should be noted that for most compounds, the maximum concentrations reported in this study were recorded at RK 148.2—a site which is in direct proximity to a WW outfall. The other three frequently detected-compounds—CAR, SUL, and TRI—followed the same pattern, with higher maximum concentrations in May and nearly identical median values between sampling periods.

Three other pharmaceuticals (ACE, DIL, and GEM) were present at less than 50% of the sites along the transect, but were generally present at sites near WWTPs. In particular, ACE and GEM were more abundant in May and exhibited greater variability between sampling periods. The occurrence of ACE dropped from 49% in May to 11% in July, and GEM experienced a

similar magnitude in decline, occurring at 37% of the sites in May and 18% in July. Aside from a few prominent peaks, concentrations generally remained below 18 ng/L for both compounds. DIL was present near WWTP outfalls along with a few sites in the lower and upper reaches of the river at low levels. Finally, ACB, FUR, LAB, PRO, RAN and VER were present ≤ 25% of the time during both sampling periods (Table 1). These compounds were present almost exclusively by WWTP outfalls. LAB and PRO were present at 6 and 8% of the sites during May, occurring slightly more frequently in July at 11 and 18%, respectively. VER was present at 6% of sites in May, compared to 22% in July. RAN was found at 8% of the sites in May and 5% in July when it was present exclusively near large WWTP outfalls. ACB was detected at 6% of sites in May and 5% in July. Concentrations of these compounds were generally higher in May than in July.

Spatial patterns identified major tributaries and WWTPs along the transect as key factors influencing pharmaceutical concentrations. Trends between sampling periods provided insight into behavior of individual pharmaceuticals. Decreased river flow during July likely increased residence time to an undetermined extent as evidenced by the salinity profiles. However, only two compounds, CAR and SUL, were generally higher along the transect in July (Figure 3). Conversely, GEM, TRI and VAL were slightly lower in July.

A number of processes may explain the behavior of some of the pharmaceuticals in the river. The sorption potential of individual pharmaceuticals gives an indication of their likelihood to be removed from the water column. The Log K_{ow}s of the pharmaceuticals in this study are low, with five having Log K_{ow}s less than 1 and only four above 3.0, indicating little potential for solid phase partitioning (Table S9). Examination of the data based on the compound's respective K_{ow}s did not reveal any consistent patterns of behavior. Similarly, distribution coefficients (K_ds)

provide direct evidence of partitioning behavior in the water column. Cantwell et al. (2016a) determined field-derived K_ds for eight of the compounds (Table S9), with four other compounds exhibiting insufficient solid-phase concentrations to determine K_ds (e.g., ACE, GEM, SUL, and VAL). Median K_d values for six of the eight pharmaceuticals were below 2.5, with the other two below 4.0. Ternes et al. (2004) observed that compounds with Log K_d values of 2.7 or less were shown to have minimal removal from the dissolved phase (< 10%) by sorption processes.

The acid dissociation constant (or pKa) is an important factor controlling the therapeutic behavior of pharmaceuticals as the degree of ionization is strongly influenced by pH, which can also have implications when pharmaceutical residues are present in aquatic systems (Cunningham, 2008). The study compounds have a broad range of pKa values, from -4.8 to 17.3 (Table S9). The pH of the receiving water could affect the degree of ionization of individual pharmaceuticals to some extent, as ionized compounds will be more soluble in contrast to their respective neutral species. This would make them less likely to partition to solid phases and potentially affect their distribution in the water column. While pH was not measured in this study, long-term values in the Hudson range from 6.4 to 8.2, with most above 7.0 (Cooper et al., 1988), which could potentially affect the behavior of some of the pharmaceuticals. Recent work, however, has not shown a relationship between pKa and solubility with a similar suite of compounds in estuarine conditions (Zhao et al., 2015).

Overall, sorption does not appear to be an important mechanism of removal for most of the compounds examined during this study, suggesting that many of the declines observed may be due to degradation by abiotic and biotic processes. A decrease in abundance and concentrations of some compounds in July suggests that degradation may have been a factor for more labile pharmaceuticals. Reduced freshwater inputs (Table S1) to the HRE (which would increase

residence time) and elevated water temperatures (Figure S1) in July may create enhanced conditions supporting degradation.

3.2.2 New York Harbor

The New York Harbor sites are located in East River, Harlem River, Newtown Creek and Gowanus Canal. The occurrence of pharmaceuticals present in NYH was relatively high, ranging from 56 to 83% and usually at slightly higher concentrations in Newtown Creek and East River. Six compounds—ATE, CAR, LOS, MET, TRI, and VAL—were present at all seven sites during both sampling periods. Additionally, ACE and SUL were present at all sites in May, while DIL had 100% occurrence in July but was not detected at all in May. PRO and VER occurred at 43% and 57%, respectively, of sites in May, while each had occurrence rates of 71% in July. LAB occurred at 14% of sites in May and 57% of sites in July. ACB was only detected in May, with an occurrence rate of 43%. RAN was detected only once in May, and FUR was not detected during either sampling period.

Median concentrations of ACE, ATE, GEM, LOS, MET, SUL, TRI, and VAL in NYH were mostly higher than in the transect. These compounds, with the exception of GEM, were higher during July, with median values ranging 7.7–78 ng/L in May and 10–95 ng/L in July. Median values remained below 9 ng/L for CAR and did not exceed 2.4 ng/L for ACB, DIL, LAB, PRO and VER.

New York Harbor has numerous large WWTPs in both the Hudson and East River tributaries that contribute approximately 3.8×10^6 m^3/d of effluent to this area (Table S7). The large volume of water entering from both the Hudson and East Rivers, already elevated in pharmaceuticals, is subjected to the Harbor's complex hydrodynamics and additional WW inputs. Here, successive

345 tidal cycles advect large volumes of water from the harbor up the river. However, no decrease in
346 percent occurrence of pharmaceuticals was observed. Tidal cycling in the lower river and harbor
347 here can cause equivalent flow in both directions. The complex hydrodynamics and dynamic
348 mixing of water combined with the location and volume of WW discharged daily into the harbor
349 explain the spatial patterns of pharmaceuticals observed in this area. These findings highlight
350 the importance of hydrodynamics along with input levels and source locations in regulating
351 contaminant concentrations in coastal rivers and embayments.

352 *3.3 Environmental perspective*

353 Comparing pharmaceutical responses in this study to other river systems provides some context
354 to the levels observed. Recently, Batt et al. (2016) conducted a national survey of
355 pharmaceuticals in 182 US rivers and streams that included 13 of the 16 compounds (except
356 ACB, LAB, and LOS) examined in this study. Between the two studies, the mean frequency of
357 detection across our sites was greater in this study (Table S10). Comparison of concentrations
358 from both studies also revealed that with the exception of VER, numerous compounds in this
359 study (e.g., ACE, ATE, DIL, FUR, GEM, MET, RAN, TRI, and VAL) were higher and the
360 others (CAR, PRO, and SUL) were nearly equal. Similar trends were found in the Garonne
361 River estuary of France with mean concentrations of CAR and PRO nearly equal to those in this
362 study, but with lower mean levels of ATE, GEM, LOS, MET, and RAN (Aminot et al., 2016).
363 Combined, the high frequency of occurrence and elevated concentrations of many of the study
364 pharmaceuticals illustrates the impact WWTP discharges have on the HRE relative to other
365 rivers (Table S10), which raises questions regarding the possibility of ecological effects.

366 Pharmaceutical compounds are frequently detected in freshwater and marine environments,
367 though they are rarely found at levels high enough to cause acute toxicity (Brausch et al., 2012).

368 However, since many pharmaceuticals (particularly highly prescribed ones) are constantly
369 entering the environment, there is interest regarding the potential for chronic effects. At some
370 sites in this study, particularly those situated by WWTP outfalls, several pharmaceuticals were
371 measured at concentrations reported to cause chronic effects to aquatic organisms: SUL (Yu et
372 al., 2011), CAR (De Lange et al., 2006), PRO (Franzellitti et al., 2011), and ACE (Parolini et al.,
373 2013). At RK 148.2, which is situated at a WWTP outfall and at low tide is essentially undiluted
374 effluent, five other compounds were measured at concentrations reported to cause chronic
375 effects: TRI (Parolini et al., 2013), RAN (Rocco et al., 2010), FUR (Rocco et al., 2010), GEM
376 (Rocco et al., 2012), and MET (Dietrich et al., 2010). Although these compounds were not
377 found at levels this high throughout the entirety of HRE, their high concentrations at several sites
378 indicate that minimum effect concentrations for a number of pharmaceuticals may be exceeded
379 near WW point sources (e.g., WWTP outfalls, CSOs).

380 *3.4 Tracer evaluation*

381 Two compounds, CAF and SUC, were evaluated to assess their efficacy as tracers of sanitary
382 wastewater in the HRE and NYH. Previously, CAF has been used to identify WW in surface
383 waters (Buerge et al., 2003), and track CSO and undocumented sanitary discharges to estuarine
384 waters (Buerge et al., 2006; Cantwell et al., 2016b). Caffeine is efficiently removed (> 95%) by
385 most sanitary WWTP processes (Buerge et al., 2003) making it well suited to identify untreated
386 WW sources (e.g., CSOs) (Benotti and Brownawell, 2009). Sucralose is used extensively as a
387 food and beverage sweetener and has also been evaluated as a WW tracer in aquatic systems.
388 (Oppenheimer et al., 2011; 2012). As opposed to CAF, SUC is highly resistant to degradation as
389 it is mostly inert to metabolic and environmental processes (Soh, et al., 2011), resulting in
390 negligible removal by WWTPs (Yang et al., 2017). The differential behavior of SUC and CAF

391 along with their elevated levels in receiving waters indicates that combined, they may
392 discriminate between sources of treated and untreated sanitary wastewater (e.g., WWTP effluents
393 and CSOs).

394 Both SUC and CAF were present at all sites and sampling periods at high concentrations,
395 reflecting their extensive use in foods and beverages as well as excipient ingredients in
396 pharmaceutical formulations. Along the transect, SUC concentrations ranged from 498 to
397 16,200 ng/L, with median values of 876 and 1180 ng/L for the May and July sampling periods,
398 respectively. This increase is likely due to the 26% decline in freshwater flow during July,
399 which increased the proportion of WW effluent in the river. Compared to SUC, CAF was an
400 order of magnitude lower along the transect, ranging from 22 to 2260 ng/L with median values
401 of 70 and 49 ng/L for May and July, respectively. For perspective, SUC and CAF concentrations
402 measured by Bernot et al. (2016) in rivers and streams throughout the US were lower than in this
403 study, with sucralose ranging from nondetect to 12,000 ng/L and caffeine ranging from
404 nondetect to 420 ng/L.

405 Along the transect, SUC showed similar trends during both sampling periods with several
406 discrete differences. SUC concentrations entering the HRE at RK 249.6 were 700 and 498 ng/L
407 in May and June, respectively (Figure 4). Concentrations spike slightly at RK 249.4 due to its
408 close proximity to a WWTP. In May from RKs 245 through 86.9, concentrations stayed within
409 the range of 700 to 1200 ng/L, excepting one large peak near a WWTP. Below RK 86.9 in May,
410 concentrations only rose over 950 ng/L at discrete locations along the transect. In July from RKs
411 245.4 through RK 148.2, concentrations rarely fell below 1300 ng/L. At the sites below that
412 point, values generally remain in the range of 800 to 1300 ng/L, again with the exception of a
413 few discrete peaks. Generally, large spikes in SUC concentrations coincided with high volume

414 WWTP discharges (e.g., RKs 148.2 and 41.8). In May there were several prominent SUC peaks
415 at RKs 19.3–12.7 that were absent in July. The sources of these peaks are unknown, but may be
416 from episodic, undocumented WW discharges.

417 Maximum levels of CAF for both sampling periods occurred at RK 41.8, which is near two
418 major WWTP discharges (Table S7). Spatial trends for CAF were also similar between
419 sampling periods with exception of RKs 28.2–0.2 during May. In May, CAF is twice the July
420 levels from RKs 28.2 through 0.2, a generalized increase that suggests discharge of untreated
421 WW. In May below RK 19.3, there were several well-defined peaks of SUC present, suggesting
422 too that there may be unidentified WW discharge in the lower segment of the river. The
423 enhanced responses of SUC throughout the river at locations with known WW outfalls combined
424 with its inert behavior supports its potential as a WW tracer in large systems such as the HRE.

425 Another objective was to examine whether tracers can explain the behavior and fate of WW
426 associated contaminants. Concentrations of SUC were compared against the study compounds
427 from the river transect. Concentrations of pharmaceuticals present > 75% of the time were
428 regressed against SUC and CAF to examine their relationships (Table S11). Coefficients of
429 determination (r^2) for SUC were uniformly higher, with r^2 values ranging 0.77–0.97 for both
430 May and July, exhibiting strong linear relationships. In contrast, r^2s for CAF were much lower,
431 ranging from 0.01 to 0.59. CAF also showed greater variability between sampling periods with a
432 lower r^2 in May. The weak relationship between CAF and the study compounds likely reflects
433 CAF's non-conservative behavior (lability) in the water column (Benotti and Brownawell, 2009).
434 SUC showed less variability between sampling periods and slightly higher r^2s for July. With
435 SUC's well documented resistance to degradation (Soh et al., 2011), the strong linear
436 relationships with these pharmaceuticals (i.e., conservative behavior) further indicates that

437 degradation or sorption processes are not a significant factor controlling their fate in the HRE
438 during our sampling period, but may vary over longer time scales. Consequently, the
439 concentrations of these compounds are controlled primarily by the volume of effluent and
440 dilution from tributaries and tidal processes. The strong spatial correlation also demonstrates the
441 potential of SUC as a tracer for recalcitrant contaminants in receiving waters emanating from
442 WWTPs.

443 Finally, the differential behavior of SUC and CAF was examined as a potential tool for
444 discriminating between WW sources in surface waters using the ratio of CAF to SUC (C/S)
445 concentrations. For example, a high C/S ratio would indicate that the relative amount of
446 untreated WW was elevated relative to treated WW, while a lower ratio would indicate a lower
447 proportion or absence of untreated WW. To test this concept, sampling was conducted in
448 Flushing Bay, a CSO impacted urbanized tidal embayment on the East River of NYH during wet
449 and dry weather conditions in July–August 2016. Water samples were collected from sites in
450 close proximity to CSOs during a release event triggered by heavy precipitation and 5 days later
451 under dry conditions. Samples collected during the CSO event all showed C/S ratios > 1 (1.1–
452 3.0), indicating a high proportion of untreated WW (Figure 5). The samples collected during dry
453 weather had C/S ratios between 0.12 and 0.2. The declines in CAF between wet and dry
454 conditions were as much as 2 orders of magnitude and clearly showed the impact of CSO
455 discharges. Ratios were also calculated for the river transect to examine how C/S ratios
456 responded in the river. Ratios along the transect ranged from a high of 0.31 (RK 41.8) to a low
457 of 0.0033 at RK 148.1, indicating an absence of untreated WW discharges during both river
458 sampling events (Figure S3), which is supported by the lack of significant precipitation during
459 both sampling events and no weather triggered CSO events in the HRE.

4. Conclusions

In this study we investigated the occurrence and fate of sixteen highly prescribed pharmaceuticals and two potential wastewater tracers in the Hudson River, a large urbanized estuary. Conducting sampling at high spatial resolution permitted evaluation of the variables controlling pharmaceutical behavior in the study area. The main conclusions were:

- The sustained discharge of WWTP effluents along with their location and magnitude were important factors for sites both in New York Harbor and the river transect, controlling both the presence and abundance of pharmaceuticals to the overall study area. Tributary inputs, river flows and tides played an important role by controlling dilution and, consequently, pharmaceutical concentrations. Because both sampling events in this study occurred under dry weather conditions, future work should include sampling under wet weather conditions to understand how the combination of CSO events and increased river flows affect the overall concentrations of pharmaceuticals.
- Sucralose was found to be ubiquitously present throughout the HRE and NYH, and exhibited a strong relationship with many of the study compounds. Since this demonstrates its potential as a tracer of wastewater derived pharmaceutical residues in the HRE, further research should examine whether this holds true for other large estuarine systems.
- The use of caffeine/sucralose (C/S) ratios accurately identified the presence of untreated sanitary water discharged during a wet weather CSO event, showing potential for detecting and locating unidentified sources of untreated sanitary wastewater released to receiving waters. The utilization of C/S ratios warrants further examination under a range of conditions, particularly in areas highly impacted by CSOs and other discharges of untreated sanitary wastewater.

- Further research is needed to reduce uncertainties and better understand the overall magnitude of risk resulting from the sustained discharge of pharmaceutical residues associated with WW discharges into effluent dominated estuaries.

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632 Figure Captions

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634 Figure 1 Map of the study area (sites identified by circles)

635 Figure 2 Frequency of occurrence (in percent) of pharmaceuticals along the river transect

636 Figure 3 Concentrations (ng/L) of frequently detected pharmaceuticals along the river transect

637 Figure 4 Caffeine and sucralose concentrations (ng/L) along the river transect

638 Figure 5 Caffeine-sucralose (C/S) ratios in Flushing Bay of NYH under wet and dry
639 conditions

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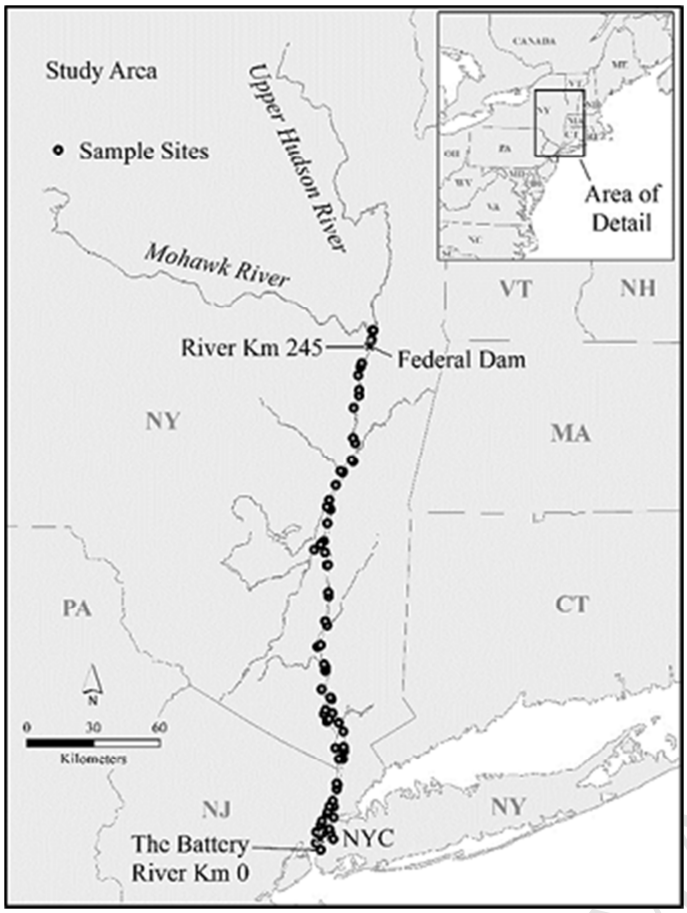
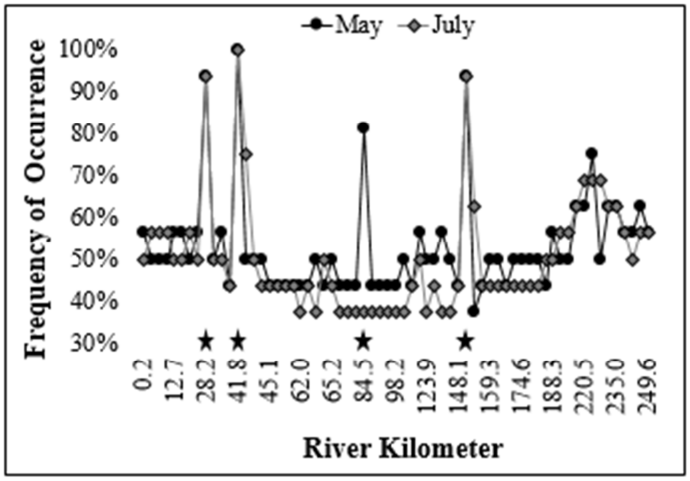
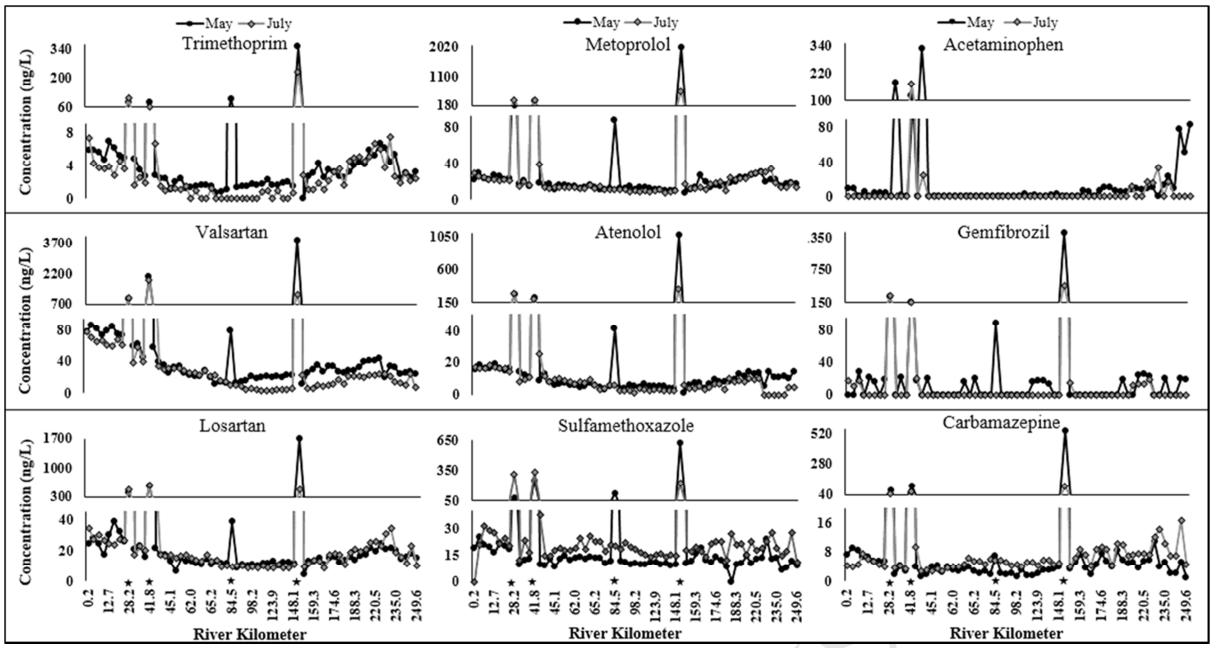
Table 1. Minimum (Min), median (Med) and maximum (Max) concentrations of study compounds (ng/L) along with their frequency of occurrence in percent (Freq).

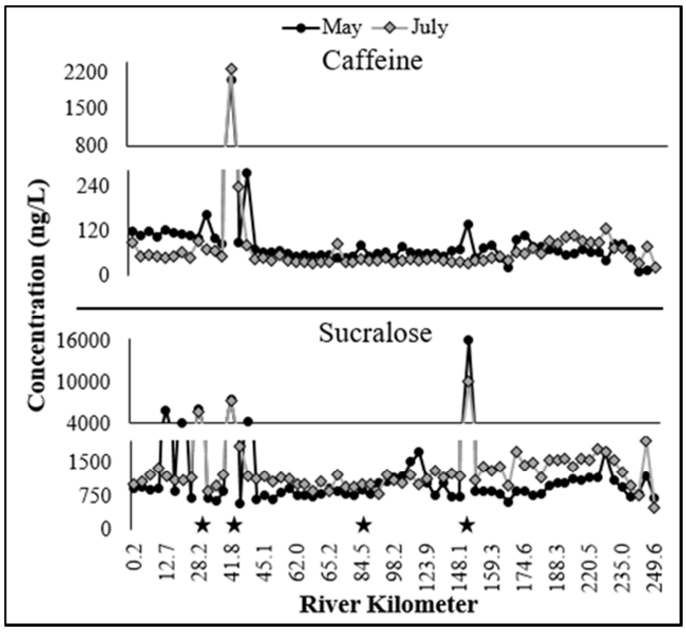
	May				July			
Compound	**Min.**	**Med.**	**Max.**	**Freq.**	**Min.**	**Med.**	**Max.**	**Freq.**
River Transect								
Acebutolol (ACB)	n.d.	8.2	22.0	6	n.d.	5.1	7.7	5
Acetaminophen (ACE)	n.d.	8.0	327.7	49	n.d.	17.5	170.6	11
Atenolol (ATE)	1.5	8.1	1074.3	100	n.d.	7.6	326.7	92
Caffeine (CAF)	23.5	70.3	2056.7	100	22.2	49.1	2265.1	100
Carbamazepine (CAR)	0.9	3.9	542.6	100	2.6	5.6	105.7	100
Diltiazem (DIL)	n.d.	0.7	73.5	20	n.d.	1.2	77.0	46
Furosemide (FUR)	n.d.	130.0	1234.8	8	n.d.	137.4	291.2	5
Gemfibrozil (GEM)	n.d.	19.9	1440.4	37	n.d.	17.4	457.4	18
Labetalol (LAB)	n.d.	122.7	304.8	6	n.d.	4.7	136.7	11
Losartan (LOS)	4.2	14.8	1699.8	100	8.3	16.9	584.6	100
Metoprolol (MET)	8.0	16.2	2020.6	100	7.7	14.1	612.2	100
Propranolol (PRO)	n.d.	8.9	134.1	8	n.d.	0.8	30.3	18
Ranitidine (RAN)	n.d.	30.1	1002.1	9	n.d.	29.1	202.0	5
Sucralose (SUC)	588.4	870.2	16203.	100	498.2	1181.2	10107.	100
Sulfamethoxazole (SUL)	n.d.	12.3	616.6	98	n.d.	19.1	336.8	98
Trimethoprim (TRI)	n.d.	2.7	350.0	98	n.d.	2.7	230.9	77
Valsartan (VAL)	11.4	28.1	3811.9	100	2.7	21.9	1852.2	100
Verapamil (VER)	n.d.	8.7	51.4	6	n.d.	0.8	18.8	22
New York Harbor								
Acebutolol (ACB)	n.d.	0.6	0.8	43	n.d.	n.d.	n.d.	0
Acetaminophen (ACE)	4.9	13.0	138.3	100	n.d.	92.3	161.7	43
Atenolol (ATE)	14.7	18.2	31.8	100	16.5	24.5	30.9	100
Caffeine (CAF)	111.9	141.7	589.5	100	78.0	142.6	520.2	100
Carbamazepine (CAR)	3.6	8.3	25.1	100	4.3	6.5	12.4	100
Diltiazem (DIL)	n.d.	n.d.	n.d.	0	2.1	2.4	5.6	100
Furosemide (FUR)	n.d.	8.8	8.8	14	n.d.	n.d.	n.d.	0
Gemfibrozil (GEM)	n.d.	26.9	43.1	86	n.d.	20.5	43.6	86
Labetalol (LAB)	n.d.	2.4	2.4	14	n.d.	2.2	4.1	57
Losartan (LOS)	23.2	33.0	48.6	100	34.2	48.2	65.9	100
Metoprolol (MET)	24.4	27.6	47.6	100	31.1	40.4	66.8	100
Propranolol (PRO)	n.d.	0.5	1.2	43	n.d.	0.4	0.6	71
Ranitidine (RAN)	n.d.	1.8	1.8	14	n.d.	n.d.	n.d.	0
Sucralose (SUC)	708.3	887.0	1251.9	100	1204.2	1386.0	1472.8	100
Sulfamethoxazole (SUL)	15.6	22.3	32.7	100	n.d.	50.0	69.0	29
Trimethoprim (TRI)	4.3	7.7	10.4	100	7.1	10.5	13.7	100
Valsartan (VAL)	60.2	77.9	117.4	100	82.4	94.9	110.7	100
Verapamil (VER)	n.d.	2.0	2.4	57	n.d.	0.5	0.6	71

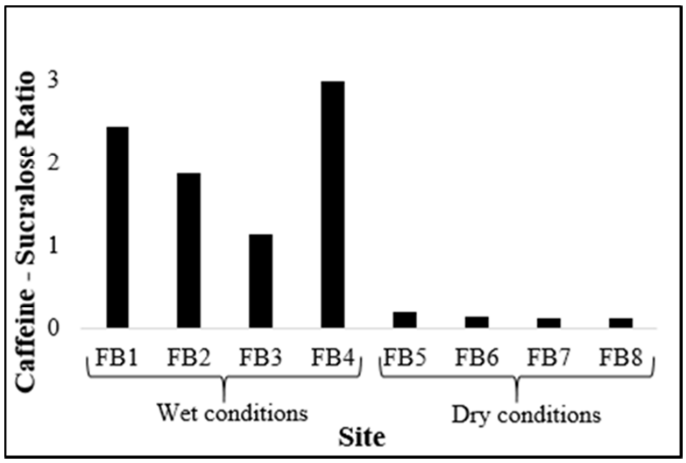
*NY Harbor sites are sites that are not located on the main Hudson River transect: East River (2), Harlem River (2), Newtown Creek (2) and Gowanus Canal











Highlights: Spatial Patterns of Pharmaceuticals and Wastewater Tracers in the Hudson River Estuary

- High resolution sampling shows the spatial distribution of pharmaceuticals.
- Tracers were successful in identifying and differentiating wastewater sources.
- Sucralose proved effective as a tracer for select pharmaceutical compounds.
- Wastewater discharges produce sustained, elevated levels of pharmaceuticals.