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Sources of pharmaceutical pollution in the New York City Watershed

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ABSTRACT

An investigation was carried out in the New York City Watershed for the presence of selected pharmaceuticals. In four seasonal sampling events between August 2003 and May 2004, surface water was collected from eight reservoir keypoints and effluent was collected from four wastewater treatment plants. We evaluated the following twelve compounds: amoxicillin, atenolol, caffeine, carbamazepine, cephalexin, estrone, 17 α -ethinylestradiol, 17 β -estradiol, ibuprofen, sulfamethoxazole, trimethoprim, and valproic acid. In the treated effluents, carbamazepine was detected most frequently (100%; concentration range: 22–551 ng/L), followed by atenolol (94%; ND — 14,200 ng/L), trimethoprim (83%; ND — 37,000 ng/L), ibuprofen (61%; ND — 14,600 ng/L), and caffeine (49%; ND — 37,200 ng/L), while estrone was detected once (56 ng/L). In the reservoir keypoint samples, only ibuprofen (2.5%; ND — 932 ng/L) and caffeine (2.9%; ND — 177 ng/L) were detected. The other analytes were not detected in any sample. It is expected that investigation of other wastewater treatment plants in the New York City Watershed would show that their effluents are also a potential source of pharmaceuticals, but that these pharmaceuticals are unlikely to be detected in the Watershed's surface waters.

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1. Introduction

Pharmaceuticals have been detected in wastewater treatment plant effluents, surface water, ground water, and drinking water. Most drug classes have been documented, including analgesics, antibiotics, antiepileptics, antihypertensives, anti-

septics, beta-blocker heart drugs, contraceptives, hormones, lipid-lowering drugs, psychotherapeutics, and X-ray contrast media (Halling-Sørensen et al., 1998). According to the National Association of Chain Drug Stores, Americans filled over 3.2 billion prescriptions in 2003, an increase of over 1 billion since 1995 (NACDS, 2005). U.S. spending for prescription drugs is

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Abbreviations: NYSDOH, New York State Department of Health; NYC, New York City; WWTP, wastewater treatment plant; HPLC, high performance liquid chromatography; MS, mass spectrometer; ESI, electrospray ionization

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projected to increase by 10.1% annually through 2011 (Heffler et al., 2005), a figure which does not include the much larger over-the-counter drug market. It is expected that as the population of the United States continues to age, pharmaceutical use will continue to grow. Clearly, with the aging of the U.S. population and rising pharmaceutical sales, increases in the potential amount of pharmaceuticals entering the waste stream are probable for the foreseeable future.

The potential for pharmaceuticals to enter the environment is not unique to New York; it has been studied in other waters of North America (Seiler et al., 1999; Kolpin et al., 2002; Stackelberg et al., 2004), South America (Stumpf et al., 1999), and Europe (Ternes, 1998; Buser et al., 1999; McArdell et al., 2003). However, the New York City Watershed is unique: it is the largest engineered surface water storage and supply source in the world (NYCDEP, 2006). It serves about 4.5 million m^3 of water daily to approximately 8 million residents of NYC, and 1 million residents in four other southern New York counties (NYCDEP, 2006). This represents almost half of New York State's population. In addition, there are over 100 wastewater treatment plants that discharge treated effluent into the watershed (NYCDEP, 2006), which could be a potential source of contamination to these important source waters. Therefore, we investigated the presence of the

selected pharmaceutical compounds in wastewater treatment plant effluents, surface water at reservoir keypoints, and water prior to chlorination and distribution in the NYC water supply.

2. Study background

2.1. Description of NYC Watershed

The NYC Watershed consists of three water supply systems: Croton, Delaware, and Catskill (Fig. 1). The watersheds of the three systems cover an area of almost 5200 km^2 . The reservoirs have a combined storage capacity of 2 billion m^3 . The Croton system has 3 controlled lakes and 12 reservoirs, with the largest being the New Croton Reservoir, with a capacity of 72 million m^3 . The Croton system normally supplies 10% of the NYC's drinking water. The Catskill system includes two reservoirs (Schoharie and Ashokan) and supplies up to 40% of the City's daily needs. The Delaware system consists of four reservoirs: Cannonsville, Pepacton, Neversink, and Rondout. These provide 50% of the NYC's daily water needs. Water from both the Catskill and Delaware systems usually passes through the Kensico Reservoir, which has a

Fig. 1 – Map of WWTP and reservoir sampling locations. August 2003–May 2004.

capacity of 1.16 billion m³ (<http://www.ci.nyc.ny.us/html/dep/watershed/html/reservoirs.html>).

2.2. Sampling locations

There were twelve primary sampling locations for the study (Fig. 1). On each side of the Hudson River (East side of Hudson, EOH; West side of Hudson, WOH), four surface water locations and two WWTPs were sampled. We collected samples of water exiting the Cannonsville, Neversink, Pepacton, Rondout, New Croton, and Kensico Reservoirs, and water entering the Kensico Reservoir via the Delaware and Catskill Aqueducts. Sampling at the DEL 18 location was prior to chlorination and entrance into the City's distribution system. No samples were collected after chlorination or from NYC's water distribution system.

The four WWTPs in the study serve varied populations and utilize varied treatment techniques, as shown in Table 1. The Carmel and Yorktown Heights plants are located in the Croton Watershed, and the Margaretville and Walton plants are located in the Delaware Watershed. These plants are small by most standards, but typical of many of the WWTPs discharging into the watershed, with daily flows between 1500 and 5700 m³/day and service area populations ranging from 800 to 10,000. Carmel uses activated sludge with post-aeration to treat waste from a suburban mix of residences and businesses, including a pharmaceutical lab. Yorktown Heights, the oldest of the four plants, uses a trickling filter and coagulation, and has no significant nonresidential sources. Margaretville is the newest and smallest of the four plants. It uses rotating biological contactors, microfiltration, and UV, and its service area includes waste from a hospital. Walton uses aeration and continuous backwash-upflow dual-sand filtration, and its service area includes a nursing home and a health care facility. None of the plants uses a combined sewer collection system.

2.3. Sample collection

During each of the four calendar seasons (beginning in August 2003 and ending in May 2004), 4-L grab samples were collected for seven consecutive days at each of 12 locations. Samples were collected in silanized 4-L amber glass bottles that were rinsed three times with the sample water prior to collection. On the sampling day, the surface water samples were collected before the WWTP effluent samples to minimize the potential for cross-contamination. An additional sample was collected on the first, third, fifth, and seventh days of each sampling event for quality control purposes; this duplicate was collected at least once for each location over the course of the study.

2.4. Selection of analytes

Analyte selection was based on a qualitative evaluation of a number of factors that would suggest the presence of these compounds in the WWTP effluent and/or the environment. Factors considered were the following: number of prescriptions written per year, amount of the drug in a daily dose, information on drug absorption and metabolism in humans, environmental degradation, and previous research (Kolpin et al., 2002). Table 2 lists 2004 prescription data for the analytes. Caffeine was also included because it is an established marker for human waste. The laboratory method was developed specifically for the eleven selected compounds.

3. Analytical methods

3.1. Chemicals and reagents

Amoxicillin, 17 α -ethinylestradiol, 17 β -estradiol, atenolol, caffeine, carbamazepine, cefadroxil, cephalixin, estrone, ibuprofen,

Table 1 – Characteristics of WWTPs and the populations served^a

	Carmel SD #2	Yorktown Heights	Margaretville	Walton
Year built	1965	1961	1998	1978
Year updated	1999	1973	–	2002
Collection system	Separate	Separate	Separate	Separate
Biotreatments used	Conventional activated sludge; step aeration activated sludge; SC	SC ^b ; trickling filter	Rotating biological contactor; SC	Extended aeration
Filters	FSR ^c	Intermittent sand filters; FSR	Microfiltration-membrane; FSR	Microfiltration-CBUDS ^d
Additional treatment	PA ^e	Chemical coagulation and settling; PA; PR ^f	Breakpoint chlorination; chemical coagulation and settling; NR ^g ; PR	Nutrient feed-ammonia; PR
Design flow (MGD)	0.35	1.5	0.4	1.17
Population served (approx.)	3000	10,000	800	3500
Population type	Suburban	Suburban	Rural	Rural
Significant sources	Pharmaceutical lab	None known	Hospital	Nursing home, health care facilities

^a From NYSDEC, 2004.

^b SC: secondary clarifier.

^c FSR: rapid sand high rate filters.

^d CBUDS: continuous backwash-upflow, dual-sand filtration.

^e PA: post-aeration.

^f PR: phosphorus removal.

^g NR: nitrogen removal.

Table 2 – Total prescription (Rx) count^a of study analytes in the United States, 2004

Rank	Product	Type	Total Rx count (in millions)	Total Rx count % change prior year	Avg dosage ^b (mg/day)	Metric tons purchased ^c (estimated)
1	Atenolol	Generic/beta-blocker	44.2	2.9	50	66
2	Amoxicillin	Generic/antibiotic	41.4	10.5	1000	414
10	Cephalexin	Generic/antibiotic	23.7	–0.2	1000	237
14	Ibuprofen	Generic/pain relief	25.2	0.7	1600	565 ^f
26 ^d	Sulfamethoxazole	Generic/antibiotic	13.6	3.3	800	109
26 ^d	Trimethoprim	Generic/antibiotic	13.6	3.3	160	22
86, 134	Sodium valproate ^e	Brand/antiepileptic	8.2	–4.0	1000	246
125	Carbamazepine	Generic/anticonvulsant	2.7	–4.1	400	32.4
Various	17 α -Ethinylestradiol	Generic/hormone	41.6 ^g	Various	Various	0.04
Various	17 β -Estradiol	Generic/hormone	10.0 ^h	Various	Various	0.01
Unknown	Estrone	Generic/hormone	Unknown	Unknown	Unknown	Unknown

^aModified from NDCHealth Corp. (2005). Information based on NDCHealth proprietary methodologies. Reflects prescription data for retail, mail order, and institutional pharmacy channels. Available at: www.drugtopics.com and http://www.ndchealth.com/press_center/uspharmaindustrydata/2004top10productsbytotalprescription.htm.

^{b,c}Average doses and tons purchased were calculated using information from www.rxlist.com and www.pdrhealth.com assuming one antibiotic prescription covers a 10-day dosing period; one ibuprofen prescription covers 14 days; 17 α -ethinylestradiol and 17 β -estradiol cover 28 days, other drugs assume one prescription covers a 30-day dosing period.

^dSulfamethoxazole and trimethoprim are generally prescribed in combination. The count given is for the combined prescriptions.

^ePrescriptions listed are combined for sodium valproate (Depakote, 5.0 million, –14.5%; Depakote ER, 3.2 million, 15.3%).

^fIbuprofen metric tons purchased does not include over-the-counter sales.

^g17 α -Ethinylestradiol prescriptions are combined for 13 generic labels. Metric tons purchased considered 0.035 mg as DDD.

^h17 β -Estradiol prescriptions are combined for Vivelle-DOT, Climara, and generic estradiol oral. Metric tons purchased considered 0.05 mg as DDD. Caffeine was not included, as it is not a prescribed drug.

sulfamethoxazole, trimethoprim, valproic acid, deuterium dioxide, 4-methylmorpholine, and D₂SO₄ were purchased from Sigma Chemical (St. Louis, MO, USA). Caffeine (trimethyl-¹³C₃), 17 β -estradiol (2,4,16,16'-d₄), isovanillic acid (ring-¹³C₆), phenacetin (ethoxy-1-¹³C), sulfamethazine (phenyl-¹³C₆), valproic acid (1,2,3,3'-¹³C₄), and vanillic acid (carboxyl-¹³C) were purchased from Cambridge Isotope Laboratories (Andover, MA, USA). Practolol was purchased from Tocris (Ellisville, MO, USA) and d₁₀-carbamazepine from C/D/N Isotopes Inc. (Quebec, Canada). Dr. Chuck Litterst from the Division of AIDS (National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA) donated tetroxoprim. The d₄-ibuprofen was synthesized using D₂SO₄ and ibuprofen. The following chemicals and materials were also used: acetone, acetonitrile, ethyl acetate, and methanol, all HPLC grade (Burdick & Jackson from VWR Scientific, West Chester, PA, USA); 88% formic acid, and 100–200 μ m silica gel (Mallinckrodt Baker Inc., Paris, KY, USA); 37–53 μ m silica gel and QM-A glass microfiber filter paper (Whatman, Maidstone, UK); ammonium formate (Anachemia Chemicals, Rouses Point, NY, USA); dimethyldichlorosilane (Supelco, Bellefonte, PA, USA); Empore™ SDB-XC 47-mm poly(styrenedivinylbenzene) extraction discs, and Empore™ Filter Aid 400 (3M, St. Paul, MN, USA); Carboxprep 200 extraction cartridges, 200 m²/g carbon surface area, and 500 mg bed weight (Restek, Bellefonte, PA, USA).

3.2. Solid-phase extraction

3.2.1. Acid/neutral analytes (17 α -ethinylestradiol, 17 β -estradiol, estrone, ibuprofen, and valproic acid)

Water samples (2 L) were adjusted to pH 2.5 using 3.4 mL 88% formic acid and spiked with 20 μ L of a mixture of internal standards (d₄-ibuprofen, 17 β -estradiol [2,4,16,16'-d₄], and val-

proic acid [1,2,3,3'-¹³C₄]) in methanol, with each standard at 10 ng/ μ L. Individual samples were extracted using a Teflon housing containing in sequence, from top-to-bottom: glass microfiber filter paper, a 1-cm layer of Filter Aid 400, glass microfiber filter paper, an SDB-XC extraction disk, and a fine mesh nylon screen followed by a wide mesh nylon screen. The assembly was then placed on a Speedisk Expanded Extraction Station (Mallinckrodt Baker, Paris, KY, US). The disk was conditioned with 15 mL of acetone, 15 mL of methanol and 20 mL of pH 2.5 distilled deionized (DDI) water. The sample was passed through the disk under vacuum at a flow rate of <100 mL/min.

After the disk had been dried for ~3 min on high vacuum, the Filter Aid 400 and filter paper were removed, and the disk was then dried for an additional 5 min. Next, the disk was transferred to a Baker SPE 24G Column Processor (Mallinckrodt Baker Inc., Paris, KY, USA) and 3 aliquots of 4 mL of pH 8.5 methanol (4-methylmorpholine/methanol, 1:1000, v/v) and 3 aliquots of 4 mL of acetone were used to elute the target compounds from the disk into a scintillation vial. A Turbopap II (Zymark, Hopkinton, MA, USA), was used for concentrating samples to 150 μ L. The water bath temperature was 40 °C, and the nitrogen flow rate was 26 psi. After the addition of 50 μ L of DDI water the sample was concentrated to a final volume of 100 μ L.

A silica gel microcolumn was used for sample cleanup. The silica gel was made with equal parts of 37–53 μ m and 100–200 μ m mesh silica gel deactivated with 3% DDI water. About 0.4 g of this silica gel mixture was sandwiched between Pyrex glass wool in an Eppendorf autopipet tip (Eppendorf, Hamburg, Germany) and the column was conditioned with 3 aliquots of 2 mL of ethyl acetate/toluene (50:50, v/v). The sample extract was then loaded onto the silica gel, and the

target compounds were eluted with 5 aliquots of 2 mL of toluene/ethyl acetate (85:15, v/v), by N₂ pressure. In the next step, the cleaned up extract was concentrated to 300 µL and then 100 µL DDI water was added. When a final volume of 90 µL was reached, the sample was transferred into a microvial insert for analysis and spiked with 10 µL of a 10-ng/µL methanol solution of the recovery standard, isovanillic acid (ring-¹³C₆).

3.2.2. Basic/amphoteric analytes (amoxicillin, atenolol, caffeine, carbamazepine, cephalexin, sulfamethoxazole, and trimethoprim) For these analytes, all glassware had to be silanized. The manufacturer silanized the inserts and microvials, and all other glassware was silanized in the laboratory. The silanizing was performed by rinsing with a solution of 10% dimethyldichlorosilane in toluene, followed by two rinses with toluene and then two rinses with methanol. Since it was impractical to segregate glassware, the silanized glassware was also used in the analysis of the acid/neutral compounds.

Carboprep cartridges were placed on a Baker SPE 24G Column Processor and conditioned with 5 mL of pH 2.5 DDI water, followed by 5 mL of DDI water. Samples (1 L) were spiked with 25 µL of an internal standard mixture in methanol, which contained cefadroxil, ampicillin, caffeine (trimethyl-¹³C₃), practolol, sulfamethazine (phenyl-¹³C₆), and tetroxoprim at concentrations varying from 1–400 ng/µL. The samples were then loaded onto the cartridges through Teflon tubing, and the vacuum was adjusted to produce a steady flow rate of about 15 mL/min. After loading, the cartridges were dried under high vacuum for 10 min. The target compounds were eluted from the cartridges, with 2 aliquots of 5 mL of pH 2.9 methanol (90 µL formic acid/100 mL methanol), 2 aliquots of 5 mL of methylene chloride/methanol (80:20, v/v), and 6 aliquots of 5 mL of acetone.

Using the Turbovap II, samples were concentrated to 200 µL and then 500 µL of DDI water was added. When a final concentration of 475 µL was reached, samples were spiked with 25 µL of a 10-ng/µL methanol solution of the recovery standard, phenacetin (ethoxy-1-¹³C), and transferred into a microvial for analysis.

3.3. Chromatographic conditions

Chromatography was performed using an Agilent 1100 series HPLC instrument (Agilent Technologies, Palo Alto, CA, USA). The injection volumes were 10 µL for the acidic analytes and 15 µL for the basic analytes. The acidic analytes were separated on a LUNA C18 LC column (150×2.0 mm I.D., particle size 3 µm; Phenomex, Torrance, CA, USA) at a 0.2-mL/min flow rate with a mobile phase of acetonitrile and a basic buffer of 10 mM N-methylmorpholine (pH 9.4). The gradient was from 15% organic phase to 95% organic phase in 19 min. A post-run time of 15 min was used in order to insure system equilibration. The basic analytes were separated on an Allure Pentafluoropropyl LC column (150×3.2 mm I.D., particle size 5 µm; Restek, Bellefonte, PA, USA) at a 0.5-mL/min flow rate with a mobile phase of acetonitrile and an acidic buffer of 8.7 mM ammonium formate and 10 mM formic acid (pH 3.5). The gradient was from 15% organic phase to 95% organic phase in 14 min. A post-run time of 15 min was used. The basic/

amphoteric fraction was also used for the analysis of carbamazepine, but chromatography was carried out with the acid method. It was found that carbamazepine was extracted with the basic/amphoteric analytes. However the acid/neutral protocol was required for LC/MS analysis.

3.4. Mass spectrometry

A Finnegan LCQ Classic quadrupole ion trap MS (Thermo Finnigan, San Jose, CA, USA), was used as a detector. The ionization was performed by ESI, producing negative molecular ions from the acidic analytes and positive molecular ions from the basic analytes. A single ion monitoring method was used for all of the analytes except for amoxicillin and cephalexin, for which an MS/MS method was used. The Xcalibur software package (Thermo Finnigan, San Jose, CA, USA), was used to control both the HPLC and MS. The ESI source parameter settings were: spray voltage: 4.5 kV, nitrogen sheath gas flow rate: 67 arbitrary units (au), capillary voltage –33 V and capillary temperature: 200 °C.

3.5. Data processing

Calibration curves were constructed to determine the response factor of each analyte relative to the response factor of its internal standard. Six calibration solutions were used with analyte concentrations ranging from the limit of detection (LOD) value to 10× LOD and a fixed internal standard concentration that varied from 4–6× LOD, depending on the analyte. Each solution was analyzed in triplicate and the average values were plotted as a regression line with analyte areas/internal standard areas on the y-axis and analyte concentrations/internal standard concentrations on the x-axis. The relative response factor (RRF) was determined from the slope of the line.

The concentrations of individual analytes were determined by the following equation:

$$C_A = \frac{\text{Analyte area}}{\text{Int. Std. area}} \times \frac{C_{\text{int}}}{\text{RRF}}$$

where C_A=analyte concentration (ng/L) and C_{int}=internal standard concentration (ng/L).

3.6. Quality Assurance/Quality Control (QA/QC)

The sample set for QA/QC consisted of field blanks, field sample duplicates, laboratory blanks (DDI and river water collected from the East Branch of the Delaware River, at a location upstream of the Margaretville WWTP), and laboratory spikes (also DDI and river). There were 56 field blanks (one per sampling day), consisting of 4-L volumes of DDI water taken to the point of sampling and transferred to another 4-L sampling container, then transported back to the laboratory with the field samples. Forty-two laboratory blanks were analyzed with the field samples, some of which were prepared from DDI water and others from river water. Only one sample from this total group of 98 blank samples showed evidence of contamination with a study analyte (trimethoprim at the method detection limit (MDL) of 4 ng/L). Prior to starting the project the MDL values for the selected pharmaceuticals were determined

using a statistical approach established by the USEPA (US Code of Federal Regulations, 2007). The procedure involved spiking seven replicate blank water samples with each pharmaceutical at a concentration resulting in an instrumental signal-to-noise (S/N) between 2.5 and 5. A S/N value of 4 was selected for this study. The MDL was then calculated with 99% confidence that the result was greater than zero by multiplying the standard deviation by 3.14, the Student's *t* value for 6 degrees of freedom at $p < 0.01$. The values (ng/L) found were as follows: valproic acid, 199; ibuprofen, 20; estrone, 30; 17β -estradiol, 40; 17α -ethinylestradiol, 39; amoxicillin, 367; caffeine, 80; cephalixin, 502; atenolol, 9; sulfamethoxazole, 111; and trimethoprim, 4. Carbamazepine was not included in the MDL study, but its MDL was estimated to be 20 ng/L based on a signal-to-noise ratio of 3:1.

In many of the spiked samples, we failed to detect either amoxicillin or cephalixin. In those samples where the penicillins were detected, there was an extremely wide range in the recovery data. Four other basic analytes (atenolol, caffeine, sulfamethoxazole, and trimethoprim) were detected in the majority of the spiked samples. However, in one sample there was no signal for atenolol and there were no signals for sulfamethoxazole in four samples. With the exception of three samples the recovery values for caffeine were close to 100% (average $\pm$ S.D., 118 ± 35). The recovery values for atenolol, sulfamethoxazole, and trimethoprim were less accurate and precise (200 ± 98 , 103 ± 102 and 164 ± 42 respectively).

Three internal standards were used in the analysis of the acid/neutral analytes, the ^{13}C -labeled analog of valproic acid and the deuterated analogs of ibuprofen and β -estradiol. In contrast to the basic/amphoteric compounds, where we had to rely on surrogates as internal standards for several compounds, we had labeled analogs for all the acid/neutral analytes, although one labeled analog had to serve as an internal standard for the three estrogens. In general, the recoveries were considerably closer to 100% than the recoveries found for the basic/amphoteric compounds (132 ± 81 for valproic acid; 139 ± 104 for ibuprofen; 70 ± 37 for estrone; 90 ± 43 for 17β -estradiol; and 71 ± 49 for 17α -ethinylestradiol).

Although carbamazepine was not designated as an analyte in the original sampling and analysis protocol, it was later included as an analyte since it was detected frequently in the pilot sampling. During the summer and fall sampling events, only the WWTP effluents were analyzed for carbamazepine. We were unable to prepare spiked QA/QC samples for these two sampling events, as there was no internal standard available. Therefore, carbamazepine results from those field samples can only be considered as estimates. A deuterium-labeled carbamazepine standard was acquired prior to the winter and spring sampling events; results from spiked QA/QC samples showed recoveries between 82% and 159%.

The recovery standards phenacetin (ethoxy- $1\text{-}^{13}\text{C}$) and isovanillic acid (ring- $^{13}\text{C}_6$) were added, respectively, to the basic/amphoteric and acid/neutral extracts just prior to analysis on the LC/MS system. It was intended that these recovery standards should be used to obtain the absolute recoveries of the internal standards added to the water samples prior to extraction. The absolute recoveries obtained in this manner proved to be erratic and unreliable, probably as a consequence of the differences between the structures of the

recovery standards and the internal standards. As an alternative approach to obtaining data on the efficiency of the sample preparation procedure, QA/QC samples were prepared with the analytes added to the water samples prior to extraction and the internal standards were then added to the extracts prior to injection into the LC/MS system. With the exception of the penicillins, the absolute recoveries for the basic/amphoteric compounds were generally in the range of 30% to 100%, although there were some recovery values outside this range.

Precision data for the field samples were obtained by collecting duplicate field samples during each sampling event. In total, 32 duplicates were collected (4 EOH duplicates and 4 WOH duplicates for each of the four sampling events). No signals for any of the analytes were found in 14 of the 16 duplicates collected at the reservoir keypoints. In the two other surface water duplicates, which were collected from WOH sampling points during the spring sampling, ibuprofen was detected with signal areas exceeding $3 \times \text{S/N}$, but at a concentration below the MDL. All the duplicates collected from the WWTPs (16 paired samples) had paired positive signals above the MDL for at least one of the five analytes detected in the study (atenolol, caffeine, carbamazepine, ibuprofen, and trimethoprim). In one of these sample pairs caffeine was detected in only one replicate while atenolol, carbamazepine, and trimethoprim were found in both replicates. In the case of ibuprofen, there were extremely large differences in two duplicate sets collected in the summer from the Yorktown WWTP effluent (100 and 22.6 ng/L from one collection and 154 and 17.7 ng/L from another collection). At this stage of the project, we did not have a complete understanding of the absolute recovery problems for the acid/neutral compounds. Consequently, the spike levels for the acid/neutral internal standards were too low, and we had to use external standards to determine the ibuprofen concentrations in the four samples. For the remaining samples containing ibuprofen (10 sample pairs), and for all the positive samples for the other analytes (15, 9, 15, and 14 sample pairs for atenolol, caffeine, carbamazepine, and trimethoprim, respectively), the data from the first duplicate were plotted against data from the second duplicate. The slopes of the regression lines were very close to the theoretical value of 1.00 (0.88–1.06) and the correlation coefficients were in the range of 0.90 to 0.98. When the results were expressed as relative percent differences (RPDs), the average RPDs were 33, 29, 35, 33, and 18% for ibuprofen, caffeine, atenolol, trimethoprim, and carbamazepine, respectively.

4. Results

Three hundred sixty-eight samples were collected over the four seasonal sampling events. At least two duplicates were collected at every location during the course of the study. The following are the sample sizes for the summer, fall, winter, and spring sampling periods: Carmel, 7, 8, 7, 7; Margaretville and Walton, 8 each season; Yorktown: 11, 8, 8, 7. Six of the twelve analytes were not detected (amoxicillin, 367 ng/L; cephalixin, 502 ng/L; 17β -estradiol, 40 ng/L; 17α -ethinylestradiol, 39 ng/L; sulfamethoxazole, 111 ng/L; and valproic acid, 199 ng/L).

Estrone, with a detection limit of 30 ng/L, was only detected once. However, every sample collected from the WWTP contained some of the targeted analytes. The same pharmaceuticals were not found in surface water samples, with a few exceptions in samples from EOH locations, where ibuprofen and caffeine were detected infrequently at three sampling points. Because there were few detections of the targeted samples from surface water locations, most of the data analysis in this report is for samples collected from the WWTPs.

Statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, North Carolina). Kruskal–Wallis (a non-parametric one-way analysis of rank scores) was used to determine if differences existed between groups. If a significant difference was found (indicated by *p*-value less than 0.05), the data was log transformed and analyzed using Tukey's studentized range test (though in some cases, Tukey–Kramer was used if sample sizes differed). Non-detects were assigned the value of one-half the MDL for use in these calculations.

4.1. Wastewater treatment plant results

A summary of the data for the five pharmaceuticals (atenolol, caffeine, carbamazepine, ibuprofen, and trimethoprim) that were found in samples of the WWTP effluent is provided in Fig. 2. All effluent samples contained at least two of these five

analytes. Most notably, caffeine was found at a concentration an order of magnitude higher in the Yorktown WWTP effluent compared to samples from the other three WWTP. Carbamazepine concentrations were very similar between Carmel, Margaretville, and Walton, and these three sites all had significantly higher concentrations than at Yorktown. The other analytes showed substantial variation and differences in mean concentrations detected in the effluent from each of the plants.

Atenolol was detected in all samples from Yorktown and Margaretville, and 28 of 29 samples from Carmel. Concentrations were generally highest at Yorktown (median: 1415 ng/L), while the maximum concentration was detected at Carmel (14,200 ng/L). Walton had significantly lower concentrations than the other sites. The mean concentration of caffeine was higher than any other analyte, though this was mainly driven by Yorktown, where it was detected in every sample, and at concentrations significantly higher than the other sites.

As with some of the other analytes, Yorktown had significantly higher concentrations of ibuprofen than the other three locations, and it was present in every sample (though below the detection limit in one sample). Trimethoprim was detected at every WWTP and with relatively high frequencies (between 70% and 100%), though concentrations at Walton were significantly lower than the other sites. At Carmel, we found a very high concentration in one sample of

Fig. 2 – Concentrations (ng/L) of target analytes in wastewater treatment plant effluents. Note: Dashed line indicates the analyte detection limit. The analytes shown are ibuprofen, caffeine, atenolol, trimethoprim, and carbamazepine. WWTPs are Yorktown (*n*=34), Carmel (*n*=29), Walton (*n*=32), and Margaretville (*n*=32), with detection frequencies shown on the figure in parentheses. Non-detects were assigned a value of 1/2 the detection limit for that analyte. Q1: 1st quartile; min: minimum; max: maximum; Q3: 3rd quartile.

37,000 ng/L, though the second highest concentration there was 8090 ng/L.

4.2. Results by day

Although the data are limited (each day of the week average is in most cases comprised of just four samples), concentrations across the seven-day week were generally consistent. Atenolol, caffeine, carbamazepine, and ibuprofen concentrations were consistent at the four treatment plants for the week, as was ibuprofen at all locations except Yorktown (which showed a Saturday decline). Trimethoprim concentrations were more varied, with concentrations at Carmel peaking on Saturdays, but over two orders of magnitude lower on Wednesdays (see Fig. 3).

4.3. Results by season

Atenolol concentrations peaked in winter at all four of the WWTPs and with the exception of samples from the summer at Walton, it was found in every sample. At Carmel and Walton, atenolol was higher in the winter than the other seasons ($p < 0.05$). At Yorktown and Margaretville, atenolol was detected in every sample, although at each site, spring concentrations were significantly lower than the other seasons.

In the summer, Yorktown had the highest median caffeine concentration (29,600 ng/L), which was more than twice that of the winter median, but there were no significant seasonal differences. Seasonal medians at the other three WWTPs ranged from below the detection limit (< 80 ng/L) up to the

summer median of 250 ng/L seen at Margaretville (where it was detected in all eight summer samples). Caffeine was not detected at Carmel, Margaretville, or Walton during the spring sampling period, nor was it detected at Carmel during the summer (see Fig. 4a). The summer sampling at Walton had just one caffeine detection, though it was found in 6 of 8 samples from the fall season.

Generally, the seasonal medians for carbamazepine were similar, especially compared to the wide variations seen with the other analytes (see Fig. 4b). All plants had their highest medians in the winter and lower medians in the summer and fall. (Note that an internal standard was not available for the summer and fall sample analysis.) Winter concentrations at Margaretville were higher than the other seasons, while at Carmel, they were lowest in the fall ($p < 0.05$ for both).

Much like caffeine, seasonal ibuprofen concentrations were generally higher at Yorktown than at the other three WWTPs. It was present in all samples from Yorktown, though it was slightly below the detection limit in one sample. The spring median concentration (5340 ng/L) was over two orders of magnitude higher than the summer median (41 ng/L). At Margaretville, ibuprofen was detected in all samples from the summer and spring, though the detected concentrations showed a much wider range in the summer (37–422 ng/L) than in the spring (35–76 ng/L). At Carmel, ibuprofen was not found above the detection limit (40 ng/L) until the spring sampling, though it was present in one summer sample.

Trimethoprim concentrations at Yorktown were significantly lower in the spring, while at Margaretville, concentrations in the fall were found to be significantly lower than summer and winter, but not spring. Winter and spring

Fig. 3 – Mean daily concentrations (ng/L) of trimethoprim in wastewater treatment plant effluents. Note: Detection limit for trimethoprim was 4 ng/L. Each daily point represents the mean of 4–6 samples.

Fig. 4— a. Seasonal caffeine concentrations (ng/L) in wastewater treatment plant effluent. Detection limit for caffeine was 80 ng/L. b. Seasonal carbamazepine concentrations (ng/L) in wastewater treatment plant effluent. Detection limit for carbamazepine was 20 ng/L. Su: summer; F: fall; W: winter; Sp: spring. Sample numbers in parentheses. Q1: 1st quartile; min: minimum; max: maximum; Q3: 3rd quartile.

samples from Carmel had the highest median trimethoprim concentrations of any location (6490 ng/L and 566 ng/L, respectively), though it was not detected there in the fall.

This contrasts with Walton, which had its highest seasonal median in the fall (43 ng/L), but no detectable concentrations of trimethoprim in the winter samples.

4.4. Results from reservoir samples

There were sporadic detections of two analytes in the reservoirs. Caffeine was detected in 7 of the 240 samples collected from the reservoirs, while ibuprofen was detected in 6 samples. Five of the caffeine detections (88–122 ng/L) and two of the ibuprofen detections (39 and 126 ng/L) were from the CROGH location. CATALUM had the remaining two caffeine detections (177 ng/L and 103 ng/L), which occurred in the summer and fall.

In addition, CATALUM and DEL18 each had two detections of ibuprofen. While CATALUM's detections were around the 20-ng/L detection limit (20 ng/L and 33 ng/L), DEL18 had detections on consecutive days of 932 ng/L and 372 ng/L. The former value is larger than that seen at three of the four WWTPs.

5. Discussion

In most studies where pharmaceuticals have been analyzed by LC/MS in either wastewater samples or river/lake water samples, the analyses were carried out in the MS/MS mode using triple quadrupole mass spectrometers (also referred to as tandem mass spectrometers) (Calamari et al., 2003; Castiglioni et al., 2006; Vanderford et al., 2003). In general, tandem MS/MS analysis of the daughter ions formed from fragmentation of molecular ions provides for both enhanced selectivity and an increased S/N compared to analysis by selected ion monitoring (SIM) of molecular ions. However, with the ion trap MS used in our study, we found that MS/MS analysis was less sensitive than SIM analysis. Therefore, with the exception of amoxicillin and cephalexin, all the pharmaceuticals were analyzed by SIM. This could account for the high detection limits of some of the pharmaceuticals found in our study relative to detection limits found in studies where samples were analyzed by MS/MS using triple quadrupole mass spectrometers (e.g. Vanderford et al., 2003).

The absolute recovery values for the acid/neutral compounds were in the range of 4.5% to 34%, which was considerably lower than the absolute recovery values obtained for the basic/amphoteric compounds. The differences in recovery values between the two groups of compounds can be explained by differences in the complexity of the sample preparation procedures used for each group of compounds. The basic/amphoteric compounds were extracted from water using a graphitized carbon cartridge and the concentrated extracts were then analyzed by LC/MS. The acid/neutral compounds were extracted with a disk containing styrene-divinyl benzene as an adsorbent, and the extracts were then solvent-exchanged for cleanup on a silica gel microcolumn prior to analysis by LC/MS. The cleanup step was required for the removal of background interference from WWTP effluent samples and from certain keypoint samples. However, the silica gel cleanup step resulted in reduced absolute recoveries. It should be understood that with the internal-standard-correction procedure we use to determine concentration levels, accurate results can be obtained when absolute recoveries are low.

While the recovery values for caffeine were very good, recoveries for atenolol, sulfamethoxazole, and trimethoprim

were less accurate and precise. This can be explained by the structures of the internal standards. The caffeine internal standard was a ^{13}C -labeled analog of caffeine and therefore this internal standard had the same chemical and physical properties as “native” caffeine prepared from the most abundant natural isotope of carbon, ^{12}C . Since labeled analogs were not available for atenolol, sulfamethoxazole, and trimethoprim, we selected surrogates as internal standards for these compounds. While these surrogates had structures closely related to the structures of the three analytes, there could have been differences in recovery and/or response in the LC/MS instrument between an analyte and its surrogate.

The penicillins also proved to be difficult to extract from water samples. Since it is recognized that the β -lactam ring in penicillins is very unstable in the presence of certain solvents, such as methanol, these compounds are generally not included in monitoring surveys of pharmaceuticals in environmental waters. In the case of amoxicillin and cephalexin, sample matrix interfered with the protonated molecular ions, which required the use of MS/MS for the analysis of these compounds, resulting in very high MDL values.

For the estrogens, the combination of our high detection limits (30–40 ng/L), short half lives (2–3 h; Yu-Chen Lin and Reinhard, 2005), and predicted removal rates during wastewater treatment processes (74–84%, Johnson et al., 2000), likely explains why we only detected E1 in one effluent sample, and E2 and EE2 not at all. Heberer (2002a) suggested WWTP effluent concentrations of EE2 should generally be less than 3 ng/L, in which case we would not have detected them. Kolodziej et al. (2003) detected estrone at a maximum concentration of 12.3 ng/L in a study of eleven WWTPs with various treatment techniques and an engineered treatment wetland, while Joss et al. (2004) found a maximum E1, E2, and EE2 concentrations of 8.6, 0.5, and 0.5 ng/L among three activated sludge WWTPs. The highest mean concentrations of E1, E2, and EE2 found by Cargouet et al. (2004) in the effluent of four French WWTPs were 7.2, 8.6, and 4.5 ng/L, respectively. Such concentrations are well below those that could have been detected using our method.

5.1. WWTP samples

A study of European WWTPs showed poor removal (<10%) of atenolol, carbamazepine, and trimethoprim using activated sludge (Paxéus, 2004). Italian WWTPs were not found to remove carbamazepine, while for atenolol, removal was higher in the summer than in the winter (55% vs. 10%) (Castiglioni et al., 2006). Another study found measurable concentrations (ranging from 3–241 ng/L) in two Italian rivers (Calamari et al., 2003). Other beta-blockers, like bisoprolol, metoprolol, nadolol, and propranolol have been detected in effluents and surface waters (Ternes et al., 1998; Huggett et al., 2003; Fonon and Sedlak, 2005).

Carbamazepine was identified in every WWTP sample in our study. However, this compound was not detected in any reservoir sample, indicating that some dilution, degradation or removal process may be at work. It has been documented that carbamazepine is resistant to degradation in WWTPs. Miao et al. (2005) found a 29% difference between influent and effluent concentrations, Heberer and Reddersen (2001) found

only an 8% difference, and others found no removal (Joss et al., 2005; Castiglioni et al., 2006). Clara et al. (2004) found no removal of carbamazepine using lab-scale experiments with varying solids retention times. Sampling at eleven full-scale WWTPs found only one with a removal rate over 20%, and no difference was found in removal efficiency between activated sludge and trickling filter plants (Clara et al., 2004). Carballa et al. (2004) could not quantify carbamazepine in any 24-h composite sample (LOQ: 74 ng/L) during their profile of an activated sludge WWTP in Spain.

At Yorktown, caffeine was detected in every sample. It is expected that most treatment facilities substantially reduce influent concentrations of caffeine (Heberer, 2002b; Miao et al., 2005). If our data represent only the small residual following caffeine's degradation, it may indicate very substantial input of caffeine to the plant, or perhaps more likely, that the plant's treatment operation degrades caffeine poorly. Lee and Rasmussen (2006) found a significant difference in caffeine concentrations between WWTPs using trickling filters and those using activated sludge, though only 6 and 8 samples (respectively) from those plants were analyzed. Although the caffeine concentrations found at Yorktown were very high compared to the other plants in our study as well as Lee and Rasmussen (2006), where the maximum reported concentration was 12,000 ng/L, they are at the low end of the range found by Weigel et al. (2004). These authors detected caffeine in wastewater effluent in the range 20,000–293,000 ng/L, as well as concentrations of caffeine in sea water ranging from 7–87 ng/L in the Tromsø Sound on the Northern Coast of Norway.

The absence of biological nitrification processes at the WWTPs in our study (along with the low 4-ng/L detection limit) may help explain why 83% of the WWTP effluent samples had detectable trimethoprim concentrations. This process was shown in laboratory reactor experiments to significantly degrade trimethoprim during treatment, while other traditional processes, like activated sludge, were not effective (Perez et al., 2005; Paxéus, 2004). Of the seven WWTPs investigated by Gros et al. (2007), the six activated sludge plants were found inefficient at removing trimethoprim and carbamazepine.

The ibuprofen concentrations seen at Yorktown are higher than what was found recently in samples from Canadian WWTPs (<25 ng/L by Miao et al., 2002; and 100–300 ng/L by Stumpf et al., 1999) and some Norwegian WWTPs (20–680 ng/L; Weigel et al., 2004), but closer to those found in Swiss WWTPs (ND — ~1300 ng/L; Tixier et al., 2003). WWTPs have been shown to remove ibuprofen efficiently, in some cases upwards of 90% removal (Joss et al., 2005), though this is considered dependent on the efficiency of the activated sludge process (Paxéus, 2004). Yorktown does not have activated sludge process, while Carmel (which had the fewest detections), does utilize this treatment technique.

5.2. Reservoir samples

In the reservoir samples, ibuprofen and caffeine were found above the detection limit in six (2.5%) and seven (2.9%) samples, respectively, of the 240 reservoir samples. However, it is unclear as to whether these compounds were present in

the reservoir water or their detection was due to a sampling or sample analysis artifact. In one case, ibuprofen was detected in a DEL 18 sample at a concentration (932 ng/L) which was above those found in most WWTP effluent samples. Unfortunately, duplicate samples were not collected from these locations on the days when caffeine or ibuprofen were detected. It should be noted that we did not find similar contamination in samples from the West of Hudson locations, and that we did not detect caffeine and ibuprofen together in any reservoir sample. Therefore, the results may indicate that caffeine and ibuprofen are intermittently distributed in the reservoir samples, or that there was contamination during the sampling and/or analysis. Buerge et al. (2006) suggest that the presence of caffeine in receiving waters is indicative of an untreated wastewater discharge, as treatment efficiencies in most WWTPs are over 99%. Although Yorktown does not have CSOs, there are other potential sources, such as septic systems or surface water runoff, which may have contributed to the caffeine detections in surface water.

5.3. Daily and seasonal variation

Few studies have evaluated a seasonality component for the pharmaceutical load in WWTP effluent. Hua et al. (2006) analyzed effluents from a Canadian activated sludge WWTP over three seasonal sampling periods, and found lower concentrations of trimethoprim in September than in the early spring and summer (means: 94, 313, and 344 ng/L, respectively). Carbamazepine concentrations (means: 344, 219, and 304, respectively) were higher than the concentrations we found at Carmel, though the Canadian WWTP is a much larger plant. Another study of eight Canadian WWTPs found a median carbamazepine concentration of 43 ng/L in the spring, and a median of 110 ng/L in the summer (Brun et al., 2006). Carballa et al. (2004) analyzed various stages of treatment in an activated sludge WWTP in three seasons, and found winter ibuprofen concentrations in the influent and effluent about twice what was detected in the fall and spring for those compartments. Castiglioni et al. (2006) reported summer and winter removal rates (RR) for an Italian WWTP; among the compounds they identified, some had lower winter RR than summer RR, such as atenolol (10% and 55%) and ibuprofen (38% and 93%), while carbamazepine showed no removal in either season.

Daily variation in pharmaceutical concentration is even sparser than seasonal data, as many studies simply do not have the sample size to analyze this data. Clara et al. (2004) provide daily carbamazepine concentrations over four 7- to 10-day periods between October 2001 and December 2002, but these are for WWTP influent; the effluent data are not provided. Joss et al. (2005) looked at 24-h intra-day variation by collecting 8-h composite influent samples, which showed that carbamazepine loading primarily occurred between 0800 and 1600 h.

6. Conclusions

Five of the twelve analytes were consistently detected in the effluent of four wastewater treatment plants within the New

York City Watershed. The type and concentration of analytes in the effluents differed between the plants and over the seasons. It is likely that the differences seen for some of the analytes (i.e. having a maximum and minimum during the same season at different plants) may be accounted for partially by the operational differences in the WWTPs, and/or the differences in populations from which the plants receive waste. However, this does not explain the variation seen at individual plants. None of the analytes was detected in the surface waters of the West of Hudson reservoir samples, but caffeine and ibuprofen were detected infrequently in several East of Hudson reservoir samples. None of the other analytes was found in the surface water samples. The fate of the discharged pharmaceuticals in the watershed was not characterized and remains unknown. It is expected that investigation of other wastewater treatment plants in the NYC watershed would show that their effluents are also a potential source of pharmaceuticals to surface waters.

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