Environ. Sci. Technol. **2010,** *44,* 4910–4916

Pharmaceutical Formulation Facilities as Sources of Opioids and Other Pharmaceuticals to Wastewater Treatment Plant Effluents

PATRICK J. PHILLIPS,*,† STEVEN G. SMITH,‡ D. W. KOLPIN,§ STEVEN D. ZAUGG,‡ HERBERT T. BUXTON,|| EDWARD T. FURLONG,‡ KATHLEEN ESPOSITO,⊥ AND BEVERLEY STINSON#

US Geological Survey, 425 Jordan Road, Troy, New York 12180, US Geological Survey, Box 25046, MS415, Lakewood, Colorado 80225, US Geological Survey, 400 S. Clinton Street, Iowa City, Iowa 52244, US Geological Survey, Suite 206, 810 Bear Tavern Road, West Trenton, New Jersey 08628, AECOM, 605 Third Avenue, New York, New York 10158, and AECOM, 14504 Greenview Drive, Suite 400, Laurel, Maryland 20708

Received February 2, 2010. Revised manuscript received April 15, 2010. Accepted May 3, 2010.

Facilities involved in the manufacture of pharmaceutical products are an under-investigated source of pharmaceuticals to the environment. Between 2004 and 2009, 35 to 38 effluent samples were collected from each of three wastewater treatment plants (WWTPs) in New York and analyzed for seven pharmaceuticals including opioids and muscle relaxants. Two WWTPs (NY2 and NY3) receive substantial flows (>20% of plant flow) from pharmaceutical formulation facilities (PFF) and one (NY1) receives no PFF flow. Samples of effluents from 23 WWTPs across the United States were analyzed once for these pharmaceuticals as part of a national survey. Maximum pharmaceutical effluent concentrations for the national survey and NY1 effluent samples were generally <1 μg/L. Four pharmaceuticals (methadone, oxycodone, butalbital, and metaxalone) in samples of NY3 effluent had median concentrations ranging from 3.4 to >400 μg/L. Maximum concentrations of oxycodone (1700 μg/L) and metaxalone (3800 μg/L) in samples from NY3 effluent exceeded 1000 μg/L. Three pharmaceuticals (butalbital, carisoprodol, and oxycodone) in samples of NY2 effluent had median concentrations ranging from 2 to 11 μg/L. These findings suggest that current manufacturing practices at these PFFs can result in pharmaceuticals concentrations from 10 to 1000 times higher than those typically found in WWTP effluents.

* Corresponding author phone: 518-285-5667; fax: 518-285-5600; e-mail: pjphilli@usgs.gov.
† US Geological Survey, Troy, NY.
‡ US Geological Survey, Lakewood, CO.
§ US Geological Survey, Iowa City, IA.
|| US Geological Survey, W. Trenton, NJ.
⊥ AECOM, New York.
AECOM, Laurel, MD.

Introduction

Over the past decade, numerous studies have documented the occurrence of pharmaceuticals in streams (*1*−*4*) and have identified wastewater treatment plants (WWTPs) as a major source of these compounds to the environment (*5, 6*). Improvement in analytical capabilities has revealed an expanding range of pharmaceuticals in the environment, including benzodiazepines (*7, 8*), barbiturates (*9, 10*), opioids (*7, 10, 11*), antidepressants (*8, 12*), and muscle relaxants (*13, 14*). The long-term effects of low-level exposure to complex mixtures of pharmaceuticals on stream biota are poorly understood, although a variety of potential adverse effects have been documented at these low levels, including acute and chronic damage (*15, 16*), accumulation in tissues (*12, 17*), reproductive damage (*18*), inhibition of cell proliferation (*19*), and behavioral changes (*20, 21*). Continued research to identify and quantify pharmaceuticals in susceptible environmental settings and to identify potential ecological effects in those settings is essential for the future protection of water quality and ecological health.

The discharges of facilities that manufacture pharmaceutical products are an under-investigated source of pharmaceuticals to the environment, with only limited data currently available worldwide. Pharmaceutical manufacturing facilities include pharmaceutical production facilities (PPF), which produce active pharmaceutical ingredients, and pharmaceutical formulation facilities (PFF), which formulate and package pharmaceutical products (*22*). Past studies of pharmaceutical sources to the environment have focused on consumer use and disposal and hospital waste (*14, 23, 24*). However, a study in India (*25*) found pharmaceutical concentrations as high as 31 000 μg/L in a WWTP effluent that receives substantial discharges from PMFs, and these discharges have resulted in nearby groundwater and surface water concentrations as high as 2500 μg/L (*26*). Similarly, diclofenec concentrations exceeded 20 μg/L in a Taiwan WWTP effluent that received PPF discharge (*27*). These concentrations are orders of magnitude higher than typical concentrations reported for WWTP effluents in the U.S. and Europe (generally <1 μg/L). To our knowledge, no study has directly measured pharmaceuticals in a WWTP receiving PFF or PPF discharges in the United States or Europe. Modeled estimates of concentrations of pharmaceuticals in a WWTP in Switzerland receiving PFF discharge using a mass balance approach ranged from <0.01 to 38 μg/L (*22*), and research has suggested that discharges from manufacturing facilities in Europe may result in observed elevated antiviral concentrations in river water (*28*).

The purpose of this paper is the following:

(1) Present the environmental occurrence of seven pharmaceuticals (Table 1) in effluents from 23 WWTPs across the United States. These pharmaceuticals represent some of the most frequently prescribed medications in the United States (*29*), and some (metaxalone, phendimetrazine) have not been previously included in effluent or stream studies.

(2) Compare the concentrations and mixtures of pharmaceuticals in two WWTP effluents that receive discharge from PFFs with those of one not receiving such PFF discharge and 23 other WWTPs from across the United States.

(3) Compare the limited available information on pharmaceuticals formulated at the PFFs to the pharmaceuticals detected in this study, including qualitatively identified compounds.

10.1021/es100356f

Published on Web 06/04/2010

TABLE 1. List of Seven Target Pharmaceuticals with Chemical Properties and Method Detection Level

compound	CAS No.[a]	compound class	Log K_{ow}[b]	water solubility (mg/L)[b]	method detection limit[c] (μg/L)
butalbital	77-26-9	barbiturate	1.87	1700	0.014
carisoprodol	78-44-4	muscle relaxant	2.36	300	0.021
diazepam	439-14-5	benzodiazepine tranquilizer	2.82	50.0	0.012
metaxalone	1665-48-1	muscle relaxant	2.60	90.7	0.011
methadone	76-99-3	opioid	3.93	48.5	0.044
oxycodone	76-42-6	opioid	0.66	4160	0.076
phendimetrazine	634-03-7	amphetamine	1.70	17300	0.021

[a] This report contains CAS Registry Numbers, which is a Registered Trademark of the American Chemical Society. CAS recommends the verification of the CASRNs through CAS Client Services. [b] Chemical properties from online database http://www.syrres.com/esc/physdemo.htm (viewed January 2008). [c] Method detection limits were determined from 10 reagent water samples fortified at 0.05 μg/L and 7 reagent water samples fortified at 0.20 μg/L.

(4) Assess concentrations of these seven pharmaceuticals in waters downstream of three select WWTPs, considering the source strength of WWTP effluents and dilution by streamflow.

Experimental Section

Site Selection and Sampling. Samples were collected from 26 WWTPs, including (1) a network of 23 WWTPs in 12 states across the United States serving a wide range of population sizes (Supporting Information Table S-1), hereafter referred to as the national survey, and (2) three select WWTPs in New York State (sites NY1, NY2, and NY3). More than half of the WWTPs in the national survey receive discharge from hospitals (Table S-1); all sites in the national survey were sampled once between 2006 and 2009, four as 24-h flow composites, and 19 as grab samples. Grab samples were generally collected between 8 a.m. and 1 p.m.

Between July 2004 and June 2009, 35−38 effluent samples (see Table S-2) were collected from sites NY1, NY2, and NY3. One of these sites (NY1) does not receive PFF or hospital input. NY2 receives approximately 20% of its flow from a PFF and also receives flow from a hospital. NY3 receives approximately 20% of its wastewater inflow from another PFF (Table S-1). Over 30 stream samples were collected within a few km of the corresponding outfalls for these three WWTPs (Table S-3) using standard width- and depth-integrating techniques. No tributaries enter the stream between the effluent discharge and the stream-sampling locations. Finally, 16 samples were collected between 2006 and 2009 from a drinking water reservoir 30 km downstream of site NY2 to assess the concentrations of pharmaceuticals in water used for human consumption. Most effluent samples and all reservoir samples were collected as grab samples, but a few 24-h flow-weighted composite samples were collected at NY1 ($n = 2$), NY2 ($n = 1$), and NY3 ($n = 3$). The median difference between the 15 paired concentrations available from the three concurrent grab and composite samples available from NY3 was 40%, and all of these differences were <70%, indicating that concentrations in simple grab samples were well within an order of magnitude of composite samples. All data presented in this paper (including blank and replicate data) are available elsewhere (*30*).

Chemical Analyses. *Sample Preparation and Analysis.* The method of analysis for the seven pharmaceuticals is based upon a previously described method developed for the determination of domestic and industrial wastewater compounds (*31*). Supporting Information pages S-10 through S-29 describe method development, performance, and qualitative analysis of additional compounds.

One-liter samples were filtered through 0.7-μm glass-fiber filters prior to solid-phase extraction (SPE), and were extracted by vacuum filtration through 500-mg OASIS-HLB-SPE cartridges. Sample extracts were analyzed by capillary gas chromatography/mass spectrometry (GC/MS) operated under full scan conditions. Results were reported only if they met qualitative GC/MS criteria (retention time, mass spectrometric ion-abundance ratios, and mass spectra) before being quantitated based on a 5−8 point calibration curve. Samples collected after March 2006 included analysis for all seven pharmaceuticals; those collected before this date lacked analysis of carisoprodol. Method detection limits [determined according to methods specified in ref *32*] ranged from 0.011 to 0.076 μg/L (Table 1).

For samples collected before April 2009, the maximum calibration points used for analysis were 4 μg/L for diazepam, 400 μg/L for metaxalone, and 40 μg/L for all other pharmaceuticals. As it became apparent that many concentrations exceeded these levels, adjustments were made to the standard operating procedure for the method to ensure accurate analysis over the extremely wide range of concentrations encountered. This included extending the upper point of the calibration curve to 4000 μg/L for metaxalone and 400 μg/L for all other pharmaceuticals after April 2009. Concentrations exceeding the calibration curve before April 2009 were censored to the maximum calibration concentration. Concentrations for six NY3 effluent samples quantified above 40 or 400 μg/L before April 2009 were determined by either (1) diluting samples, (2) extracting lesser amounts of sample, or (3) reanalyzing frozen archived samples.

Method Performance. Different spiking experiments (two reagent set spike experiments at low and medium concentrations, three effluent spike experiments at low, medium, and high concentrations, and a stream spike experiment at medium concentrations; see pages S-15 to S-19 in the Supporting Information) were included to characterize method performance. Of the 14 reagent set spikes, only the mean recovery for the low concentration (0.2 μg/L) carisoprodol spike (140%) lies outside the 60−130% range, and only the two oxycodone spikes (low level at 46% and high level at 34%) have RSDs (relative standard deviations) > 30%. Of the 19 effluent spikes, two mean recoveries−methadone for the moderate spike (59%) and oxycodone for the low-level spike (170%)−have mean recoveries outside the 60−130% range. Only one of the 19 effluent spikes, the low level methadone spike, has an RSD >30% (31%).

The spiking results show that the effluent concentrations for the seven pharmaceuticals in this study have low bias and variability. Although the low-level reagent set spikes indicate that carisoprodol may have a positive bias for low concentrations, the other reagent spike and effluent spikes for carisoprodol range from 94 to 113%, suggesting no bias. The methadone spike recovery for the effluent spike at middle range (8 μg/L) concentrations indicates a slight low bias (59%), yet the other two methadone effluent spikes for low (0.2 μg/L) and high (≥90 μg/L) range concentrations (63 and 91%, respectively) show no bias. The results indicate a positive

bias for oxycodone for low (0.2 μg/L) effluent concentrations, yet the two other oxycodone effluent spikes for moderate (8 μg/L) and high (≥24 μg/L) concentrations have mean recoveries of 94 and 70%, respectively. The high RSDs for reagent set spikes suggest that oxycodone concentrations may be more variable than other pharmaceuticals in this study, however the effluent spikes for oxycodone all have RSDs < 30%.

The stream spike recoveries for butalbital, carisoprodol, diazepam, and metaxalone were between 60 and 130%, and RSDs were less than 30%, indicating low bias and variability. Because of the low (32%) and variable (RSD of 48%) recovery for methadone stream spikes, streamwater data for methadone are only reported qualitatively (as percent detection). The low recoveries for stream spikes for oxycodone and phendimetrazine (both 57%) suggest that the stream concentrations for these two pharmaceuticals may be biased low. In addition, the RSD for the oxycodone stream spike was 36%, indicating a higher variability for stream concentrations for this pharmaceutical than the others.

Quality Control. Sixty-nine field blanks were collected and analyzed during the study: 22 collected before March 2006 were analyzed for all of the target pharmaceuticals but carisoprodol, and the 47 collected after March 2006 were analyzed for all seven pharmaceuticals. Field blanks were prepared from laboratory-grade organic-free water and were processed and handled using the same methods as WWTP-effluent and stream samples. Three analytes were detected in field blanks: butalbital (two blanks ranging from 0.045 to 0.051 μg/L), oxycodone (two blanks, ranging from 0.15 to 0.73 μg/L), and metaxalone (seven blanks ranging from 0.068 to 1.0 μg/L). Blank detections were associated with effluent samples containing high pharmaceutical concentrations (>100 μg/L) and were attributed to the carryover of high concentrations to later samples in the same sample set. Concentrations in environmental samples within 10 times the blank concentrations collected during the same week were censored to a nondetection. Metaxalone blank contamination also occurred in 20% of method blanks, therefore metaxalone concentrations below 3 μg/L (10 times the 90th percentile of field blank concentrations) were censored to a nondetection.

Analyses of 36 replicate samples yielded 85 paired-replicate detections of analytes, and 6 unpaired replicate detections (a detection in only one of the paired samples). All but one of the unpaired detections occurred for concentrations <0.2 μg/L. Median relative percent differences (RPDs) were similar among analytes, ranging from 3.9% for metaxalone to 13% for oxycodone. RPDs were somewhat greater for low concentration comparisons (9.9% for concentrations <0.2 μg/L) compared to high concentration comparisons (4.3% for concentrations >10 μg/L).

Results

National Survey of WWTP Effluent. Five of the seven pharmaceuticals tested were detected in at least one effluent collected from the 23 WWTPs included in the national survey (Figure 1). Butalbital (83%) was the most frequently detected compound, followed by oxycodone (56%) and carisoprodol (43%). Maximum concentrations ranged from 0.1 μg/L. (diazepam) to 0.31−0.73 μg/L. (butalbital, carisoprodol, methadone, and oxycodone). Metaxalone and phendimetrazine were not detected in these samples. The concentrations for most of these pharmaceuticals are similar to concentrations of pharmaceuticals found in other studies of WWTP effluents in the U.S. and Europe (*7*−*11*, *14*). This study, however, provides the first data for some of these pharmaceuticals in the U.S.

The median total pharmaceutical concentration (equal to the sum of detected concentrations of all seven analytes

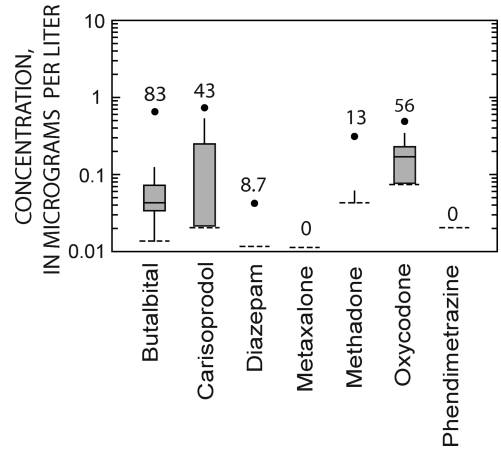

FIGURE 1. Concentrations of seven pharmaceuticals analyzed in effluent from 23 wastewater treatment plants sampled across the United States between 2006 and 2009. Box plots depict range of concentrations, with top whisker equal to 90th percentile of concentrations, bar at the top of box equal to the 75th percentile, bar at the middle of the box equal to the 50th percentile, bar at the bottom of the box equal to the 25th percentile, and bottom whisker equal to the 10th percentile. Dots above the top of the whisker represent maximum concentrations, number above boxplot refers to percent of samples with a positive detection. Dashed line at bottom of boxplot or whisker denotes method detection limit.

for each sample) for the 14 WWTPs that receive discharge from a hospital facility (0.32 μg/L) was not significantly different ($p > 0.05$; Kruskall−Wallace test) from the median total pharmaceutical concentration in samples from the eight WWTPs without hospital input (0.096 μg/L; see Figure 2A). However, the WWTPs that received hospital waste had significantly higher daily flows than sites not receiving hospital waste ($p < 0.05$; Kruskall−Wallace test), complicating this comparison. Direct measurement of hospital effluents is necessary to effectively characterize pharmaceutical contributions from hospitals (*24*).

Concentrations of Pharmaceuticals in NY1, NY2, and NY3 Effluents, 2004−2009. The median total pharmaceutical concentration in samples of NY1 effluent (a WWTP receiving neither hospital nor PFF input) was 0.38 μg/L, and thus was comparable to those for samples in the national survey (Figure 2A, B). By contrast, the median total pharmaceutical concentration in samples from NY2 effluent (26 μg/L) and NY3 effluent (450 μg/L), both of which receive substantial PFF discharge, were significantly higher than that for NY1 effluent (Figure 2B).

Median total pharmaceutical concentrations in samples of NY2 and NY3 effluents were generally 30 to almost 500 times higher than total pharmaceutical concentrations typically found in the national effluent survey. None (0 of 161) of the individual pharmaceutical concentrations determined for the national survey were greater than 1 μg/L. Similarly, only 1.6% (4 of 242) of individual pharmaceutical concentrations in samples of NY1 effluent exceeded 1 μg/L. However, 36% (84 of 236) of the individual pharmaceutical concentrations in samples of NY2 effluent and 61% (155 of 254) of the individual pharmaceutical concentrations in samples of NY3 effluent exceeded 1 μg/L (Figure 3).

Median concentrations for the five pharmaceuticals (butalbital, metaxalone, methadone, oxycodone, and phendimetrazine) most commonly detected in samples of NY3 effluent ranged from 0.5 to >400 μg/L; median concentrations for the four pharmaceuticals (butalbital, carisoprodol, diazepam, and oxycodone) most commonly detected in samples of NY2 effluent ranged from 0.74 to 11 μg/L (Figure 3). By contrast, median concentrations for the two phar-

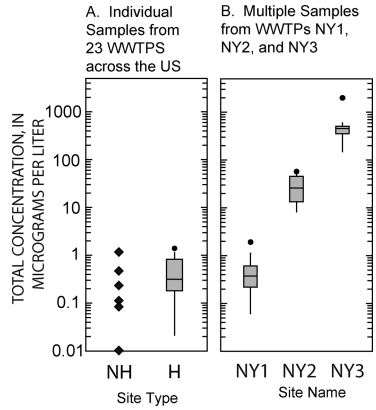

FIGURE 2. Total concentration of seven pharmaceuticals detected in wastewater treatment plant (WWTP) effluent samples for (A) individual samples from 23 WWTPs across the United States, and (B) multiple samples from WWTPs NY1, NY2, and NY3. NH = WWTPs that do not receive discharges from hospitals. H = WWTPs that receive discharges from hospitals. Individual concentrations are plotted for NH sites because less than 12 samples are available for this category. Concentrations plotted along *x*-axis (at 0.01 ug/L) denote nondetects. Site NY1 does not receive discharge from a hospital or a pharmaceutical formulation facility (PFF). Site NY2 receives discharge from a hospital and approximately 20% of its discharge from a PFF. Site NY3 receives approximately 20% of its discharge from a PFF, but does not receive discharge from a hospital. For sites NY1, NY2, and NY3, only those samples with determinations for all seven analytes are included in the total concentration calculation. An explanation of a box plots is given in Figure 1. Total concentrations for H site type are not significantly different from NH site type for Wilcoxon sum rank test. Total concentrations for NY3 are significantly greater than NY1 and NY2, and total concentrations for NY2 samples are significantly greater than NY1 samples by Tukey nonparametric test. For sites NY1, NY2, and NY3, only those samples with determinations for all seven analytes are included in the total calculation (samples collected before 2006 did not include analysis for carisoprodol).

maceuticals (butalbital and oxycodone) most commonly detected in samples of NY1 effluent were 0.10 and 0.19 μg/L, respectively (Figure 3). Maximum concentrations of oxycodone and metaxalone in samples of NY3 effluent were 1700 and 3800 μg/L, respectively, and maximum concentrations of three other pharmaceuticals (butalbital, methadone, and phendimetrazine) ranged from >40 to >400 μg/L. Two pharmaceuticals (butalbital and carisoprodol) had maximum concentrations >40 μg/L in samples of NY2 effluent. Thus, the concentrations of many of the individual pharmaceuticals in samples of NY2 and NY3 effluent were between 10 and 1000 times higher than those found in (1) the NY1 effluent samples, (2) the samples collected in the national survey of 23 WWTP effluents (including those receiving hospital discharges), and (3) effluents in other studies (cited above). These concentrations, however, are similar to those observed in a WWTP receiving PPF effluent in India (*25*).

The effluent samples from NY2 and NY3 contained complex mixtures of pharmaceuticals. Many of the samples of NY3 effluent (15 of 38, or 39%) had four or more pharmaceuticals with concentrations >10 μg/L, and many of the samples of NY2 effluent (15 of 35, or 43%) had two or more pharmaceuticals with concentrations >1 μg/L. Concentrations of four pharmaceuticals exceeded 40 μg/L in a sample of NY3 effluent collected in February 2009 (butalbital 110 μg/L, metaxalone 230 μg/L, methadone 41 μg/L, and oxycodone 1700 μg/L).

It has been hypothesized that current Good Manufacturing Practice and Effluent Emission (use and disposal) regulations of the U.S. Food and Drug Administration (FDA), manufacturing effluent discharge and emission regulations of the U.S. Environmental Protection Agency (EPA), and the inherent value of active pharmaceutical ingredients would restrict the loss of pharmaceutical products from manufacturing facilities (*33*). However, the results presented here indicate that concentrations of pharmaceuticals for WWTPs receiving substantial discharges from a PFF can exceed 1000 μg/L. These concentrations are substantially higher than those (1) predicted by models based on normal consumer use of pharmaceuticals (*34*), (2) modeled for a PFF in Switzerland (*22*), and (3) cited as representative of maximum WWTP effluent concentrations (*35*). These results demonstrate the need for environmental data from a variety of sources, including PFFs, to verify models and other approaches to estimating source loads and predicting environmental pharmaceutical concentrations (*36*).

Relation of Pharmaceutical Concentrations to Production Data. Complete data on pharmaceuticals formulated at the PFFs discharging to WWTPs NY2 and NY3 are not available and were estimated based on several sources: (1) direct FDA identification of select pharmaceuticals formulated at these sites (*37*), (2) a New York State Report indicating use of two pharmaceuticals at the PFF discharging to NY3 (*38*), (3) a Web site operated by The U.S. National Institutes of Health (NIH) that provides labels for select pharmaceuticals that identify the company marketing the pharmaceutical or the company manufacturing the pharmaceutical (*39*), and (4) manufacturers' Web sites that list the pharmaceuticals marketed by the owners of the PFFs (*40, 41*). The first two sources, although the most accurate, include few pharmaceuticals. The last two sources can confirm that the owner of the PFF markets the pharmaceuticals included in the study, but do not necessarily indicate that the pharmaceutical is produced at a specific PFF. FDA (*37*) noted that over 100 products were formulated at the PFF discharging to NY2, and that the list provided of pharmaceuticals formulated at both PFFs was not complete. A list of the target pharmaceuticals and additional pharmaceuticals qualitatively identified in effluent samples from NY2 and NY3 along with information on whether they are manufactured or marketed by the owner of the PFF are given in Supporting Information Tables S-4 and S-5.

One (methadone) of the five pharmaceuticals commonly detected in NY3 effluent were identified by the FDA as formulated at the PFF discharging to NY3 (Table S-5). The two pharmaceuticals (oxycodone and metaxalone) found in NY3 effluent at concentrations greater than 1000 μg/L were not identified by the FDA as formulated at the PFF discharging to NY3. Metaxalone, however, was identified as formulated at this site by both New York State (*38*) and the NIH Web site (*39*). Both the NIH Web site and the manufacturer's Web site indicate that oxycodone and the other pharmaceuticals detected at high concentrations at NY3 effluent are marketed by the corporation operating this PFF (Table S-5; *40*). Only one (oxycodone) of the four pharmaceuticals commonly detected in NY2 effluent was identified by the FDA as formulated at the PFF discharging to NY2 (Table S-4; *37*). The manufacturer's Web site, however, indicated that oxycodone and the other three pharmaceuticals (butalbital, carisoprodol, and diazepam) were marketed by the corporation operating this PFF (*41*).

During the course of the study, 19 additional pharmaceuticals or pharmaceutical degradates in samples from NY2 and NY3 effluents were qualitatively identified using authentic standards (Tables S-4 and S-5). Seven of these pharmaceuticals were identified by the FDA as being formulated by the PFFs discharging to these sites. In addition, 14 other pharmaceuticals were identified by FDA as formulated at these sites, but were not included as target analytes

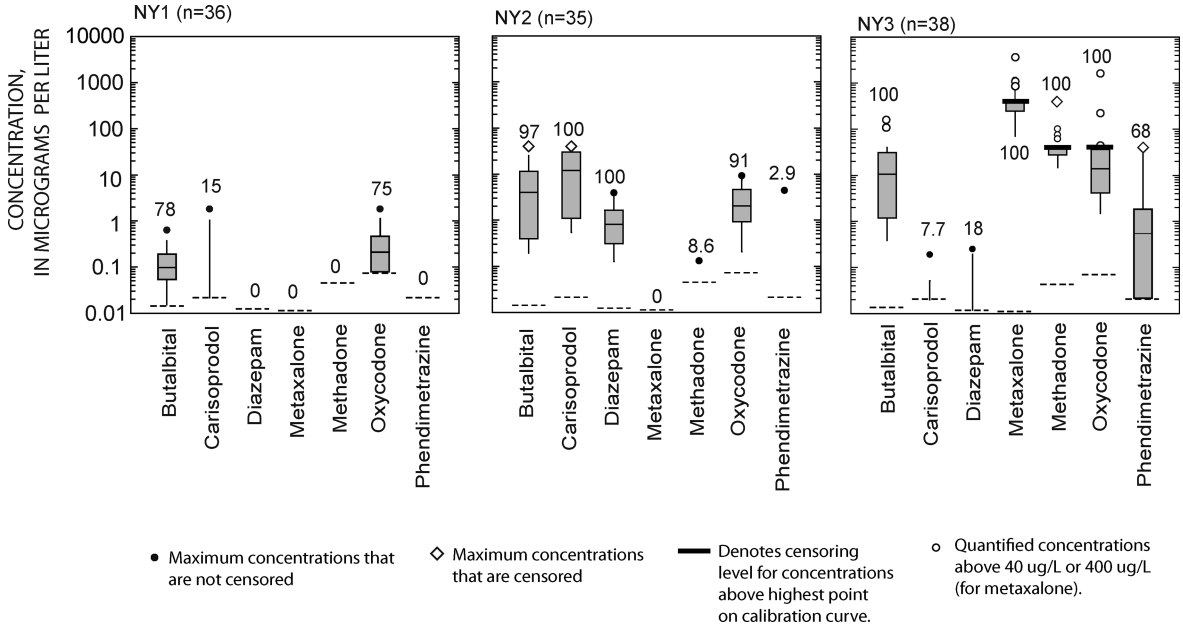

FIGURE 3. Concentrations of seven pharmaceuticals analyzed in samples of effluent from wastewater treatment plants (WWTPs) NY1, NY2, and NY3 during 2004−2009. Site NY1 does not receive discharge from a hospital or a pharmaceutical formulation facility (PFF). Site NY2 receives discharge from a hospital and approximately 20% of its discharge from a PFF. Site NY3 receives approximately 20% of its discharge from a PFF, but does not receive discharge from a hospital. Box plots depict range of concentrations, and are explained in Figure 1. Number above boxplot refers to percent detection. Numbers of samples for each site are indicated next to the site name. Twenty four samples were analyzed for carisoprodol at each site. Concentrations of methadone, oxycodone, carisoprodol, and phendimetrazine above 40 μg/L and metaxalone above 400 μg/L were frequently censored because many of these concentrations were above the maximum point on the calibration curve. Concentrations quantified above these levels plotted as open circles were below the maximum point on the calibration curve. Boxplots for pharmaceuticals with censoring in more than 25% of the samples (including methadone, oxycodone, and metaxalone in NY3 samples) were denoted by a boxplot truncated at the upper end with a bar. Dashed line at bottom of boxplot or whisker denotes method detection limit.

nor were they qualitatively identified (seeTables S-4 and S-5). These results indicate that the pharmaceuticals included in this study may only represent a fraction of the pharmaceuticals potentially present in the effluent at these sites.

Carisoprodol concentrations in NY2 effluent and corresponding downstream samples decreased after early 2008, and butalbital concentrations in NY2 effluent and corresponding downstream samples increased after early 2008 (Supporting Information Figure S-1). The limited data from the drinking water reservoir 30 km downstream from NY2 also indicate that carisoprodol concentrations decreased and butalbital concentrations increased since early 2008 (Figure S-1). NY3 effluent concentrations for methadone and metaxalone were consistently high in samples collected between 2004 and 2009, while oxycodone and butalbital concentrations varied temporally (Figure S-2). These data provide evidence that the emission of pharmaceuticals from PFFs is not short-term (on the order of 1 day) as suggested previously (*22*). Temporal variations in pharmaceutical concentrations in effluent of WWTPs with PMFs may relate to operational changes in the facilities, or seasonal differences in removal at the WWTP. These relations cannot be determined without information on pharmaceutical use, production, and other operational practices in such facilities. The lack of a single reliable source of data on pharmaceuticals used at PFFs hampers the ability to fully identify the suite of pharmaceuticals that may be present in WWTP effluents receiving these discharges as well as downstream waters that may include water used for human consumption.

Concentrations of Pharmaceuticals Downstream of NY1, NY2, and NY3 Effluents. Stream pharmaceutical concentrations frequently exceeded 1 μg/L in samples collected downstream from the NY2 discharge (Supporting Information Figure S-3). Over half of the stream samples collected below the NY2 discharge had two or more pharmaceuticals with concentrations greater than 1 μg/L. The pharmaceuticals with the highest concentrations in stream samples below the NY2 discharge (Figure S-3) correspond to the pharmaceuticals with the highest concentrations in samples from NY2 effluent (Figure 3). Pharmaceutical concentrations in the stream below the NY2 discharge are generally higher than those typically found in WWTP effluent samples (Figure 1) due to a combination of high effluent concentrations and limited dilution by the receiving stream (Table S-3; Figure S-4). These results suggest that future research should be conducted to determine whether these pharmaceutical concentrations are affecting aquatic biota.

Pharmaceutical concentrations in samples downstream of NY1 discharge rarely exceeded 0.1 μg/L (Figure S-3), reflecting the lower pharmaceutical concentrations in NY1 effluent samples compared to NY2 effluent samples. Although concentrations in samples collected from the NY3 effluent often exceeded 10 μg/L (Figure 3) only two pharmaceuticals (metaxalone and oxycodone) exceeded 1 μg/L in samples collected downstream of the NY3 discharge (Figure S-3). The lower concentrations of pharmaceuticals in samples downstream of NY3 compared to samples downstream of NY2 can be attributed to the high amount of dilution (0.17% of flow derived from effluent downstream of NY3, compared to 15%−24% for the other two sites; see Table S-3) at this site.

Assessing PMFs as Sources of Pharmaceuticals. This study demonstrates that while an ever broader range of pharmaceuticals are commonly found in WWTP effluents and streams below these discharges (generally at <1 μg/L) specific sources such as PFFs can lead to circumstances where pharmaceutical concentrations are 10−1000 fold higher than generally measured in WWTP effluent samples without such input. Thus, because current modeling approaches are based on only consumer use and disposal and do not take into account inputs from PMFs they may significantly underes-

timate potential maximum pharmaceutical concentrations from WWTP effluents. Furthermore, toxicological assessments based on subppb levels of pharmaceuticals in streams are unlikely to adequately account for the potential deleterious effects of both high individual chemical concentrations and chemical mixtures resulting from PMF discharges. Access to additional information on pharmaceutical use and discharges by PMFs is needed to accurately predict the concentrations and ecological effects of these under-investigated sources. Until such information is available, a forensic approach similar to the one used in this research will be needed to accurately determine the complex range of pharmaceuticals originating from such PMF discharges.

Acknowledgments

This research was funded by the State of New York, Department of Environmental Conservation, and the USGS Cooperative Water and Toxic Substances Hydrology Programs. We thank numerous wastewater treatment plant operators for access to their plants, and the following USGS employees: Mick Baldys, John Byrnes, Ann Chalmers, Dan Edwards, Anne Ernst, Michael Focazio, Adam Foster, James Gray, Michelle Hladik, Barbara Mahler, Mike Myers, Jeff McCoy, Elizabeth Nystrom, Nick Paretti, Kevin Richards, Paul Stackelberg, Tia-Marie Stevens, Steve Sando, and Carolyn VanAlstyne. The New York City Department of Environmental Protection offered constructive comments on early drafts. The use of trade, product, or firm names in this article does not imply endorsement by the U.S. Government.

Supporting Information Available

Pages S-2 through S-9 include Supplemental Figures S-1 through S-4 and Tables S-1 through S-5, which give additional details on sites sampled and qualitatively identified compounds in NY2 and NY3 effluent samples. Pages S-10 through S-28 include details on the analytical method, and include tables S6−S16. This material is available free of charge via the Internet at http://pubs.acs.org.

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