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Pharmaceutical manufacturing facility discharges can substantially increase the pharmaceutical load to U.S. wastewaters

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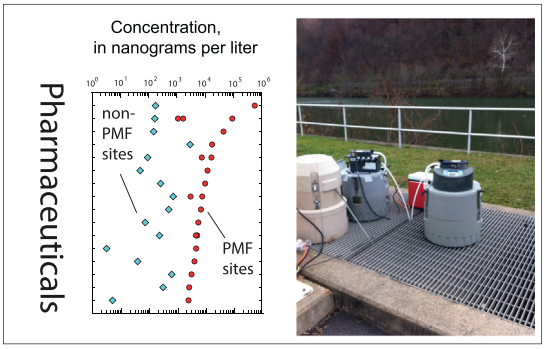
HIGHLIGHTS

- PMFs can contribute substantial concentrations of pharmaceuticals to WWTPs.
- 33 pharmaceuticals were much higher at PMF sites compared to non-PMF sites.
- 7 pharmaceuticals exceeded 10,000 nanograms per liter.
- Production information was good predictor of high concentration for bupropion only.
- Pharmaceutical discharges from manufacturers can substantially vary temporally.

GRAPHICAL ABSTRACT



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ABSTRACT

Discharges from pharmaceutical manufacturing facilities (PMFs) previously have been identified as important sources of pharmaceuticals to the environment. Yet few studies are available to establish the influence of PMFs on the pharmaceutical source contribution to wastewater treatment plants (WWTPs) and waterways at the national scale. Consequently, a national network of 13 WWTPs receiving PMF discharges, six WWTPs with no PMF input, and one WWTP that transitioned through a PMF closure were selected from across the United States to assess the influence of PMF inputs on pharmaceutical loading to WWTPs. Effluent samples were analyzed for 120 pharmaceuticals and pharmaceutical degradates. Of these, 33 pharmaceuticals had concentrations substantially higher in PMF-influenced effluent (maximum 555,000 ng/L) compared to effluent from control sites (maximum 175 ng/L). Concentrations in WWTP receiving PMF input are variable, as discharges from PMFs are episodic, indicating that production activities can vary substantially over relatively short (several months) periods and have the potential to rapidly transition to other pharmaceutical products. Results show that PMFs are an important, national-scale source of pharmaceuticals to the environment.

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1. Introduction

The occurrence and fate of pharmaceuticals, hormones and other contaminants of emerging concern (CECs) in the aquatic environment has been well documented over the past 15 years and is now recognized as a worldwide environmental concern (Ashton et al., 2004; Bruchet et al., 2005; Kolpin et al., 2002; Papageorgiou et al., 2016; Weigel et al., 2004). There is mounting evidence of the uptake of pharmaceuticals to both aquatic and terrestrial organisms (Blanco et al., 2017; Grabicova et al., 2015; Ismail et al., 2014; Miller et al., 2016; Zhao et al., 2015) with a range of biological effects including endocrine disruption, changes in behavior, and impacts on nutrient cycling (Baldigo et al., 2015; Borgatta et al., 2016; Brodin et al., 2013; Jonsson et al., 2015; Melvin, 2017; Parrott and Metcalfe, 2018; Richmond et al., 2017; Schoenfuss et al., 2016). The potential effects of mixtures of pharmaceuticals (e.g., synergistic effects), such as a compounding impact of antibiotic and antimicrobial exposure to aquatic ecosystems, have also been documented (Bradley et al., 2017; Vasquez et al., 2014). Numerous sources of pharmaceuticals to the environment have been documented including wastewater treatment plants (WWTPs) (Glassmeyer et al., 2005), onsite septic systems (Phillips et al., 2015; Schaider et al., 2016), landfills (Masoner et al., 2016), combined sewer overflows (Phillips et al., 2012), hospitals (Azuma et al., 2016; Daouk et al., 2016), livestock operations (Campagnolo et al., 2002; Kim et al., 2013), and pharmaceutical manufacturing facilities (PMFs) (Larsson et al., 2007; Phillips et al., 2010).

PMFs are a poorly understood source of pharmaceutical compounds (both active ingredients and their degradates) to the environment. An early consideration by Kummerer (2009) was that PMFs would be a negligible source of pharmaceuticals to the environment, either through direct discharge to surface waters or via discharge to WWTPs because of good manufacturing practice regulations and the high economic value of active pharmaceutical ingredients. Nevertheless, previous research has documented elevated pharmaceutical concentrations in the wastewaters of PMFs, in the effluent of WWTPs accepting PMF inputs, and corresponding points downstream from discharge points (Creusot et al., 2014; Larsson et al., 2007; Lin et al., 2008; Phillips et al., 2010; Qiting and Xiheng, 1988). In fact, emissions from a PMF can be a substantial environmental discharge of pharmaceuticals at levels exceeding concentrations acutely toxic to aquatic organisms and the environmental risks associated with PMF discharges are more severe than discharges ultimately resulting from consumer use (Larsson, 2014). Environmental risks associated with PMF discharges can include promoting the spread of antibiotic resistance (Sidrach-Cardona et al., 2014), toxicity to aquatic invertebrates (Carlsson et al., 2009), impacting gene expression in fish (Beijer et al., 2013; Gunnarsson et al., 2009), and endocrine disruption in fish (Baldigo et al., 2015; Sanchez et al., 2011; Schoenfuss et al., 2016).

Research on PMFs as sources of pharmaceuticals to the environment has primarily focused on PMFs that directly discharge their wastewaters into receiving water-bodies. Research in Taiwan found PMFs to be an important source of pharmaceuticals and detected 41 of 97 measured pharmaceutical compounds, with diclofenac having a median concentration exceeding 10,000 ng/L (Lin et al., 2008). In a follow-up study, maximum sulfamethoxazole and cccd 1,000,000 ng/L in Taiwanese PMF waste streams (Lin and Tsai, 2009). However, research analyzing the effluent of WWTPs that receive PMF input is limited. Several studies have focused on a PMF-impacted WWTP near Hyderabad, India that received waste inputs from over 90 bulk pharmaceutical manufacturers (Carlsson et al., 2009; Fick et al., 2009; Gunnarsson et al., 2009; Larsson et al., 2007; Rutgersson et al., 2014). This research documented three pharmaceuticals (ciprofloxacin, losartan, and cetirizine) at concentrations > 1000,000 ng/L in WWTP effluent samples (Larsson et al., 2007). High pharmaceutical concentrations were also detected in groundwater (5 pharmaceuticals each exceeding 1,000 ng/L) and lakes (2 pharmaceuticals each exceeding 1,000,000 ng/L) down gradient from this PMF-impacted WWTP (Fick et al., 2009).

While previous research identifies PMFs as potential environmental sources of pharmaceuticals, it is unknown whether PMFs are isolated sources or a widespread, national-scale source. In response to this research gap, a national-scale study across the United States was conducted to address a broader spatial scale, range of WWTP sizes, and suite of pharmaceuticals and related organic wastewater chemicals than was previously available. The complete data for this study is available in the Supplementary Data and in a U.S. Geological Survey (USGS) ScienceBase Data Release (Scott et al., 2018). Additionally, to our knowledge, this study is the first of its kind to select sampling sites based on pharmaceutical production information.

2. Methods

2.1. Site selection

The national sampling network for this study included 13 WWTPs that receive PMF waste inputs (hereafter referred to as PMF sites coded P##), six WWTPs that do not receive PMF waste (hereafter referred to as non-PMF sites coded N##), and one WWTP that was sampled before (P14) and after (N02) a PMF production phase-out and closure. Sampled WWTPs were located across the United States in areas where pharmaceutical manufacturing industry is common, spanning six U.S. Environmental Protection Agency regions (Table S1). Participation of WWTPs in this study was contingent upon anonymity; exact locations of WWTPs are, therefore, not provided. Additional sampling site information, including treatment technology and size of each WWTP, is provided in Table S1. The WWTP that was sampled pre- and post-PMF closure was extensively sampled previously (Phillips et al., 2010); trends of concentrations over time were assessed for a subset of pharmaceuticals (Colella, 2014).

To further focus the network design for this study, production information was obtained for seven primary pharmaceuticals: bupropion (BUP), carbamazepine (CBZ), oxycodone (OXY), prednisone (PRD), tamoxifen (TMX), sulfamethoxazole (SMX), and 17-α-ethynylestradiol (EE2). These pharmaceuticals were selected because they had (1) the potential for adverse environmental impacts (e.g., endocrine disruption), (2) widespread documented occurrence in WWTP effluent, (3) high consumer usage, and (4) the availability of analytical methods to measure them in environmental samples. In addition to receiving waste from PMFs producing the primary pharmaceuticals, PMF sites were chosen that represent a range in WWTP capacities (30 L/s to 9900 L/s) (Table S1).

The latest available production data, which included manufacturing location, tradename, active ingredients, potency of product, and dosage form, of seven specific pharmaceuticals was provided by a federal agency. Location and contact information on the specific WWTP that each PMF discharged to was also provided by a separate federal agency. Finally, the WWTPs confirmed that they received PMF waste.

Pharmaceutical production data had several limitations. Available PMF production data were from about 5 to 7 years prior to the dates of sample collection. In some cases, discussions with local plant operators or reviews of publicly available information indicated the potential for substantial changes in PMF production and/or operation between the historical production data and the time of sample collection. In addition, no data were provided as to the quantitative estimates of the amounts of these specific pharmaceuticals formulated, the timing of the formulation, or whether other pharmaceuticals were also being produced at the PMFs in question. Previous research at one of the PMF sites shows that pharmaceutical concentrations can have considerable temporal variability (Colella, 2014; Phillips et al., 2010). Nevertheless, our study is unique in its use of pharmaceutical production data to design