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Influence of hydrologic and anthropogenic drivers on emerging organic contaminants in drinking water sources in the Susquehanna River Basin

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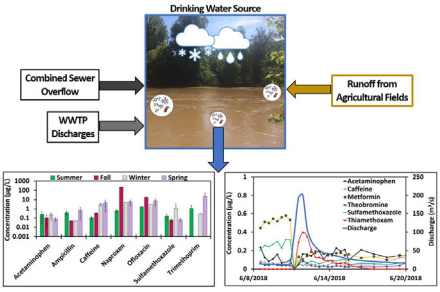
HIGHLIGHTS

- Common human pharmaceuticals were detected in >80% of drinking water source samples.
- EOCs occurred at higher concentrations in colder rather than warmer months.
- Concentration-discharge (C-Q) relationships helped to classify transport dynamics.
- C-Q relationships identified likely sources and pathways contributing to EOCs.
- Observed EOCs posed high risks to aquatic organisms but not to human health.

GRAPHICAL ABSTRACT



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ABSTRACT

Occurrence of emerging organic contaminants (EOCs) in surface water bodies can cause adverse effects on non-target organisms. When surface waters are used as drinking water sources, temporal variability in EOC concentrations can potentially impact drinking water quality and human health. To better understand spatiotemporal variability of EOCs in drinking water sources in Central Pennsylvania, EOCs were evaluated in six drinking water sources during a two-year study period (April 2016–June 2018) in the Susquehanna River Basin (SRB). The study was conducted in two phases: Phase I was a spatially distributed sampling approach within the SRB focusing on seven human pharmaceuticals and Phase II was a temporally intensive sampling regime at a single site focusing on a broader range of EOCs. Concentration-discharge relationships were utilized to classify EOC transport dynamics and understand the extent to which hydrologic and anthropogenic factors, such as surface runoff and wastewater effluent, may contribute to EOC occurrence. Overall, EOCs were present at higher concentrations in colder seasons than warmer seasons. Thiamethoxam, a neonicotinoid insecticide, and caffeine exhibited accretion dynamics during high-flow periods, suggesting higher transport during surface runoff events.

Abbreviations: EOCs, Emerging organic contaminants; PPCPs, Pharmaceuticals and personal care products; LOD, Limit of detection; LOQ, Limit of quantification; WWTPs, Wastewater treatment plants; CSO, Combined sewer overflow; RQ, Risk quotient; PNEC, Predicted no effect concentration; BCF, bioconcentration; BMF, biomagnification; TOC, Tortal organic carbon; SRB, Susquehanna River Basin; CV, Coefficient of variation; C-Q, Concentration-discharge.

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Seasonal variations
Ecological and human health risk

Human pharmaceuticals known to persist in wastewater effluent were inversely correlated with discharge, indicating dilution characteristics consistent with diminished wastewater signals during high-flow periods. Acetaminophen exhibited near-chemostatic transport dynamics, indicating nonpoint source inputs during high-flow periods. Risk calculations revealed that although EOCs posed medium-to-high risk to aquatic organisms, human health risk through fish consumption was low.

1. Introduction

Understanding natural and anthropogenic drivers influencing surface water quality in drinking water sources is critical to protecting ecological and human health. Most emerging organic contaminants (EOCs) currently lack water quality standards in natural and engineered systems despite known environmental impacts ranging from persistence, bioaccumulation, toxicity, endocrine disrupting potential on sensitive non-target organisms, and antibiotic resistance (Boxall et al., 2012; Ebele et al., 2017; Leet et al., 2011; Scott et al., 2016).

Widespread occurrence of EOCs in aquatic ecosystems is affected by proximity to human, agricultural, and industrial wastewater sources (Kolpin et al., 2002; Bradley et al., 2017; Zhang et al., 2016a,b). Furthermore, EOCs exhibit temporal variations associated with seasonal and demographic factors influencing consumer use and disposal patterns of pharmaceuticals and personal care products (PPCPs) (Glassmeyer et al., 2009; Vatovec et al., 2016; Yu et al., 2013), wastewater treatment plant (WWTP) removal efficiencies (Hedgespeth et al., 2012; Sun et al., 2016), and land applications of manure, biosolids, and pesticides (Bernot et al., 2013; Healy et al., 2017). Observed temporal fluxes in surface water are influenced by seasonal hydroclimatic patterns resulting in either dilution (Reif et al., 2012; Lei et al., 2019) or contaminant mobilization from diffuse nonpoint sources (Benotti and Brownawell, 2007; Tran et al., 2019). Thus, EOC occurrence in surface water sources is not only influenced by point and nonpoint sources, but also hydroclimatic variability throughout the watershed that can induce a range of contaminant transport responses.

Contaminant transport as a function of hydroclimatic conditions and subsequent impact on surface water quality is largely understood for conventional pollutants such as nutrients, suspended sediments, and pathogens (e.g., *Cryptosporidium parvum* and *Escherichia coli*). However, few studies focus on EOC variability as a function of streamflow conditions (Benotti and Brownawell, 2007; Launay et al., 2013; Pailler et al., 2009; Zhang et al., 2016a,b) primarily due to higher EOC analytical costs in comparison to conventional water pollutants and quality parameters. Moreover, studies examining EOC variability over seasons or hydrologic conditions generally conduct minimal sampling campaigns that are likely not fully representative of the range of seasonal and hydrologic variability (Cantwell et al., 2018; Loraine and Pettigrove, 2006; Mijangos et al., 2018; Moreno-González et al., 2013), while studies conducting rigorous sampling focus on trends at a few locations, potentially limiting generalizability of findings (Gall et al., 2011; Pailler et al., 2009).

EOC transport dynamics during high and low streamflow conditions are compound and site specific. Launay et al. (2013) investigated pollution dynamics in a catchment in Germany influenced by urban runoff and reported caffeine, N, N-Diethyl-m-toluamide (DEET), 2-methylthio-benzothiazole (MTBT), and carbamazepine concentration increases during high-flow conditions associated with combined sewer overflow (CSO) events. In an estuary in Jamaica Bay, NY, caffeine, codeine, cotinine, sulfamethoxazole, and trimethoprim exhibited lower concentrations following wet weather events, while acetaminophen and nicotine concentrations remained relatively constant in dry and wet weather conditions (Benotti and Brownawell, 2007). Therefore, understanding dominant drivers of temporal variations of EOCs in impacted surface water is essential for ecological and human health risk characterization, for estimating influent loads to drinking water treatment plants, and for designing best management practices to reduce EOC occurrence in the environment.

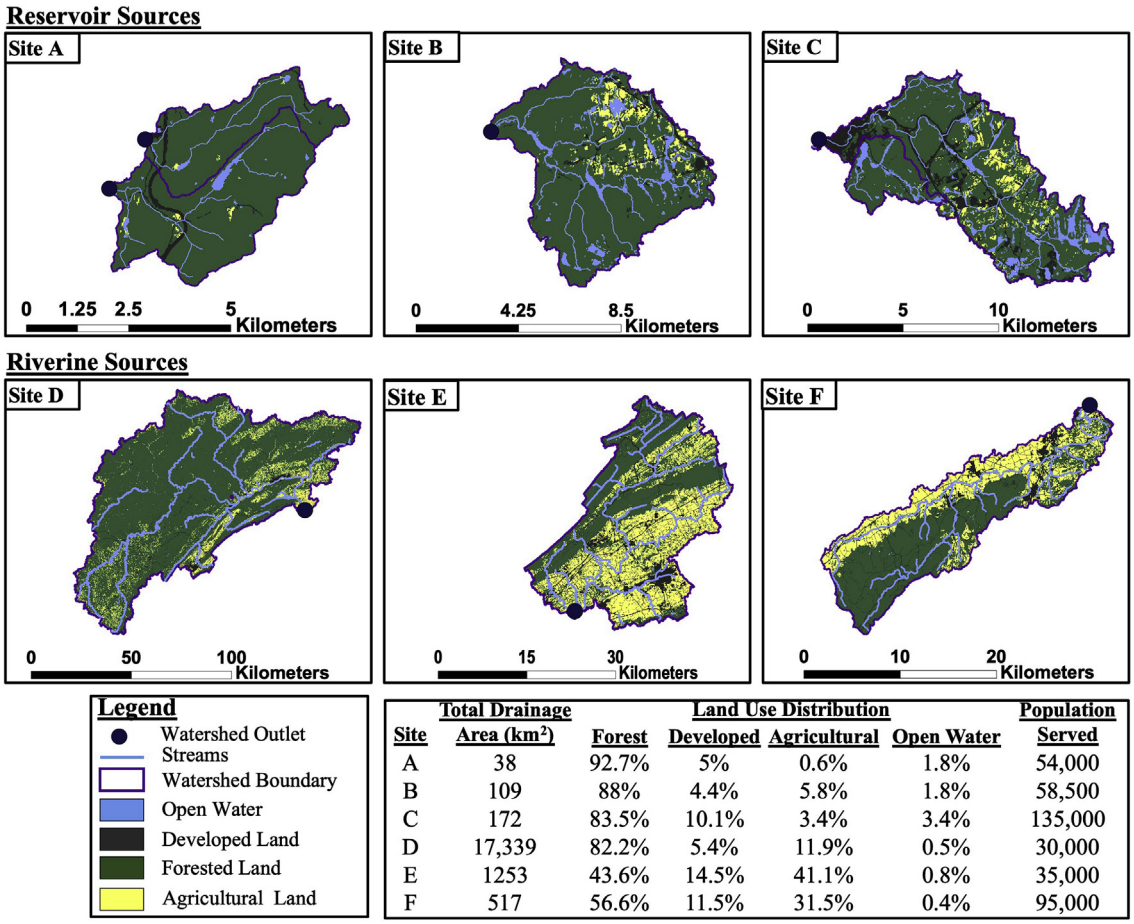
This study evaluated spatial and temporal variations of EOCs at six surface drinking water sources in the Susquehanna River Basin (SRB). Sampling was conducted in two phases: Phase I was spatially distributed within the SRB and Phase II was a temporally intensive sampling regime at one site focusing on a broader range of EOCs. Concentration-discharge (C-Q) relationships were developed to evaluate influences of hydrologic drivers on EOCs and variability as a function of flow conditions. Results were used to understand the role of various anthropogenic sources, in EOC occurrence in aquatic environments. Risk assessments were conducted to understand potential aquatic and human health risks posed by detected EOCs.

2. Methodology

2.1. Site description

In collaboration with PA American Water company, six drinking water sources located in mid-to-upper and mid-to-lower regions of the Susquehanna River Basin (SRB) were selected as study sites. With a generally gently rolling to hilly terrain, the Susquehanna River Basin is the largest sub-watershed of the Chesapeake Bay, supplying ~50% of its fresh water (Zhang et al., 2010). The climate of the region is humid, with an average annual precipitation of ~1000 mm/yr and an annual average air temperature of ~14 °C. Discharge in the Susquehanna River is greatest in the spring season due to contributions from snowmelt and rainfall, while flow in the drier winter months consists primarily of baseflow contributions.

Sampling locations are confidential drinking water intakes each serving as drinking water sources for 50,000–135,000 people. Sites A, B, and C are reservoir sources while D, E, and F are riverine sources. The land use distributions and drainage areas in the surface watersheds of the study sites are provided in Fig. 1. In brief, the land use composition varied between the sites with sites E and F containing substantially more agricultural land than other sites; sites C, E, and F containing roughly double the percentage of developed land as sites A, B, and D; while Sites E and F had the lowest forested land cover (Fig. 1). Stormwater and wastewater within the studied watersheds are nearly all separate systems; however, some of the older municipalities have combined sewer systems, with site D's watershed containing 4 combined sewer system outfalls. Other sources of EOCs include onsite wastewater systems in highly forested areas that are not served by a municipal wastewater treatment plant (WWTP). The watersheds for sites D and E are the only watersheds that contain municipal WWTPs, with 10 in the watershed for site D and 2 in the watershed for site E.



Site	Total Drainage Area (km²)	Land Use Distribution				Population Served
		Forest	Developed	Agricultural	Open Water	
A	38	92.7%	5%	0.6%	1.8%	54,000
B	109	88%	4.4%	5.8%	1.8%	58,500
C	172	83.5%	10.1%	3.4%	3.4%	135,000
D	17,339	82.2%	5.4%	11.9%	0.5%	30,000
E	1253	43.6%	14.5%	41.1%	0.8%	35,000
F	517	56.6%	11.5%	31.5%	0.4%	95,000

Fig. 1. Land use maps and site characteristics of study sites in the Susquehanna River Basin.

2.2. Sample collection

This study was conducted in two phases. Phase I (April 2016–December 2017) was spatially distributed whereby grab water samples were collected at monthly and bimonthly intervals from all six sites and samples from each set of source type (riverine and reservoir) were collected on the same day. This sampling method was selected to provide a snapshot of seasonal fluctuations of EOCs in drinking water sources. All samples were collected in 250 mL amber glass bottles with polytetrafluoroethylene (PTFE)-lined caps following EPA method 1694 (US EPA, 2007). Water quality indicators including temperature, pH, conductivity, and dissolved oxygen were recorded *in-situ* using calibrated handheld meters. Natural organic matter in source water was characterized in terms of total organic carbon (TOC). TOC samples were collected in 250 mL clear polyethylene terephthalate (PET) bottles and analyzed at Penn State Institutes of Energy and the Environment (PSIEE) Water Quality Laboratory in University Park, PA.

In Phase II (January–June 2018), time-weighted discrete sampling as a function of discharge was conducted to evaluate concentration variation with changes in flow conditions. This sampling regime was conducted at site E, which had the greatest percentages of developed and agricultural land as well as 2 WWTPs upsteam of the DWTP intake. An automated ISCO 3700 sampler fitted with twenty-four 350 mL glass bottles was programmed to collect stream water samples at 3–12 h intervals depending on flowrate when sampling commenced. Sampling dates and times were determined using near-real time United States Geological Survey (USGS) streamflow data from a USGS station located ~10 km upstream from site E. A Campbell Scientific Inc. CR850 datalogger equipped with water level, temperature, dissolved oxygen, and pH sensors was deployed and programmed to scan each sensor every second and store averages every 60 min. Water level measurements were correlated (R^2 = 0.9) with reported USGS discharge data. Samples to assess concentrations during baseflow conditions were collected following a short dry spell of no recorded precipitation (rainfall or snowfall) for at least 3 d prior to storm sampling, as the average time between precipitation events in PA is 3 d. Storm samples were collected during high-flow events in the upper 20th percentile. All samples were preserved on ice during transportation to laboratories and stored at 4 °C before processing within 48 h of collection. Samples for EOCs were analyzed at the United States Department of Agriculture-Agricultural Research Service (USDA-ARS) laboratory.

2.3. Sample processing and targeted analysis of EOCs

In Phase I, all water samples were analyzed for seven human pharmaceutical compounds, including four antibiotics (ampicillin, sulfamethoxazole, ofloxacin, and trimethoprim), two analgesics (acetaminophen and naproxen), and a stimulant (caffeine). These compounds have a wide range of physico-chemical properties (Table S1) and are representative of a broader array of PPCPs. Caffeine and acetaminophen were included due to common household usage and their utility as human wastewater indicators. Along with sulfamethoxazole and trimethoprim, these compounds

are among the most frequently detected in PA waters (Reif et al., 2012). However, ampicillin, naproxen and ofloxacin remain understudied.

In Phase II, 13 more compounds, including human and veterinary antibiotics (chlortetracycline, tetracycline, oxytetracycline, erythromycin, sulfadiazine, sulfadimethoxine, sulfamethazine, and tylosin), an antimicrobial (triclosan), an antihistamine (cimetidine), an antidiabetic (metformin), a caffeine metabolite (theobromine), and a neonicotinoid insecticide (thiamethoxam) were targeted for analysis (Table S1). These compounds were selected based on standard availability and analytical capabilities, frequency of use, and an anticipated occurrence in surface water due to previously documented seasonal consumption and use patterns (Singer et al., 2014).

Samples were analyzed and quantified using a high-resolution accurate mass (HRAM) Q Exactive Orbitrap mass spectrometer (ThermoFisher Scientific, Bremen, Germany), interfaced to a chromatography system through a heated electrospray injection (HESI) source. The instrument was calibrated within a linear range of 0.1–500 μg/L using both isotope labelled and non-labelled aqueous standards. The limit of detection (LOD) and quantification (LOQ) was 0.01 μg/L (signal to noise ratio ≥3) and 0.1 μg/L (signal to noise ratio ≥10), respectively, for all compounds except ofloxacin, which had an LOD and LOQ of 0.3 μg/L and 3 μg/L, respectively. Analytes measured between LOD and LOQ were reported as LOQ/2. More details on analytical procedures are summarized in Kibuye et al. (2019a).

Field blanks were obtained by transporting two 500 mL bottles of Nanopure® water to each sampling site and transferring to a 250 mL amber glass sampling bottle. Each travel blank sample consisted of250 mL of Nanopure® water transported to sampling sites but not opened in the field. Detected EOCs in blanks were averaged and used to censor surface water concentrations.

2.4. Statistical analysis

Data analyses were performed using IBM SPSS Statistics version 23 (SPSS Inc., Chicago, Illinois, USA). A general linear model analysis of covariance (ANCOVA) was used to test for fixed effects of season and source water type on pharmaceutical concentrations and on the influence of five covariate variables: pH, water temperature, dissolved oxygen, conductivity, and TOC. ANCOVA assumptions were checked using Pearson's correlation analysis. Three covariates-water temperature, dissolved oxygen, and conductivity were significantly correlated ($\alpha = 0.01$) thus only water temperature, pH, and TOC were included in the ANCOVA model. To check for significance of source type and site differences, a one-way ANOVA test was performed. Further post-hoc analysis using Tukey's Honestly Significant Difference (HSD) test was applied when there was a significant difference between means. All statistical hypotheses were tested at $\alpha = 0.05$ except for Pearson's correlation tests, where $\alpha = 0.05$ and 0.01 were employed.

2.5. Concentration-discharge (C-Q) relationships and CV_C/CV_Q ratios

Relationships between concentration (C) and discharge (Q) were employed to characterize contaminant transport dynamics using a power-law relationship, $C = aQ^b$, where a and b are empirical constants (Vogel et al., 2005). When C and Q are plotted on a log-log scale, slopes (b values) can be used to characterize C-Q patterns (Vogel et al., 2005) as dilution ($b < 0$), accretion ($b > 0$), or chemostatic ($b \approx 0$) (Basu et al., 2010; Gall et al., 2015; Miller et al., 2019; Vogel et al., 2005). C-Q relationships were developed using concentrations > LOQ for the most frequently detected compounds in Phase II. To explore howconcentration and flow variability influenced contaminant transport, a ratio of coefficients of variation (CV) for concentration (CV_C) and flow (CV_Q) was employed following Thompson et al. (2011). A high CV_C/CV_Q ratio occurs when concentration variability is greater than flow variability, while a low ratio indicates large flow variability and small concentration variability (Gall et al., 2013; Thompson et al., 2011). Thompson et al. (2011) further suggested a CV_C/CV_Q <0.3 as a nonparametric indicator of chemostatic dynamics ($b \approx 0$), in which concentration variability is sufficiently small that flow variability emerges as the dominant drive of contaminant transport, while ratios >0.3 indicate episodic transport dynamics, in which concentration and flow variability are important.

2.6. Ecological risk calculations

To estimate environmental risk posed by measured EOCs in aquatic systems, risk quotients (RQs) were calculated for representative trophic levels including algae, *Daphnia*, and fish. Predicted no effect concentration (PNEC) of EOCs were estimated using literature-derived acute toxicity data for algae, *Daphnia*, and fish by dividing EC50 or LC50 (concentrations at which 50% of population exhibits a response or dies, respectively; Table S1) by an assessment factor of 1000. RQs associated with respective EOCs were calculated by dividing average measured environmental concentrations (MECs) by corresponding estimated PNEC values (Sanderson et al., 2003).

$$PNEC\left(\mu g\ L^{-1}\right) = \frac{EC_{50}}{1000} \quad (1)$$

$$RQ = \frac{MEC}{PNEC} \quad (2)$$

Calculated risk quotients for individual compounds (RQ_j) were summed to estimate a total RQ (RQ_T), as:

$$RQ_T = \sum_j RQ_j \quad (3)$$

Relative risk contributions of individual EOCs at any given time were estimated for seven EOCs in Phase I and 20 EOCs in Phase II, as follows (Ginebreda et al., 2010):

$$Relative\ Risk\ Contribution\ of\ EOC_j(\%) = \frac{RQ_j}{RQ_T} \times 100 \quad (4)$$

2.7. Human health risk calculations

A human health risk assessment via fish consumption was performed using average concentrations measured in Phase I. Concentrations in fish tissue were predicted as (Muñoz et al., 2010):

$$C_{fish} = C_{Water} \times BCF_{fish} \times BMF_{fish} \quad (5)$$

where C_{fish} is the predicted concentration in fish ($\mu g kg^{-1}{}_{wt}$), BCF ($L kg^{-1}_{wt}$) and BMF (dimensionless) are bioconcentration and biomagnification factors in fish, respectively. BCF was calculated using guidelines by the European Commission's Technical Guidance Document on Risk Assessment (European Commission, 2003) as:

$$Log(BCF) = 0.85 * Log(K_{ow}) - 0.7 \quad (6)$$

A BMF of unity was used for EOCs based on estimations from the European Commission (2003). Human exposure dose through

hypothetical consumption of fish from the studied surface waters was calculated as:

$$Dose\left(\mu g\ kg_{bw}{}^{-1}\ d^{-1}\right) = \frac{C_{fish} \times Intake_{fish}}{BW} \quad (7)$$

where C_{fish} is estimated concentration in fish, BW (60 kg) is 50th percentile adult body weight (de Jesus Gaffney et al., 2015), and $Intake_{fish}$ is the average fish consumption rate (0.02 kgd^{-1}) in the U.S. (National Marine Fisheries Service, 2015). RQs were calculated as ratios between doses and EOC acceptable daily human intakes (ADI) obtained from literature. RQs <0.1 and >1 indicate low and high risk, respectively, while RQs between 0.1 and 1 indicate moderate risk.

3. Results and discussion

3.1. Occurrence in the Susquehanna River Basin

During the study, EOC concentrations spanned one to two orders of magnitude. In Phase I, sulfamethoxazole (54%), acetaminophen (42%), and caffeine (35%) were the most frequently detected, while trimethoprim, naproxen, ofloxacin and ampicillin were detected in <35% of samples (Fig. 2). Although among the least frequently detected, naproxen, ofloxacin and trimethoprim exhibited the highest average concentrations of 31.38, 9.95, and 3.28 μg/L, respectively (Fig. 2). Of the most frequently detected pharmaceuticals, caffeine had the highest average concentration (2.15 μg/L), while sulfamethoxazole and acetaminophen had lower average concentrations (0.73 and 0.20 μg/L, respectively). Ampicillin (0.26 μg/L) was the least frequently detected compound among the lowest mean concentrations.

In Phase II, the most frequently detected compounds were acetaminophen (89%), theobromine (89%), caffeine (87%), and metformin (84%) (Fig. 2). Thiamethoxam, naproxen and sulfamethoxazole were detected in 21%, 17%, and 16% of samples, respectively, as opposed to <2% for ofloxacin, oxytetracycline, tetracycline, tylosin, sulfadimethoxine, and sulfamethazine. Ampicillin, trimethoprim, triclosan, chlortetracycline, erythromycin, cimetidine and sulfadiazine were not detected in any sample.

The selected EOCs have been previously detected in surface water sources. A nationwide study investigating the occurrences of various EOCs in drinking water sources in the US reported a higher detection frequency in the surface water sources than groundwater sources and found that among highest detections in surface water sites were non-prescription drugs, antibiotics, and pesticides (Focazio et al., 2008). More recently, Bradley et al. (2017) monitored a comprehensive list of EOCs in 38 streams across the US and reported caffeine and metformin among the 10 most frequently detected organics present in 66–84% of all sites which is consistent with findings in this study. Reif et al. (2012) collected samples from streams used as drinking water sources in the state of Pennsylvania and found pharmaceuticals to be the most frequently detected class of EOCs with the most detected compounds being caffeine (71%), sulfamethoxazole (40%), acetaminophen (25%), and trimethoprim (8%). Similarly, average concentrations measured in the present study were within the same order of magnitude with the statewide study apart from concentrations measured in Phase I for ofloxacin and trimethoprim that were an order of magnitude higher. In general, human pharmaceuticals were detected at a higher frequency than veterinary antibiotics in Phase II of the current study. This can potentially be attributed to higher WWTP contributions compared to discharges from concentrated animal feeding operations (CAFOs) among other diffuse sources. In a stream influenced by CAFOs, Bernot et al. (2013) found veterinary antibiotics to be most abundant adjacent to the CAFO discharges but overall, higher detection frequencies for human than veterinary antibiotics were observed.

Although among the least frequently detected in Phase II (<2%), ofloxacin (3.16 μg/L), oxytetracycline (0.41 μg/L), tetracycline (0.39 μg/L), and tylosin (0.71 μg/L) exhibited the highest concentrations (Fig. 2). Most of these are veterinary antibiotics that were likely present due to intermittent precipitation events mobilizing them from diffuse agricultural sources via surface runoff (Bernot et al., 2013; Fairbairn et al., 2015), but their occurrence may have been influenced by factors including potential inputs from CAFOs, timing of precipitation events in relation to manure or biosolid applications, occurrence in applied manure, biodegradation rates or sorption potential, and timing of sampling events to capture nonpoint source inputs (Bernot et al., 2013).

3.2. Spatial variation and influence of source water type

No significant concentration variation ($p > 0.05$) among sites was observed. However, detection frequencies were correlated with dominant land use within watersheds. There were comparatively fewer detections at sites in watersheds with high (>83%) forested and low (<10%) urban and agricultural land uses (Fig. 3a). Similar findings were reported by Reif et al. (2012) and were associated with reduced point and nonpoint sources impacting water quality. However, variations in abundance of EOCs among the watersheds could also be due to other wastewater sources such as septic systems. Despite being one of the most forested watersheds (Fig. 1), site D exhibited moderately high concentrations and detection frequencies. This could be because the watershed contained 10 WWTP effluent discharge locations, as well as 4 combined sewer system outfalls. Forested land uses may also have an increased density of on-site domestic wastewater treatment systems, such as septic systems, acting as sources of EOCs to underlying aquifers (Conn et al., 2006; Del Rosario et al., 2014; Schaider et al., 2016). Kibuye et al. (2019b) detected various pharmaceuticals in private wells in central PA in areas dominated by forested land use. Surface water is known to be susceptible to EOC contamination from groundwater impacted by septic effluent (Standley et al., 2008).

In a study comparing occurrence of EOCs across a variety of drinking water sources, Wang et al. (2011) indicated that detection frequencies and measured concentrations were higher in riverine sources as opposed to lakes and reservoirs. However, in the current study there was no significant variations in detections between riverine and reservoir sources. Detection frequencies were >5% higher in riverine than reservoir sources for acetaminophen, ampicillin, caffeine, and sulfamethoxazole (Fig. 3b). Average concentrations for ampicillin and trimethoprim were higher in riverine than reservoir sources, while average concentrations of acetaminophen, caffeine, naproxen, and ofloxacin were similar across source types. Lower concentrations and detection frequencies in reservoir sources are attributed to higher forested land uses and lower agricultural and developed land uses within watersheds (Fig. 3a). Lower detection frequencies and concentrations in lakes and reservoirs have also been attributed to longer residence times that promote environmental attenuation, such as sorption to sediments and biodegradation (Glassmeyer et al., 2017). However, such attenuation processes are dependent on physico-chemical characteristics and overall EOC loading rates from point and non-point sources. Interestingly, only sulfamethoxazole had a statistically significant ($p < 0.05$) concentration variation between source types, with higher average concentrations in reservoir than riverine sources. In conjunction with detection frequencies, findings suggest sulfamethoxazole is continually entering surface water at low levels

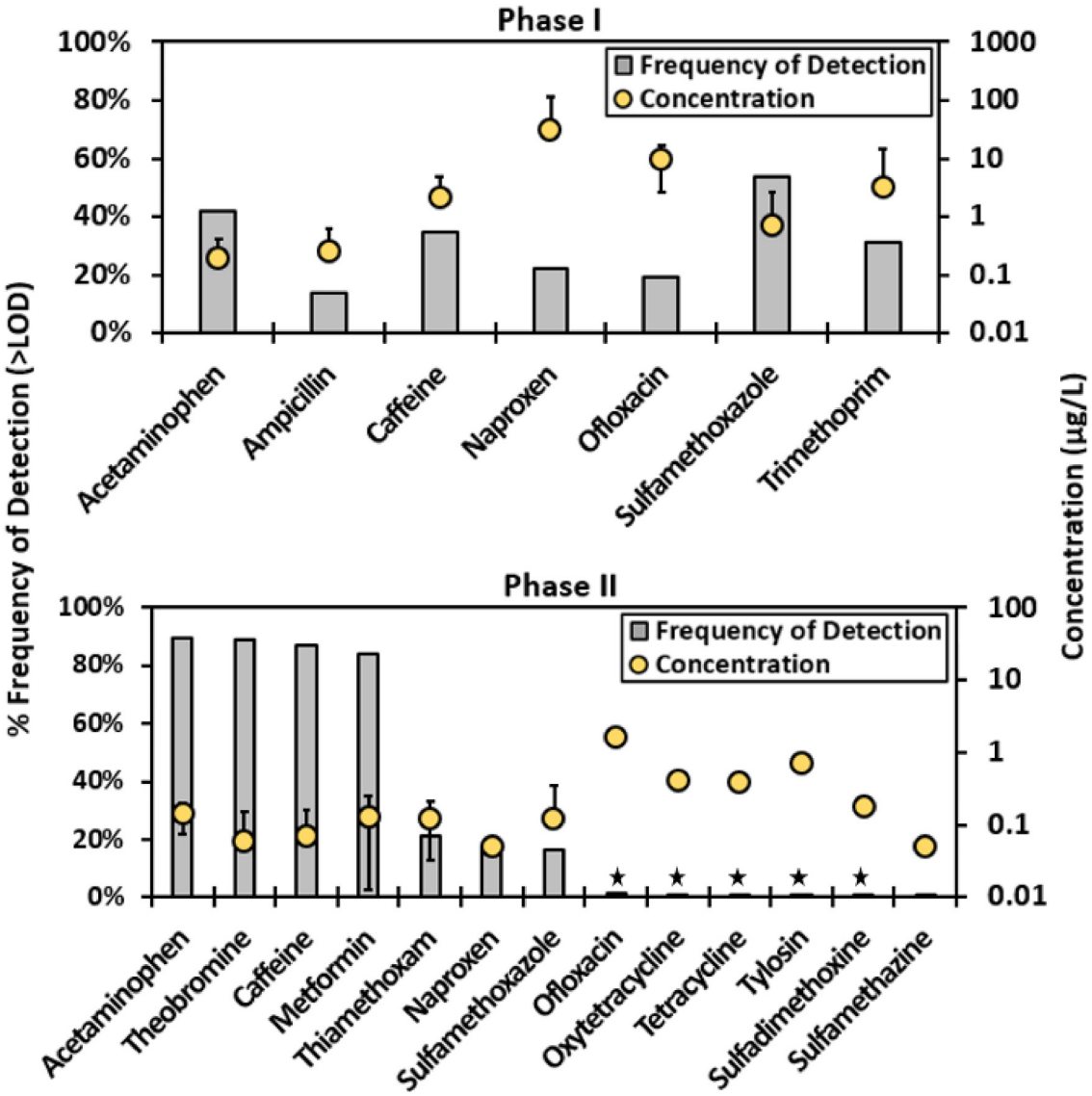


Fig. 2. Detection frequencies and mean concentrations > LOD in Phase I (n = 78) and Phase II (n = 161). Error bars represent standard deviations (although sometimes they are too small to extend beyond the symbol) and stars indicate EOCs detected > LOQ only once in Phase II.

but, due to its slow biodegradation rates in a water-sediment system (Xu et al., 2011), it can build up in lentic waters such as reservoirs.

3.3. Seasonal variations

Only acetaminophen, caffeine, naproxen, and sulfamethoxazole had statistically significant ($p < 0.05$) seasonal concentration variation in Phase I. The highest average concentrations were recorded in the winter, spring, fall and winter seasons, respectively for acetaminophen (0.29 µg/L), caffeine (2.39 µg/L), naproxen (160 µg/L), and sulfamethoxazole (3 µg/L). Ampicillin (0.36 µg/L) and trimethoprim (11.6 µg/L) depicted the highest averages in the spring while ofloxacin (15.8 µg/L) was highest in the fall. EOCs investigated in Phase I were human pharmaceuticals that were likely present in surface water largely due to wastewater discharges. Accordingly, higher surface water concentrations in the colder seasons (Fig. 4) have also been reported in other studies (Azzouz and Ballesteros, 2013; Hedgespeth et al., 2012; Wang et al., 2011; Mu et al., 2017) and is attributable to factors such as reduced WWTP removal efficiencies in the colder seasons (Hedgespeth et al., 2012; Kibuye et al., 2019a; Vieno et al., 2005) as well as increased consumer pharmaceutical use (Yu et al., 2013). Concentrations may also be higher due to environmental factors such as reduced in-stream dilution due to low stream flow conditions in winter (Reif et al., 2012; Wang et al., 2011), and lower in-stream microbial and photolytic degradation rates because of the low temperatures and reduced solar irradiation (Vieno et al., 2005). Since spring streamflow is often high due to regional snowmelt and high precipitation, higher concentrations in the spring may also be as a result of potential pharmaceutical inputs from CSO discharges along with surface runoff contributions from biosolids-amended soils. Baseflow contributions in the winter season may also result in inputs from groundwater impacted by septic systems.

Lower concentrations in the summer are attributed to lower consumption rates and faster in-stream degradation rates as opposed to lower degradation rates during peak consumer use in colder months (Vieno et al., 2005). Despite generally lower EOC concentrations in the summer months, detection frequencies were higher (Table S2). These sustained lower concentrations are

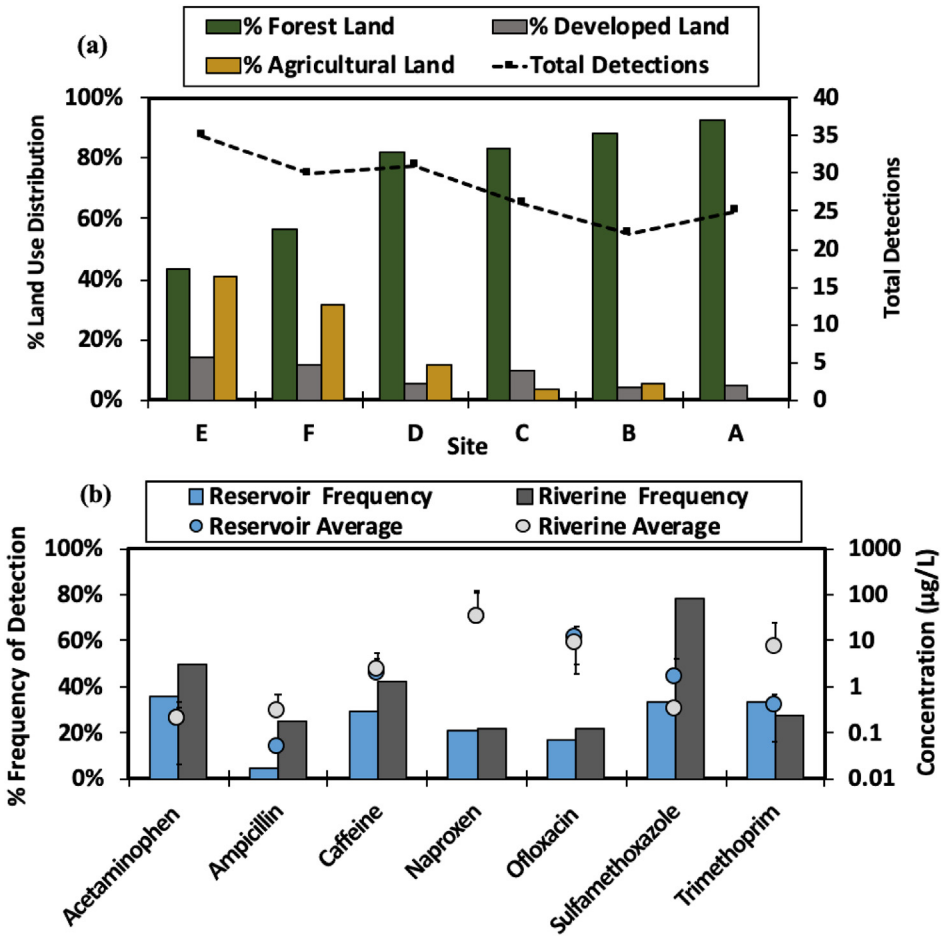


Fig. 3. (a) Total detection > LOD in samples collected in Phase I by land use distribution in respective study site watersheds; (b) Detection frequencies > LOD and mean concentrations by source water types (riverine and reservoirs) during Phase I. Error bars represent standard deviations.

consistent with groundwater sources, such as septic tanks, as well as low concentrations in wastewater effluent that are not diluted by large surface runoff events. Similar findings on detection frequencies were reported by Reif et al. (2012), such that antibiotics were detected at higher frequencies in PA waters during summer and fall which are periods of low, baseflow-dominated streamflow. Although sorption to sediment is a potential sink for EOCs in aquatic environments (Hajj-Mohamad et al., 2017; Kunkel and Radke, 2008; Xu et al., 2011), other studies have also identified sediment as sources of EOCs to water via desorption, depending on their degree of ionization in aqueous environments (Martínez-Hernández et al., 2014). Sorbed EOCs can further be remobilized especially during high flow events (Hajj-Mohamad et al., 2017), resulting in higher aqueous phase concentrations. Overall, the detection of selected EOCs throughout all sampling seasons (Fig. 4) can be seen as an indication of the pseudo-persistence of these chemicals due to a combination of sustained usage of some EOCs that are either consumed regularly (i.e., caffeine) or that treat chronic health conditions (i.e., painkillers and other prescription medications) and due to continuous release into aquatic environments from domestic and municipal wastewater sources, among other diffuse sources.

In Phase II, a wide variety of EOCs were analyzed (Fig. S1). Significant seasonal influences ($p < 0.05$) were observed for agricultural pesticide thiamethoxam which was predominantly detected in spring, reflecting its common use as a corn seed treatment. Higher mobilization from agricultural sources is also expected due to increased surface runoff events in the spring. Similarly, Gómez et al. (2012) reported significant increase in pesticide concentrations in May and June coinciding with peak application period in the watershed. The most frequently detected compounds acetaminophen (89%), theobromine (89%), caffeine (87%), and metformin (84%) exhibited insignificant seasonal variations ($p > 0.05$) as concentrations and detection frequencies were similar in winter and spring (Table S3; Fig. S1). Ofloxacin was detected once in spring and winter; however, it was present at a higher concentration in winter consistent with observations from Phase I. Oxytetracycline, tetracycline, tylosin, sulfadimethoxine, and sulfamethazine were only detected in winter and were present in <2% of samples.

3.4. Concentration-discharge (C-Q) relationships

Metformin and sulfamethoxazole exhibited dilution responses ($b < 0$), with inverse relationships between concentration and discharge (Figs. 5, S2, S3, & S4). Metformin and sulfamethoxazole are human pharmaceuticals with low WWTP removal efficiencies (Blair et al., 2013; Benotti and Brownawell, 2007; Kibuye et al., 2019a). Therefore, higher inputs from WWTP effluent are expected relative to other pharmaceuticals. Consequently, metformin and sulfamethoxazole exhibited higher surface water concentrations during low-flow conditions when wastewater effluent contribution to total streamflow is greater. Similar findings were reported in an estuary where sulfamethoxazole concentrations decreased with increasing flow (Benotti and Brownawell, 2007)

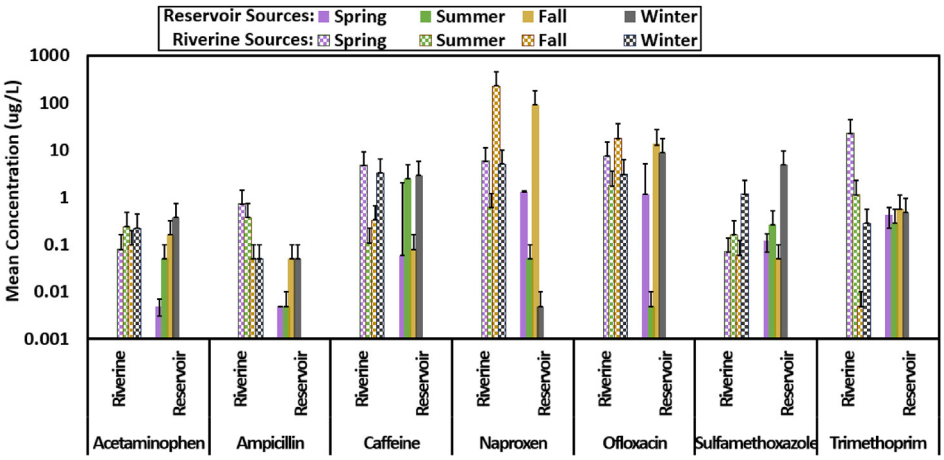


Fig. 4. Seasonal variations in mean concentrations in samples collected in Phase I by source water types (riverine and reservoirs). Concentrations > LOD and <LOQ are reported as LOQ/2.

and in a statewide study in PA where detection frequencies decreased during high-flow conditions (Reif et al., 2012). Furthermore, a model by Benotti and Brownawell (2007) concluded pharmaceuticals with low removal extent in WWTPs are diluted during wet weather indicating wastewater dilution by storm runoff is a major process controlling transport. EOCs can often be remobilized during high flow events to increase surface water level. Desorption studies for sulfamethoxazole by Martínez-Hernández et al. (2014) reported sorption irreversibility at environmentally relevant pH values, suggesting remobilization during high-flow events may be a contributing factor to the dilution trends observed.

Thiamethoxam, a neonicotinoid insecticide used to control a broad spectrum of crop insects, and caffeine indicated accretion patterns ($b > 0$) since concentrations increased with increasing flow (Fig. 5). Nonpoint source contaminants, including veterinary pharmaceuticals and pesticides, occur in surface water sources at higher frequencies and concentrations during periods coinciding with increased application and precipitation (Gómez et al., 2012). Similarly, insect repellant DEET and fungicide MTBT had the highest concentrations in an urban catchment in Germany following storm events (Launay et al., 2013). Observed accretion dynamics for nonpoint source contaminants were consistent with observations in other watersheds that have found surface runoff as the major transport pathway into surface water sources (Fairbairn et al., 2015; Gómez et al., 2012; Launay et al., 2013).

Caffeine concentrations are reported to increase with flowrates (Benotti and Brownawell, 2007; Buerge et al., 2006; Launay et al., 2013), which is consistent with the accretion dynamics ($b > 0$) observed in this study. The typically high removal efficiency for caffeine through WWTPs during baseflow is reduced during high-flow conditions when residence time through WWTPs is decreased (Phillips et al., 2012). Additionally, stormwater dilution effects are offset by contributions from other sources withn the watershed. When identifying EOC sources in a watershed in Southeastern Minnesota, Karpuzcu et al. (2014) concluded potential caffeine contributions from runoff across biosolid amended soils since caffeine couldn't be linked to one dominant land use in the watershed. Furthermore, an in-stream profile of caffeine in a mixed land use watershed suggested that the temporal variations of its concentrations reflected a mixed source pattern characteristic of runoff contributions in addition to WWTP effluent (Fairbairn et al., 2015). Caffeine is positively charged at environmentally relevant pH values; therefore, its sorption to sediments is enhanced by electrostatic interactions (Lin et al., 2010). Since sediments act as sinks for caffeine in aqueous environments, desorption can result in increased aqueous phase concentrations (Martínez-Hernández et al., 2014), especially during high-flow periods when sediments can act as a source due to remobilization of sorbed species because of flushing from stormwater (Hajj-Mohamad et al., 2017). The caffeine metabolite, theobromine, exhibited a weak C-Q relationship ($b = 0.05$) and a high CV_C/CV_Q ratio (0.82), suggesting that flow variability is the dominant driver of the observed transport dynamics (Thompson et al., 2011). As a caffeine metabolite, chemical and environmental factors affecting metabolite formation processes can further influence theobromine's concentration.

No strong C-Q relationship was observed for acetaminophen, as reflected by a near-zero slope (Fig. 5). The lowest CV_C/CV_Q ratio of the selected EOCs suggests that its transport was the least influenced by concentration variability since it was measured within similar ranges during both low and high-flow periods. However, other studies have reported increases in acetaminophen concentrations during high-flow periods (Buerge et al., 2006; Launay et al., 2013; Reif et al., 2012). Such variations may be due to differences in site and flow characteristics between studies. Since acetaminophen is efficiently removed in WWTPs, inputs from untreated sources including CSOs (Benotti and Brownawell, 2007) and runoff from biosolid amended soils (Karpuzcu et al., 2014) during high-flow conditions likely offset the dilution effect from stormwater by contributing to maintain relatively constant concentrations for acetaminophen. Benotti & Brownawell (2007) reported similar findings indicating that acetaminophen levels remained relatively constant in an estuary during both dry and wet weather monitoring. Similarly, in a study to characterize how land use, and seasonal and hydrologic factors influence instream profile of EOCs, Fairbairn et al. (2015) found that acetaminophen depicted mixed-transport characteristics such that concentrations were influenced by a variety of other diffuse sources in addition to WWTP effluent. Although sorption to sediments is considered a negligible sink for acetaminophen (Lin et al., 2010), acetaminophen sorbed to sediments can also be remobilized during high flow events (Hajj-Mohamad et al., 2017).

3.5. Ecological and human health risk assessment

In Phase I, naproxen and ofloxacin posed high risk ($RQ > 1$) to fish, *Daphnia*, and algae in riverine and reservoir sources, while acetaminophen and sulfamethoxazole generally posed low risk ($RQ < 0.1$) (Table S4). Moreover, highest RQs were observed in fall,

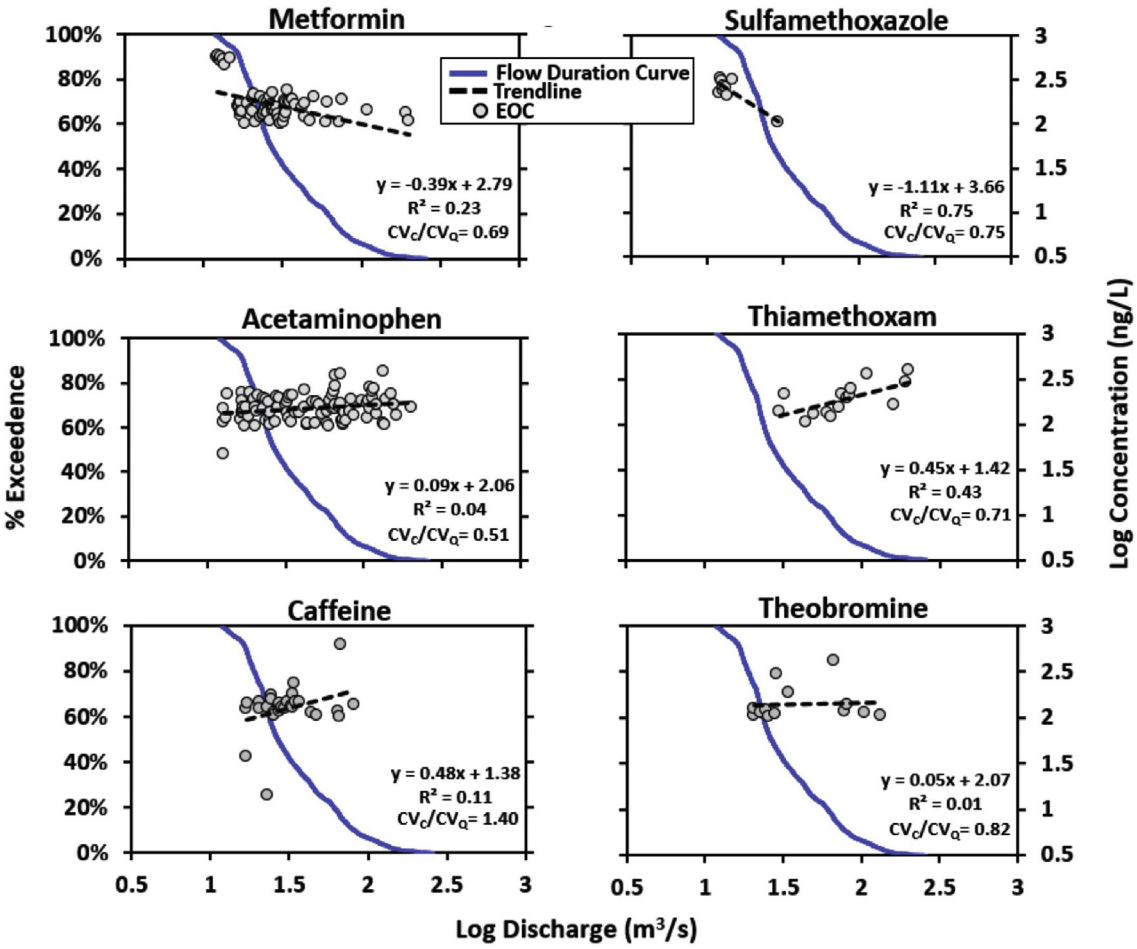


Fig. 5. Concentration-discharge (C–Q) relationships for EOCs present > LOQ at site E plotted with a flow duration curve. CV_C and CV_Q represent coefficients of variation for EOC concentration and discharge, respectively.

winter, and spring, in similarity with relatively high concentrations measured during these seasons (Table S4). In Phase II, calculated RQs per compound for fish, *Daphnia*, and algae were low (RQ < 0.01) consistent with relatively lower concentrations measured in comparison to Phase I. The highest RQs for fish, *Daphnia*, and algae were for ofloxacin (RQ = 0.023), thiamethoxam (RQ = 0.021), acetaminophen (RQ = 0.02), and tylosin (RQ = 20.74); respectively (Table S5). Although using seasonal averages is an adequate indicator of relative risk posed by EOCs, the RQ index doesn't provide information on the degree of potency on a temporal scale which is an important factor since organisms respond differently to acute and chronic exposures. For instance, toxicity studies on the antibiotic ciprofloxacin found no acute toxicity to fish, however chronic exposure of *Daphnia* to ciprofloxacin resulted in impairments on growth and reproduction ages that affect the maintenance of the natural populations (Martins et al., 2012).

For Phase I, naproxen and ofloxacin contributed to most of the total risk to all three non-target species (Fig. 6). For Phase II, the major contributions to risk for fish, *Daphnia*, and algae were attributable to thiamethoxam, acetaminophen, and tylosin, respectively. Since RQs are calculated as a function of measured concentrations and corresponding PNEC, EOCs measured at the highest concentrations and those with relatively lower PNECs posed the highest risk levels. Therefore, significant differences seen in relative risk contributions of EOCs between Phase I and II of sampling were due to temporal variations in the detection and measured concentrations of EOCs. Similarly, for both sampling phases, percent contributions for each EOC varied seasonally, reflecting seasonal risk dynamics to aquatic species. During Phase II, the major contributions for fish were attributable to thiamethoxam and were highest in May and June. This suggests a high relative risk during the spawning and early developmental period for fish populations in the Northeastern U.S. Laboratory toxicity tests have revealed thiamethoxam posed early life stage toxicity with endpoints including egg hatching, mortality, and growth rate (Finnegan et al., 2017). Higher exposure concentrations and subsequent risks are also anticipated during this period as high concentrations are transported to streams due to increased agricultural use and more surface runoff events in the spring.

Human health RQs were calculated for Phase I samples and most EOCs posed low human health risk (RQ < 0.01) through fish consumption (Table S6). The highest RQ corresponds to naproxen (RQ = 0.2), which had the highest bioaccumulation factor in fish (100 Lkg_{wt}^{-1}) and was measured at the highest concentrations in surface water samples collected in Phase I. However, the human health risk assessment is limited due to empirical estimations of human exposure through fish consumption and since the calculated RQs do not include low-level chronic exposure that may occur through other exposure pathways. Other exposure routes, such as drinking water and consumption of agricultural produce (Kibuye et al., 2019a; Prosser and Sibley, 2015; Schwab et al., 2005), can also contribute to overall risk. Although earlier studies have

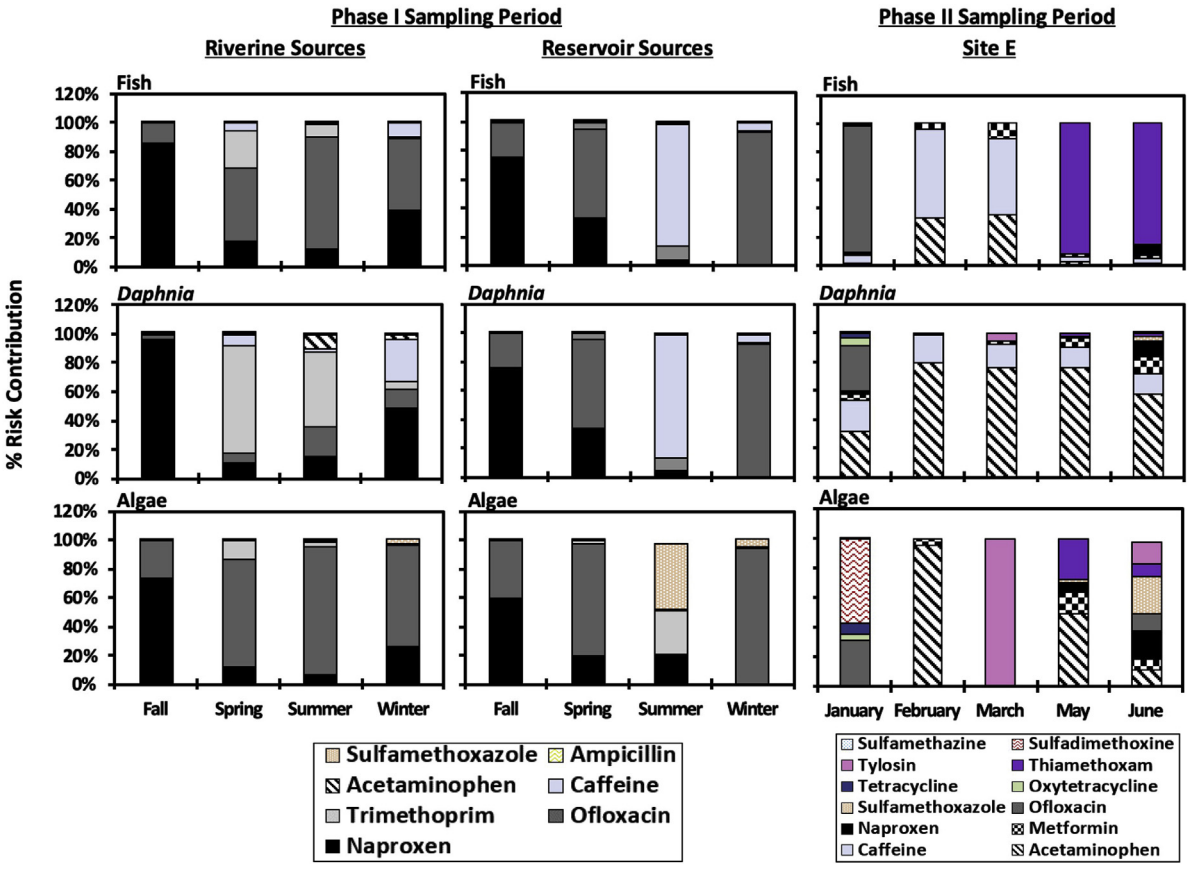


Fig. 6. Relative Risk contributions (%) of each EOC to overall risk quotients for fish, *Daphnia,* and algae.

concluded such exposure routes also pose minimal risks to human health (de Jesus et al., 2015; Prosser and Sibley, 2015), there are concerns regarding the potential additive or synergistic effects on human health from mixtures of EOCs originating from multiple exposure routes (Bull et al., 2011). Furthermore, the associated risks to sensitive populations are not known.

4. Conclusion

Twenty EOCs were evaluated to determine how seasonality, hydrologic conditions, and source water type influenced concentrations in six drinking water sources during a two-year period in the SRB. Acetaminophen, caffeine, and sulfamethoxazole, three human pharmaceuticals commonly associated with WWTP inputs, were spatio-temporally ubiquitous as they were consistently among the most abundant across seasons and source water types. However, higher concentrations were recorded in colder seasons corresponding to high consumer use and lower environmental attenuation rates. No significant variations in concentration among sites were observed; however, EOC occurrences were generally lower in reservoir than riverine sources likely due to higher forested land use and increased residence times for natural attenuation in reservoir source sites.

Although flow is thought to be a major factor influencing EOCs in surface water, few studies have focused on the variability of EOC concentrations as a function of flow. Our results found that WWTP-associated EOCs with consistent loading to aquatic systems, including metformin and sulfamethoxazole, depicted dilution dynamics, since WWTP signals are diminished during high-flow periods. In contrast, EOCs from agricultural sources, such as thiamethoxam, exhibited accretion responses, with elevated concentrations during higher flow conditions, as the dominant transport pathway is surface runoff. Although caffeine and acetaminophen are generally removed fairly well through WWTPs, their elevated or sustained concentrations, respectively, during high-flow events suggest potential additional sources, such as enhanced connectivity to diffuse sources of EOCs in shallow lateral flow (i.e., septic tank leach fields), surface runoff from biosolids-amended fields, and desorption from streambed sediments.

Our findings indicate significant influence of streamflow conditions on EOCs, which should be considered when estimating or modeling EOC levels in drinking water intakes, as well as when designing best management practices to reduce EOCs in aquatic systems. Since this study only focused on aqueous phase concentrations, we cannot assess the potential sediment-bound contributions to concentrations that may be present in high and low flow conditions. While further research is necessary to quantify the contributions of various sources and pathways for EOCs in the watershed, this C-Q analysis provides insight into the potential importance of each pathway during different times when various sources and pathways may be most active in influencing the presence and concentrations of EOCs in surface water bodies. The risk assessments conducted for this study found that although EOCs in aquatic systems posed minimal human health risk through fish consumption, risk quotients were mostly moderate to high (>0.1) for aquatic organisms and depicted temporal variations that highlighted potential for aquatic organism risks to be greatest during time periods most important for critical developmental stages (e.g., spawning).

Author contributions statement

Faith A. Kibuye: Conceptualization, Methodology, Field Work, Writing – Original draft preparation. Heather E. Gall: Supervision, Conceptualization, Data analysis, Writing-Original draft preparation. Tamie L. Veith: Supervision, Data analysis, Writing – Reviewing and editing. Kyle R. Elkin – Methodology, Data analysis. Herschel A. Elliott – Supervision, Conceptualization, Writing – Reviewing and editing. Jeremy P. Harper – Methodology, Field work. John E. Watson – Supervision, Conceptualization, Writing – Reviewing and editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2019.125583.

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