ABSTRACT

Timing Matters: Defining Temporal Occurrence and Associated Water Quality Hazards for Contaminants of Emerging Concern in Municipal Effluent

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To understand environmental hazards and risks posed by contaminants of emerging concern (CECs) it is imperative to define the magnitude, frequency and duration of exposure, because temporal variability of CECs from effluent discharges remain relatively unstudied. The primary objective of the current study was to understand temporal variability of the occurrence and hazards associated with targeted pharmaceuticals in effluent discharges over a one-year period. Though assessment of water quality is often targeted during summer months in some regions, significant ($p<0.05$) temporal variability of occurrence and associated hazards of target analytes were observed during other times of the year. Based on the compounds we selected and a recommended safety factor, water quality hazards to aquatic organisms exceeded therapeutic hazard ratios for all compounds examined except for acetaminophen, caffeine, and ketamine. However, antibiotics did not exceed resistance selection thresholds. These results suggest effluent discharges of CECs should be examined across seasons.

Timing Matters: Defining Temporal Occurrence and Associated Water Quality Hazards for Contaminants of Emerging Concern in Municipal Effluent

by

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A Thesis

Approved by the Department of Environmental Science

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CHAPTER ONE

Pharmaceutical Variability in Wastewater Effluent and Associated Hazards

Introduction

The occurrence and effects of pharmaceuticals and personal care products (PPCP) in the environment have been increasingly studied over the last decade [1]. Much uncertainty remains regarding effects of long-term, low level exposures to pharmaceuticals in the environment, and this knowledge gap has been identified as one of the top twenty most pressing research questions needed to understand environmental risks of PPCPs [2]. As point sources from wastewater treatment plants are the primary sources of PPCPs in the environment, the difficulties of determining the effects of therapeutics are compounded by the fact that concentrations of pharmaceuticals in wastewater effluent vary through time, to the point that conclusions regarding exposure estimates and potential hazards depend on when samples were collected [3]. Fluctuations in PPCPs introductions to receiving systems can be attributed to many sources, including treatment technologies, seasonal allergies, regional demographics and population changes [4,5], dilution, live entertainment events [6], drug marketing and societal acceptance [7], and other factors that may not yet be understood. Within any longer-term period of time, short term fluctuations occur on the order of minutes as human behavior dictates the release of pharmaceuticals and other down the drain chemicals to sewage and introduction to water reclamation systems [8].

Understanding environmental introduction concentrations (EICs) to surface waters at different temporal scales is critical to characterize the magnitude, frequency and duration of exposure and associated hazards and risks. Unfortunately, an understanding of the temporal variability of EICs of PPCPs is lacking. Only 35 studies in the literature studied the variability of PPCPs in wastewater effluent in terms of concentrations discharged to aquatic ecosystems (Table 1). Following a review of these 35 previous contributions, there remains limited resolution of EICs among temporal scales. For example, 22 studies examined seasonal variability, 6 explored monthly variability, 3 reported weekly variability, 4 studied daily variability, and 3 identified hourly variability of diverse target analytes. In fact, only 3 papers attempted to examine the influence of different temporal scales within the same study, and few attempted to translate such observations to estimate corresponding water quality hazards through time. Given such inconsistencies and associated gaps in available data, an understanding of the magnitude, frequency and duration of exposure, and hazards and risks associated with environmental discharges of pharmaceuticals remains elusive.

In arid and semi-arid regions of developed countries, chronic exposures to pharmaceuticals in effluent-dominated and dependent surface waters represent worst-case exposure and hazards for aquatic life [9]. A model was initially proposed by Huggett et al. [10] to prioritize pharmaceuticals for study by evaluating potential hazards to fish by estimating the concentration of pharmaceutical in fish blood plasma. This model was based on an empirical model of Fitzsimmons et al. [11] and was subsequently modified [12–14] to yield a therapeutic hazard value (THV) [15]. A THV can be interpreted as the concentration of a drug in water that may be expected to reach a mammalian therapeutic dose in fish plasma. To provide context for THVs for environmental monitoring, Gaw and Brooks [7] proposed therapeutic hazard ratios (THRs), which simply indicate if a measured concentration of a medicine is predicted to be potentially hazardous through time. However, THVs cannot be easily applied for antibiotics because these medicines target microorganisms. Bengtsson-Palme and Larsson [16] proposed a novel means of identifying environmental hazards posed by antibiotics, which estimates a concentration expected to promote evolution of antibiotic resistance. To translate antibiotic measurements to hazards during temporal water quality monitoring studies, in the present thesis I developed resistance hazard ratios (RHRs) to help understand if measured concentrations of antibiotics in effluent discharges have the potential to select for antibiotic resistance.

The goals of this thesis were to fill data gaps regarding the variability of EICs of select pharmaceuticals across different temporal scales, and to assess the corresponding variability of temporal hazards posed by these pharmaceuticals. This study investigated temporal scales of increasing resolution: seasonal, weekly, and daily periods. I then evaluated the critical monitoring period routinely employed by regulatory agencies to determine if samples collected during the summer months adequately characterize water quality hazards associated with pharmaceuticals entering aquatic systems. I hypothesized that concentrations of pharmaceuticals, other wastewater constituents and routinely water quality parameters would not significantly differ among seasons, between weekdays and weekends, and during different times of day.

Table 1. Review of studies assessing variability of PCPPs in wastewater effluent.

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Berset *et al.* (2010) [17]	Daily	Bern, Switzerland		Daily 24-hour composite samples	August 22nd - September 4th, 2009	Direct Injection HPLC-MS/MS	Benzoylecgonine increased slightly on Saturday and Sunday v. weekdays.
Pedrouzo *et al.* (2011) [18]	Daily	Vila-Seca, Spain	Mechanical treatment, biological treatment, chlorination, coagulation with Al_2SO_4 and flocculation, laminar clarification, and sand filtration	Daily 24-hour composite samples	November 2009	LC-MS/MS	No significant variability in tertiary effluent.
Repice *et al.* (2013) [19]	Daily	Verona, Italy	Primary settling, pre-denitrification, oxidation-nitrification, and secondary settling	24-hour composite samples	July 25th - August 9th 2010	HPLC-MS	Benzoylecgonine exhibited peaks on Saturday, Sunday, and Monday when compared to the rest of the week. Carbamazepine concentrations were stable throughout monitoring period.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Vatovec et al. (2016) [5]	Daily	Burlington, VT, USA		24-hour composite sample	May 1st - May 10th 2014	HPLC-MS/MS	Antihistamines increased over sampling period except for hydroxyzine. Omeprazole and esomeprazole increased over sampling period. Diltiazem, norverapamill, and atenolol increased over sampling period. Cotinine decreased over sampling period.
Anumol *et al.* (2016) [20]	Hourly	Chennai, India	Aerated lagoon; Clarification/ Flocculation; Filtration with chlorine addition	Bi-hourly grab samples	Early Summer 2014	LC-MS/MS	Sucralose increased around meal times. Caffeine spiked at 5 PM. Iohexol, TCPP, and acesulfame had fairly constant effluent concentrations.
Kanda *et al.* (2003) [21]	Hourly	United Kingdom	Conventional activated sludge process with trickling filters	Time weight composite samples	Late Autumn and Early Winter (2001)	GC-MS	Ibuprofen concentrations are higher during the middle of the day than during mornings and evenings.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Bahlmann *et al.* (2012) [22]	Monthly	Berlin, Germany	Conventional Activated Sludge Treatment	24 hour composite samples, many times a week, grab samples	March - August 2010	LC-MS/MS	Caffeine displayed no significant variability. Carbamazepine remained constant except for a spike in mid-May. Cetirizine had highest concentrations in mid-April and early May.
Choi *et al.* (2008) [23]	Monthly	Seoul, South Korea	All employ secondary treatment with activated sludge	Monthly grab samples	April, June, and August 2005	LC-MS	Caffeine concentrations were highest in June
Lacey *et al.* (2012) [24]	Monthly	Dublin, Ireland	Ringsend: Activated sludge and UV (summer months) Leixlip: Activated sludge Swords: Activated sludge	Monthly 24-hour composite samples	August 2007 - July 2008	LC-MS/MS	Cumulative effluent concentrations were lowest between November and February. Concentrations were also notably lower in September across all three plants.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Stamatis and Konstantinou (2013) [25]	Monthly	Agrinio City, Greece	Pre-treatment for solid and grit removal, anoxic tank, secondary conventional activated sludge biological treatment, secondary clarification tank, and tertiary treatment with sand filtration and a chlorination unit	Grab samples	April 2007 - May 2008	GC-MS	For tertiary effluent: Gemfibrozil and metabolite clofibric acid show no obvious trend throughout year. Paracetamol and metabolite salicylic acid decreased slightly in winter months. Diclofenac exhibits lower concentrations from May to August. Carbamazepine higher in May to July. Triclosan showed higher concentrations in spring and early summer.
Heffron *et al.* (2016) [26]	Monthly; Weekly	Charleston, IL, USA	Preliminary , primary, and secondary treatment, with aerobic an anaerobic digestion	Bi-weekly grab samples	January - December 2013	ELISA	Estradiol concentrations higher in Fall Semester (January, February, and March) than Summer or Spring Semesters.
Golovko *et al.* (2014) [27]	Seasonal	České Budějovice, Czech Republic	Biological activated sludge process with partial nitrification and thermophile anaerobic sludge stabilization	24-hour composite samples (collected every 15 minutes)	March 2011 - February 2012	LC-MS/MS	Antibiotics azithromycin, erythromycin, clarithromycin, trimethoprim, sulfamethoxazole, and sulfasalazine exhibited lower concentrations in the summer. Venlafaxine concentrations were highest in late fall/early winter.

Table 1 (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Hedgespeth *et al.* (2012) [28]	Seasonal	Charleston County, SC, USA	Charleston Water System (CWS): Primary and secondary treatment methods with sodium hypochlorite disinfectant Mount Pleasant Waterworks (MPW): Primary and secondary treatment methods with sodium hypochlorite disinfectant and anoxic basin	Monthly 24-hour composite samples	Spring (March 2010, April and May 2009), Summer (June, July, August 2009), Fall (September, October, November 2009), Winter (December 2009, January and February 2010)	HPLC-MS	CWS: Acetaminophen, cotinine, and triclosan had highest concentrations in February. Caffeine was higher in Fall than Summer. Fluoxetine was higher in Fall than Spring. MPW: Caffeine, triclocarban, and triclosan had highest concentrations in February.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Hua *et al.* (2006) [29]	Seasonal	City of Windsor, Canada	Two activated sludge-type secondary wastewater treatment systems	Grab samples once a week for a month	September 2002, March-April 2003, June 2003	HPLC-MS/MS	Ibuprofen, clofibric acid, fenoprofen, and ketoprofen concentrations appear to be random across 3 seasons. Carbamazepine, naproxen, bezafibrate, pentoxifylline, cyclophosphamide, and cotinine concentrations were relatively consistent across seasons. Diclofenac and trimethoprim concentrations were considerably higher in early spring and summer compared to fall.
Jiang *et al.* (2014) [30]	Seasonal	Kenting area in southern Taiwan	Nanwan WWTP: Primary and secondary treatment Kenting WWTP: Primary, secondary, and chlorination	Grab samples	Off-Season (October 2010), Dry Season (March 2011), Youth Festival (April 2011), Peak/Wet Season (August 2011)	LC-MS/MS	Illicit drug concentrations were highest during the Youth Festival, followed by the peak season, dry season, and off-season. Analgesics displayed highest concentrations during the Youth Festival, followed by the dry season.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Jin *et al.* (2008) [31]	Seasonal	Wuhan, China	Primary and secondary treatment	Grab samples in morning and afternoon	December 2004 - August 2005	GC-MS	4-nonylphenol and 4-tert-octylphenol concentrations were highest in summer and lowest in winter. Estrone concentrations were higher in winter than in summer. Estradiol, estriol, diethylstilbestrol, and bisphenol-A varied little amongst different seasons.
Lindholm-Leto *et al.* (2016) [32]	Seasonal	Jyväskylä, Finland	Aerobic degradation with chemical coagulation	Pooled 24-hour composite samples	Summer 2013 and Winter 2015	LC-MS/MS	Higher concentrations of ketoprofen, ibuprofen, and naproxen were detected in summer compared to winter. Diclofenac concentrations were higher in summer than winter.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
MacLeod and Wong (2010) [33]	Seasonal	Alberta, Canada	Long retention waste stabilization ponds/aerated lagoons	1-1.5 month long POCIS disc sample	July 2007 - April 2008	LC-MS/MS	Clarithromycin, codeine, diclofenac, erythromycin, naproxen, and propranolol displayed higher concentrations during winter sampling periods. Celecoxib concentrations were highest from July - September and lowest from January - April. Citalopram concentrations were lowest from August - December. Gemfibrozil concentrations were highest from July - August. Sotalol concentrations were highest from December - January. Temazepam displayed lowest concentrations from October - December. Atenolol, carbamazepine, metoprolol, triclosan, and trimethoprim did not display significant temporal variability.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Papageorgiou *et al.* (2016) [34]	Seasonal	Volos, Greece	Screen and grit removal, primary sedimentation, activated sludge, aerobic tanks, secondary sedimentation	24-hour composite samples for 6 consecutive days	2013-2014, covering all 4 seasons	HPLC-MS, HPLC-MS/MS	Nimesulide presented highest concentrations in summer. Most antibiotics were only detected in the spring, except for ciprofloxacin, which had higher concentrations in summer, winter, and autumn. Sildenafil concentraitons were highest in summer.
Pereira *et al.* (2016)[35]	Seasonal	5 Regions (North, Center, Lisbon and Tagus Valley, Alentejo, and Algarve) in Portugal	Ranging from secondary to tertiary with UV disinfection	24-hour composite samples	Spring (May 14th - June 4th 2013), Summer (July 11th - August 14th 2013), Autumn (October 24th - November 7th 2013), Winter (January 30th - February 11th 2014)	LC-MS/MS	No significant variability was found.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Santos *et al.* (2009) [36]	Seasonal	Seville, Spain	Primary settling and activated sludge secondary treatment	Daily 24-hour composite samples	June 2004 - June 2005	HPLC with diode array and fluorescence detectors	No significant variability was found.
Sari *et al.* (2014) [37]	Seasonal	Istanbul, Turkey	WWTP 1: Screening, grit removal, anaerobic-anoxic-aerobic units, secondary sedimentation, sand filter, tertiary treatment, and UV disinfection WWTP 2: Screening, grit removal, primary sedimentation, anaerobic-anoxic-aerobic units, secondary sedimentation, and tertiary treatment	Daily 24-hour composite samples	July 2012 - July 2013	LC-MS/MS	WWTP 1: Diclofenac concentrations were highest in Fall, followed by Spring, Summer, and Winter. WWTP 2: Diclofenac concentrations were highest in Winter, followed by Spring, Fall, and Summer.
Spongberg and Watters (2008) [38]	Seasonal	Northwest Ohio, USA		Grab samples	September 6th 2006, December 4th 2006, and March 2nd 2007	LC-MS/MS	Generally no significant variability was found, although clarithromycin and diclofenac were higher in March, and sulfamethoxazole was higher in September.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Sui *et al.* (2011) [39]	Seasonal	Beijing, China	WWTP A: Membrane Bioreactor (MBR) and Convential Activated Sludge (CAS), in parallel WWTP B: Biological Nutrient Removal (BNR)	Monthly grab samples	February 2009 - January 2010	UPLC-MS/MS	Sulpiride, caffeine, chloramphenicol, trimethoprim, diclofenac, propranolol, metoprolol, carbamazepine, clofibric acid, bezafibrate, and gemfibrozil had lower concentrations in summer season and higher concentrations in winter season.
Sun *et al.* (2014) [40]	Seasonal	Xiamen, China	Primary treatment process, Orbal oxidation ditch process and a UV disinfection process	Grab samples	August 28th 2012 December 3rd 2012 March 6th 2013 May 30th 2013	LC-MS/MS	Methyl paraben, codeine, ketoprofen, propyl paraben, diclofenac acid, ibuprofen, and triclosan concentrations were greatest in March. Triclocarbon concentrations were lowest in August. Mefanamic acid, ibuprofen, and diclofenac acid concentrations were lowest in December.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Sun *et al.* (2016) [41]	Seasonal	Xiamen, China	WWTP 1: Primary sedimentation, biological aerated filters (BAF), UV disinfection WWTP 2: Primary sedimentation, orbal oxidation ditches, secondary sedimentation, UV disinfection WWTP 3: Primary sedimentation, anaerobic/anoxic/oxic tanks, secondary sedimentation, chemical disinfection	Grab samples	February 20th, May 8th, August 11th, November 12th 2014	LC-MS	Higher concentrations of PPCPs were present in February when compared to August.
Tsui *et al.* (2014) [42]	Seasonal	Hong Kong, China	Stonecutters Island (A): Chemically enhanced primary treatment and chlorination; Shatin (B): Screening settlement ofgrit, primary sedimentation, aerationand biological treatment with activated sludge and UV-disinfection; Shek Wu Hui (C): Screening settlement of grit, primary sedimentation, aeration and biological treatment with activated sludge, UV-disinfection, and micro-filtration/reverse osmosis; Wan Chai East (D): Preliminarily screening of objects > 6mm in diameter	A,B,C: 24-hour composite samples D: Grab samples	Dry Season (February and November 2012), Wet Season (May and August 2012)	HPLC-MS/MS	Methoxydibenzoylmethane (BMDM), benzophenone-1 (BP-1), benzophenone-3 (BP-3), benzophenone-8 (BP-8), ethylhexyl salicylate (EHS), and 2-ethyl-hexyl-4-trimethoxycinnamate (EHMC) concentrations were higher in wet season than dry season. Benzophenone-4 (BP-4) did not show a seasonal pattern.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Vidal-Dorsch *et al.* (2012) [43]	Seasonal	Southern California, USA	Hyperion Treatment Plant: Sedimentation and activated sludge Joint Water Pollution Control Plant: Secondary treatment Orange County Sanitation District Plant: Secondary/advanced primary (50/50) Point Loma Wastewater Treatment Plant: Sedimentation and screening	Grab samples	Quarterly over a 1 year period	GC-MS/MS and LC-MS/MS	No significant variability was found.
Vieno *et al.* (2005) [44]	Seasonal	Turku, Finland	Activated sludge compartment with addition of ferric salt	24-hour composite sample	September 16th, March 16th, May 18th, August 17th 2003	HPLC-MS/MS	Benzafibrate, ketoprofen, and naproxen had highest concentrations in March (winter) and lowest in September. Diclofenac had highest concentrations in March and lowest in May. Ibuprofen had highest concentrations in March.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Yang *et al.* (2011) [45]	Seasonal	Gwinnett County, GA, USA	Primary clarification, activated sludge treatment, secondary clarification, membrane microfiltration units, GAC absorption beds, ozone contact chambers	Monthly 24-hour composite samples	January - December 2008	LC-MS/MS	No significant variability was found.
Yu *et al.* (2013) [4]	Seasonal	Riverside County, CA, USA	All employed primary process using screens, settling tanks, and skimmers, in addtion to: WWTP 1: Oxidation Ditch WWTP 2: Continuous-flow suspended-growth process with anaerobic, anoxic, and oxic stages WWTP 3: Modified Bardenpho process, initial anaerobic zone WWTP 4: Bardenpho process, continuous-flow suspended-growth process with alternating anoxic/aerobic/anoxic/aerobic WWTP 5: Continuous-flow suspended-growth process with anaerobic, anoxic, and oxic stages	24-hour composite samples, collected on Wednesday and Thursday	Summer (August 2010) and Winter (February 2011)	GC-MS	Bisphenol A, estrone, 4-n-nonylphenol, 4-tert-octylphenol, aspirin, diclofenac, gemfibrozil, ibuprofen, ketoprofen, naproxen, paracetamol, and triclosan had higher concentrations in winter than in summer. Carbamazepine and clofibric acid had higher concentrations in summer than in winter.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Nelson *et al.* (2011) [46]	Seasonal; Hourly	Los Angeles, CA, USA	Tertiary treatment with nitrification/ denitrification and chlorination/ chloramination/ dechlorination	Hourly sample collection	July 8th-9th 2008, May 18th-19th 2009, October 19th-20th 2009	HPLC-MS/MS	Trimethoprim, sulfamethoxazole, naproxen, diclofenac, furosemide, triclosan, and estrone display intense pulses over 3-6 hours in the late afternoon and early evening. Naproxen exhibits a bimodal pattern. Erythromycin, azithromycin, iopromide, iohexol, atenolol, propranolol, gemfibrozil, DEET, 4-nonylphenol, and 4-tert-octylphenol display broad changes over 6-15 hours. Carbamazepine, primidone, fluoxetine, metoprolol, triclocarban, phenytoin, and TCEP showed little daily variability. DEET concentrations were higher in May than October. Peak concentrations differed for sulfamethoxazole, naproxen, azithromycin, gemfibrozil, diclofenac, nonylphenol, atenolol, and trimethoprim even though baseline conentrations were similar across seasons. TCEP, triclocarban, primidone, fluoxetine, propranolol, metoprolol, and iohexol had similar concentrations for all seasons.

Table 1. (continued)

Author(s) and Date	Scope	Location	Effluent Type/Treatment Technology	Sampling Frequency	Season	Analytical Methods	Variability
Bueno *et al.* (2012) [47]	Seasonal; Monthly	Madrid, Spain; Almeria, Spain	All WWTPs employ pre-treatment for solid removal, a primary treatment to eliminate suspended material, an activated sludge biological treatment and a final clarification	24-hour composite samples	January 2007-October 2008	GC-MS and LC-MS/MS	Total concentration of PPCPs were greatest in the summer and lowest in the winter.
Kosonen and Kronberg (2009) [48]	Weekly	Turku, Finland	Biological and chemical processes including a denitrification-nitrification process for nitrogen removal	64-hour composite samples	March - September 2007	LC-MS/MS	Antihistimines cetirizine, acrivastine, and fexofenadine displayed increasing concentrations from March to May, followed by a drop in June and a stable period until July, where the concentrations reached lowest values in the late summer.
Stülten *et al.* (2008) [49]	Weekly	Germany	Single-stage biological treatment	24-hour composite samples	April - June 2007	LC-MS	Highest concentrations of diclofenac were recorded from mid-April to mid-May, before decreasing and remaining constant the rest of the sampling period.

Materials and Methods

Site Description

This thesis research occurred at the Waco Metropolitan Area Regional Sewerage System (WMARSS), located in Waco, Texas, USA. WMARSS is a regional water reclamation that serves the cities of Waco, Woodway, Robinson, Lorena, Lacy-Lakeview, Hewitt, and Bellmead, an area with a 2013 population of 181,452 people. There is also a transient student population of approximately 33,000 (Baylor University, McLennan Community College, Texas State Technical Institute). WMARSS is permitted for a mean discharge of 45 million gallons per day, with a two-hour peak flow of 57,800 gallons per minute. Raw wastewater entering the plant is screened and then pumped to primary clarifiers, allowing solids to settle. Water then passes through an aeration basin before entering secondary clarifiers for further settling. At this point, part of the clarified effluent is diverted for tertiary filtration. Water that is not filtered is then mixed with the filtered water, where it is chlorinated, de-chlorinated, and discharged to the Brazos River. The hydraulic retention time (HRT) when raw wastewater enters the plant until final effluent discharge is typically 12 hours. Samples in this study were collected from effluent after dechlorination and immediately prior to discharge to the Brazos River.

Temporal Sampling Approach

Grab samples of dechlorinated effluent were collected in duplicate each month for one year to test my hypothesis related to seasonal variation of pharmaceutical EICs. In each of these months, samples were collected on a Thursday and the subsequent Sunday at 7:00 PM to evaluate potential day of week influences on pharmaceutical occurrence and concentration. This 7:00 PM sampling time accounted for the 12 hour HRT of WMARSS and thus was intended to capture morning inputs to the water reclamation plant. I examined daily variability by performing a high-resolution sampling scheme each quarter, during which grab samples were collected in duplicate every 6 hours in order to evaluate whether pharmaceutical EICs were influenced by time of day. In July 2016, a weeklong intensive sampling event occurred to characterize potential day of week and time of day influences on the occurrence of pharmaceuticals during a critical monitoring period. In this sampling effort, grab samples were collected in duplicate every day for one week, at 7:00 AM and 7:00 PM, here again to characterize pharmaceutical inputs during mornings and evenings.

All wastewater effluent was collected in 4-L amber glass bottles and transported on ice back to the laboratory. To aid effluent sampling, these 4-L amber glass bottles were filled from a smaller 750 mL Nalgene bottle attached to a large pole, which is used by WMARSS staff during routine effluent water quality monitoring. Samples for a matrix spikes and duplicate samples were collected in the same manner. Field blanks were collected by leaving sample bottles open for the duration of the sampling event before sealing them and filling them with Nanopure water in the laboratory. All samples were stored at 4°C until solid phase extraction (SPE). SPE was performed for all samples within 48 hours of collection.

Routine Water Quality Parameters

Water quality parameters were measured using a calibrated Yellow Springs Instruments XLM600 data sonde. Measurements of effluent temperature, pH, dissolved oxygen, and specific conductivity were recorded during every sampling event. For Thursday and Sunday sampling events, the instrument was calibrated before the first sampling event of each day according to the user manual (YSI 6-Series Multiparameter

Water Quality Sondes User Manual, Yellow Springs, OH, USA). A post-sampling calibration check occurred after the last sampling event of each day. The post-sampling calibration for Thursday served as the calibration prior to sampling on Sunday. For the weeklong sampling effort in July 2016, a calibration was completed before the first event and after the last event. The pH was calibrated by using a two-point calibration curve at values of 7.00 and 10.00 (Fisher Scientific, Hampton, NH, USA). Specific conductivity was calibrated by using a conductivity standard of 1412 μS/cm (BDH, Poole, Dorset, UK). Dissolved oxygen was calibrated by using the sea level air pressure recorded at the Waco Regional Airport (NOAA) and adjusting for the altitude of the airport. Dissolved oxygen membranes were replaced as needed.

Chemicals and Analytical Standards

All chemicals and their corresponding isotopically-labeled analogs were obtained with various vendors. Acetaminophen, acetaminophen-*d*4, amitriptyline, amitriptyline-*d*3, aripiprazole, aripiprazole-*d*8, benzoylecgonine, benzoylecgonine-*d*3, buprenorphine, buprenorphine-*d*4, caffeine, carbamazepine, carbamazepine-*d*10, diltiazem, diphenhydramine, diphenhydramine-*d*3, duloxetine, duloxetine-*d*3, fluoxetine, fluoxetine-*d*6, ketamine, ketamine-*d3*, methylphenidate, methylphenidate-*d*9, norfluoxetine, norfluoxetine-*d*6, promethazine, promethazine-*d*3, and sertraline were obtained as certified analytical standards from Cerilliant (Round Rock, TX, USA). Amlodipine, amlodipine-*d*4, caffeine-*d*9, desmethylsertraline, desmethylsertraline-*d*4, diclofenac, diclofenac-*d*4, diltiazem-*d*3, erythromycin-*d3*, propranolol, propranolol-*d7*, sertraline-*d*3, sulfadimethoxine-*d4*, sulfathiazole-*d4*, sulfamethoxazole, sulfamethoxazole-*d4*, trimethoprim, and trimethoprim-*d9* were purchased from Toronto Research Chemicals

(Toronto, ON, CA). Erythromycin, norfloxacin, norfloxacin-*d5*, sulfadimethoxine, sulfathiazole, and sucralose were acquired from Sigma-Aldrich (St. Louis, MO, USA) and sucralose-*d*6 was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). All chemicals were reagent grade and used as received. HPLC grade methanol (MeOH) and methyl tert-butyl ether (MTBE) were obtained from Fisher Scientific (Fair Lawn, NJ, USA), formic acid was purchased from Sigma-Aldrich (St. Louis, MO, USA), and a Thermo Barnstead™ Nanopure™ (Dubuque, IA, USA) Diamond UV water purification system was used throughout sample analysis to provide 18 MΩ water.

Sample Processing

Duplicate water samples for targeted analytes were collected using acetone cleaned 4 L amber glass bottles. Water samples were filtered and concentrated to SPE cartridges following previously reported methods [50–52] with minor modifications. Briefly, samples were filtered through three different sized filters to remove particulates: a glass fiber filter (1.0-μm pore size, Pall Corporation, Port Washington, NY, USA), a nitrocellulose filter (0.45-μm pore size, GE Healthcare, Little Chalfont, BUX, UK), and a Nylaflo™ filter (0.2-μm pore size, Pall Corporation, Port Washington, NY, USA). 2 L were separated in two volumetric flasks for extraction of 1 L with an Oasis HLB (6 cc, 200 mg, Waters Corporation, Milford, MA, USA) cartridge and 1 L with a Strata SCX (6 cc, 500 mg, Phenomenex, Torrance, CA, USA) cartridge. 50 μL of prepared 2000 (ng mL^{-1}) internal standard was spiked in each sample. Strata SCX samples were then spiked with an additional 100 μL of 85 % phosphoric acid and 5 mL of MeOH. Oasis HLB cartridges were pretreated with 5 mL MTBE, 5 mL MeOH, and 5 mL nanopure water respectively. Strata SCX cartridges were pretreated with 5 mL MEOH and 5 mL nanopure water respectively. Samples were extracted via a 24 port Visiprep™ vacuum manifold (Supelco Inc., Bellefonte, PA, USA) with a flow rate of approximately 10 ml/min. Oasis HLB cartridges were eluted with 5 mL MeOH and 5 mL 10:90 (v v^{-1}) MeOH:MTBE. Strata SCX cartridges were first washed with 5 mL of aqueous 0.1% HCl solution, then eluted with 5 mL MeOH and 6 mL 5:95 (v v^{-1}) NH_4OH:MeOH. Eluates were blown to dryness under a gentle stream of nitrogen in a Turbovap (Zymark, Hopkinton, MA, USA) set to 45°C, then reconstituted to 1 mL with 5:95 (v v^{-1}) MeOH:aqueous 0.1% formic acid. Reconstituted samples were syringe filtered using a BD 1 mL TB syringe (BD, Franklin Lakes, NJ, USA) and Acrodisc® hydrophobic Teflon Supor membrane syringe filters (13-mm diameter; 0.2-μm pore size, Pall Corporation, Port Washington, NY, USA) and placed in 2 mL analytical vials (Agilent Technologies, Santa Clara, CA, USA) for analysis.

Instrumental Analysis

Samples were analyzed using isotope-dilution liquid chromatography-tandem mass spectrometry (LC-MS/MS) with an Agilent Infinity 1260 autosampler/quaternary pumping system, Agilent jet stream thermal gradient electrospray ionization source (ESI), and model 6420 triple quadrupole mass analyzer (Agilent Technologies, Santa Clara, CA, USA). A binary gradient method consisting of aqueous 0.1 % formic acid as solvent A, and MeOH as solvent B, was used. Separation was performed using a 10 cm × 2.1 mm Poroshell 120 SB-AQ column (120Å, 2.7 μm, Agilent Technologies, Santa Clara, CA, USA) preceded by a 5 mm × 2.1 mm Poroshell 120 SB-C18 attachable guard column (120Å, 2.7 μm, Agilent Technologies, Santa Clara, CA, USA). The flow rate was held constant at 0.5 mL/min with a column temperature maintained at 60 °C. The injection volume was 10 μL. Multiple reaction monitoring (MRM) transitions for target analytes and associated instrument parameters were automatically determined using MassHunter Optimizer Software (Agilent Technologies, Santa Clara, CA, USA) by flow injection analysis. Cycle time was adjusted to 500 ms for acquisition of data.

In this thesis, method detection limits (MDLs) represented the lowest concentrations of an analyte that were reported with 99% confidence that the concentration was different from zero in a given matrix. The EPA guideline (40 CFR Part 136, Appendix B) for generating MDLs were followed using 8 replicates and the spiking level for each analyte was 1 ng/L. After analysis, MDLs were calculated by multiplying the standard deviation resulting from 8 replicates by the one-sided student's *t*-value for the corresponding number of samples. Less than MDL observations were defined as analytes that were detected in the matrices, but below corresponding MDLs.

Quantitation was performed using an isotope dilution calibration method. Calibration standards, containing mixture of internal standards and variable concentrations of target compounds, were prepared in 95:5 0.1% ($v\ v^{-1}$) aqueous formic acid–methanol. The linear range for each analyte (0.1 – 500 ng mL^{-1}) was confirmed from plots of sensitivity (i.e., response factor; RF) versus analyte concentration. Our criterion for linearity required that the relative standard deviation of RFs for standards spanning the noted range was ≤ 15%. Internal standard calibration curves were constructed for each analyte using eight standards that were within the corresponding linear range. Calibration data were fit to a linear regression, and correlation coefficients (r^2) for all analytes were ≥ 0.995. Quality assurance and quality control measures included running a continued calibration verification (CCV) sample every five samples to check calibration validity during the run. A criterion of ± 20% of CCV concentration was held to be acceptable for all analytes. One blank (i.e., reference water with internal standards only), one field blank, and duplicate matrix spikes were included in each analytical sample batch.

Statistical Analysis

Statistical analysis was performed using SigmaPlot by Systat Software (San Jose, CA, USA). One-way ANOVAs with a post hoc Holm-Sidak test were used to identify differences in pharmaceutical concentrations among seasons and among different times of day. If the data did not meet assumptions of one-way ANOVA, data were transformed or the nonparametric Kruskal-Wallis test was used. T-tests were used to detect differences in concentrations among days of the week, and between morning and evening sampling efforts during the weeklong study in July 2016. If the data did not meet T-test assumptions, the nonparametric Mann-Whitney test was employed. Half the MDL was utilized for statistical analyses if target analytes were not detected or detected below MDLs [53].

THR Analysis

To complete the objectives of this thesis, effluent was evaluated to determine whether concentrations of pharmaceuticals were predicted to accumulate in fish plasma equaling mammalian therapeutic levels. I utilized an equation for blood:water partitioning derived by Fitzsimmons et al. [11] (Equation 1) and substituted the liposome:water partitioning coefficient (Log K_{Lipw}) derived by Escher et al. [12] (Equation 2) for log K_{OW}.

$$P_{B:W} = (10^{0.73 \log Kow} \cdot 0.16) + 0.84 \qquad (1)$$

$$\text{Log } K_{Lipw} = 0.78 \cdot \log K_{OW} + 1.12 \qquad (2)$$

Following recommendation of Brooks [15] and recently applied by our research team [14], a therapeutic hazard value was then calculated for non-antibiotic pharmaceuticals (Equation 3).

$$THV = C_{max}/\log P_{B:W} \tag{3}$$

As introduced above, I used these THVs to calculate THRs by dividing the environmental concentration (EC) by the THV, which indicates whether a concentration of a given pharmaceutical poses a therapeutic hazard to aquatic organisms. A safety factor of 1000 was applied, as recommended by Huggett et al. [10], to account for extrapolation from humans to animals, mammalian to non-mammalian species, and for sensitivity differences (Equation 4).

$$THR = (EC/THV) \times 1000 \tag{4}$$

Because this is a hazard quotient, a THR greater than 1 indicates that a potential hazard is present. Analogous to how the hazard index (HI) is used as an ecological screening assessment for mixtures in the environment [54], the THRs for all compounds can be summed to predict their cumulative potential hazard to fish (Equation 5). This method is limited as different mechanisms of action exist for all of the pharmaceuticals in question, and the sum of the THR does not take into account other contaminants in the environment that were outside the suite of chemicals in this thesis.

$$HI = \Sigma(THR) \tag{5}$$

RHR Analysis

Antibiotics were evaluated to determine whether exposure to measured concentrations would be predicted to result in selection for antibiotic resistance. As introduced above, Bengtsson-Palme and Larsson [16] estimated PNECs (Predicted No

Effect Concentration) for resistance selection by dividing the minimal inhibitory concentration (MIC), analogous to a LOEC (Lowest Observed Effect Concentration), by a safety factor of 10. Similar to THRs, resistance hazard ratios were calculated for the measured antibiotic concentrations to explore whether there was potential for selection of antibiotic resistant bacteria (Equation 6) in effluent discharges.

$$RHR = EC/PNEC_{Resistance} \tag{6}$$

Similar to the THR approach, an RHR greater than 1 suggests that a potential hazard is present. All RHRs may be summed to initially screen for cumulative effects of antibiotic resistance development.

Probabilistic Calculations

In the present thesis, probabilistic distributions are derived to predict exceedances of THVs and MSCs, and to compare wastewater in this study to other effluents in the literature. To construct these distributions, data were first ranked by percent rank using the Weibull formula (Equation 7), where j is the plotting position (percent rank), *i* is the numerical rank, and n is the total number of data points in the data set.

$$j = (i * 100) / (n + 1) \tag{7}$$

These values were then plotted against concentration on a log scale, and distributions were interpreted using the centiles on the Y-axis.

Results

Effluent Discharge Changes Though Time

While the mean discharge volume increased from summer to spring, any differences among seasons were not significant (p = 0.193) (Figure 1). When discharge was compared with concentrations of the conservative tracer sucralose via linear regression to assess possible dilution effects, there was a slightly negative, though not significant ($p = 0.52$), relationship (Figure 2). While dilution may have some influence on the concentrations detected, my analysis showed that dilution alone could not explain differences in sucralose concentrations. In fact, total monthly rainfall, which could be expected to influence discharge if infiltration from defective underground infrastructure, was not significantly related to changes in discharge (Figure 1). In addition, an unknown amount of flow was diverted for a power plant prior to where I recorded it, so I could not account for this volume during such analyses.

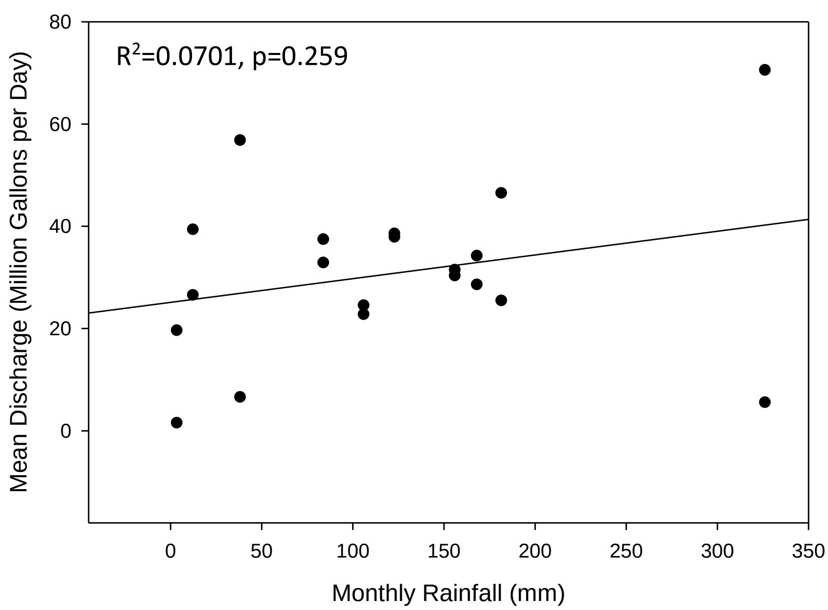

Figure 1. Relationship between effluent discharge and corresponding monthly rainfall (mm) (R^2=0.0701, p=0.259, N=20) from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA, during a 1 year study. Rainfall data was absent for July and parts of June, so these months were omitted.

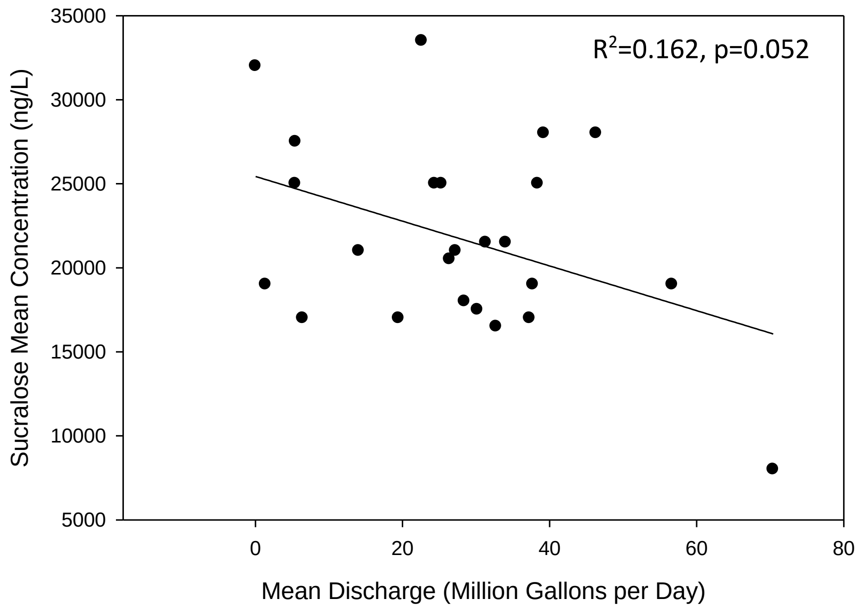

Figure 2. Relationship between sucralose concentration (ng/L) versus discharge (R^2=0.162, p=0.052, N=24) in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

Seasonal Variability of Effluent Water Quality

Effluent pH and temperature (^oC) were water quality parameters that displayed seasonal variability when compared to summer months. The pH was greater in winter when compared to summer (Figure 3). Both summer and autumn seasons had significantly ($p < 0.05$) greater effluent temperature than the winter (Figure 4). Complete water quality data can be found in Table 2. A complete list of detected analytes, their concentrations, and associated hazards found in this study is provided in Appendix A.

Analysis of the anthropogenic tracer compounds caffeine, carbamazepine, and sucralose revealed no significant differences between seasons, suggesting temporal occurrence differences for medicines and drugs of abuse result from varying consumption.. Compared to summer, which occurs during the critical period for surface water quality monitoring in Texas, the drug of abuse ketamine and the cocaine metabolite benzoylecgonine were significantly higher ($p<0.05$) in the autumn and winter, but not spring. Methylphenidate did not differ significantly across seasons (Figure 5). The antibiotic erythromycin exhibited significantly higher concentrations in the autumn, winter, and spring periods ($p<0.05$) when compared to summer (Figure 6). Targeted SSRIs, acetaminophen and diphenhydramine did not significantly ($p>0.05$) differ among seasons.

THRs for all compounds across all seasons were less than the hazard threshold of 1 before the addition of a 1000-fold safety factor recommended by Huggett et al (2003) and employed previously by our research team [50]. After application of this safety factor, THRs for all compounds except acetaminophen, caffeine, and ketamine exceeded the threshold of 1. RHRs were less than 1 for all antibiotics. However, general trends among compounds were present throughout different seasons. The THR for the common medicine for attention deficit disorder and prescription drug of abuse methylphenidate peaked in autumn and decreased in the following seasons. RHRs for all antibiotics generally increased from summer through spring (Figure 7). THRs for the SSRIs and pharmaceuticals acetaminophen and diphenhydramine remained relatively constant throughout the year. Because pharmaceuticals in the environment are present in mixtures, a total THR was calculated. Total unadjusted THR was similar for summer, autumn, and spring, but approached and even exceeded the hazard threshold of 1 in the winter. SSRIs made up the largest percentage of total THR.

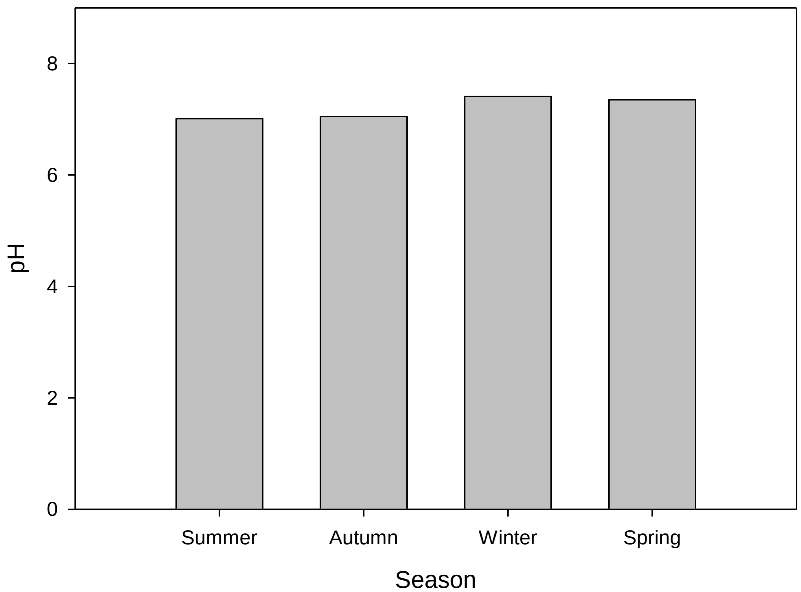

Figure 3. Median pH recorded (N=6) among seasons in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

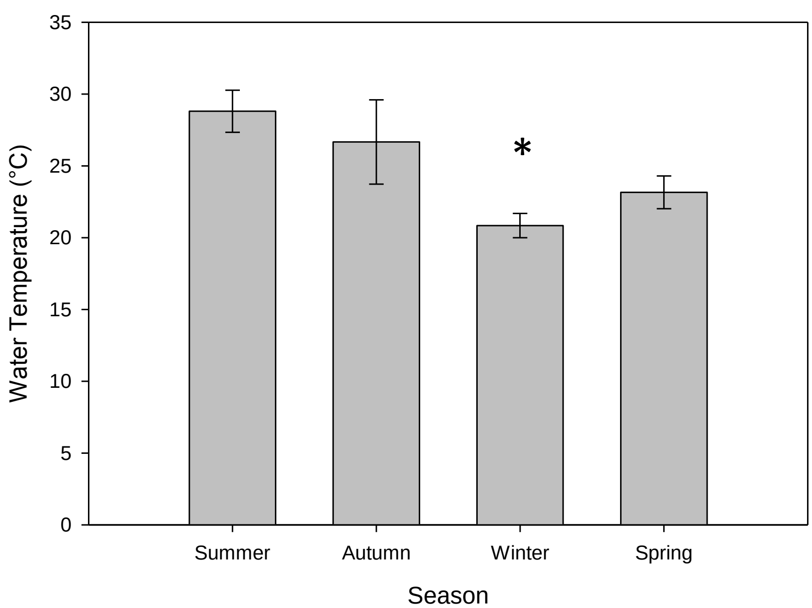

Figure 4. Mean seasonal effluent temperature (Mean ± SD, *:$p<0.005$, N=6) from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

Table 2. Routine water quality of effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

Date	Time	Mean Discharge (MGD)	Sp. Cond (ms/cm)	pH	DO (mg/L)	Water Temp (°C)
8/20/2015	1900	56.66	0.925	7.05	8.28	29.64
8/23/2015	1900	6.44	0.858	6.8	8.35	30.17
9/24/2015	0100	5.713	0.922	7.31	6.97	29.79
9/24/2015	0700	2.068	0.957	6.44	6.23	29.22
9/24/2015	1300	5.798	0.946	7.08	6.95	29.84
9/24/2015	1900	1.3805	0.955	6.75	6.36	29.72
9/27/2015	0100	3.3815	0.941	7.1	4.91	29.67
9/27/2015	0700	13.032	0.926	7.41	4.88	29.26
9/27/2015	1300	22.509	0.9	6.93	5.37	29.56
9/27/2015	1900	19.465	0.871	6.81	6.67	29.33
10/22/2015	1900	5.4065	0.996	7.31	7.21	28.87
10/25/2015	1900	70.407	0.814	6.84	6.57	24.22
11/19/2015	1900	31.319	0.771	7.26	8.23	24.46
11/22/2015	1900	30.1875	0.811	7.44	9.18	23.37
12/17/2015	0100	37.974	0.84	7.45	5.69	21.18
12/17/2015	0700	31.6625	0.845	7.32	6.29	21.14
12/17/2015	1300	38.149	0.856	7.37	6	21.48
12/17/2015	1900	37.2815	0.876	7.5	6.35	21.38
12/20/2015	0100	31.223	0.865	7.27	9.62	21.03
12/20/2015	0700	25.525	0.864	7.25	10.29	20.91
12/20/2015	1300	40.9	0.844	7.14	9.31	21.1
12/20/2015	1900	32.734	0.847	7.2	9.26	21.18
1/14/2016	1900	39.221	0.905	7.33	9.18	20.24
1/17/2016	1900	26.405	0.845	7.37	10.65	19.54

Table 2. (continued)

Date	Time	Mean Discharge (MGD)	Sp. Cond (ms/cm)	pH	DO (mg/L)	Water Temp (°C)
2/18/2016	1900	22.6235	0.918	7.45	8.59	20.8
2/21/2016	1900	24.376	0.838	7.53	8.88	21.9
3/17/2016	0100	39.2565	0.947	7.37	8.36	22.04
3/17/2016	0700	29.2745	0.966	7.35	8.49	22.18
3/17/2016	1300	39.6125	0.944	7.4	8.46	22.42
3/17/2016	1900	37.7295	0.953	7.27	8.32	22.42
3/20/2016	0100	32.5485	0.926	7.3	8.75	21.32
3/20/2016	0700	18.857	0.912	7.44	9.67	21.06
3/20/2016	1300	33.5185	0.905	7.36	9.52	21.35
3/20/2016	1900	38.394	0.916	7.33	9.44	21.38
4/14/2016	1900	25.304	1.012	7.43	9.05	23.55
4/17/2016	1900	46.344	0.907	7.48	8.84	23.18
5/19/2016	1900	34.055	0.744	7.37	9.49	23.68
5/22/2016	1900	28.429	0.885	7.26	10.27	24.7
6/16/2016	0100	22.6165	0.909	7.48	7.81	26.25
6/16/2016	0700	12.8745	0.926	7.42	7.78	26.1
6/16/2016	1300	18.4885	0.924	7.18	8.6	26.81
6/16/2016	1900	14.0475	0.881	7.37	8.59	26.86
6/19/2016	0100	13.796	0.902	7.17	8.22	26.74
6/19/2016	0700	21.4525	0.894	7.2	8.31	26.39
6/19/2016	1300	26.2135	0.914	7.12	8.23	27.16
6/19/2016	1900	27.224	0.883	6.97	8.12	27.07
7/25/2016	0700	0.1515	0.876	7.65	7.97	28.68
7/25/2016	1900	2.412	0.867	7.08	7.69	28.83
7/26/2016	0700	14.994	0.916	7.34	7.98	28.58

Table 2. (continued)

Date	Time	Mean Discharge (MGD)	Sp. Cond (ms/cm)	pH	DO (mg/L)	Water Temp (°C)
7/26/2016	1900	20.7585	0.93	7.19	9.44	29.38
7/27/2016	0700	14.6285	0.937	7.38	8.67	29.22
7/27/2016	1900	23.907	0.942	7.24	8.06	29.93
7/28/2016	0700	13.2985	0.913	7.32	8.02	29.06
7/28/2016	1900	5.461	0.91	7.23	8.05	29.17
7/29/2016	0700	0.1295	0.956	7.03	8.38	28.63
7/29/2016	1900	6.9805	0.937	7.19	8.65	29.75
7/30/2016	0700	17.6455	0.958	7.34	8.36	29.42
7/30/2016	1900	23.0495	0.939	7.17	9.01	30
7/31/2016	0700	0.3255	0.922	6.63	8.02	29.13
7/31/2016	1900	0.0125	0.907	6.6	6.74	29.9

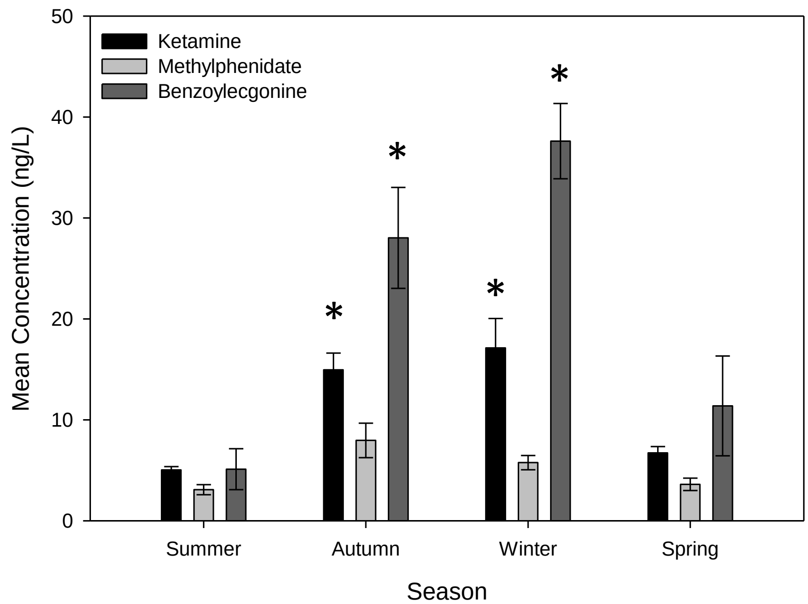

Figure 5. Mean concentration of the cocaine metabolite benzoylecgonine, and drugs of potential abuse (ketamine, methylphenidate) in effluent by season (ng/L) (±SE, *:p<0.05, N= 4 for ketamine in summer and autumn, 6 for methylphenidate and benzoylecgonine) from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

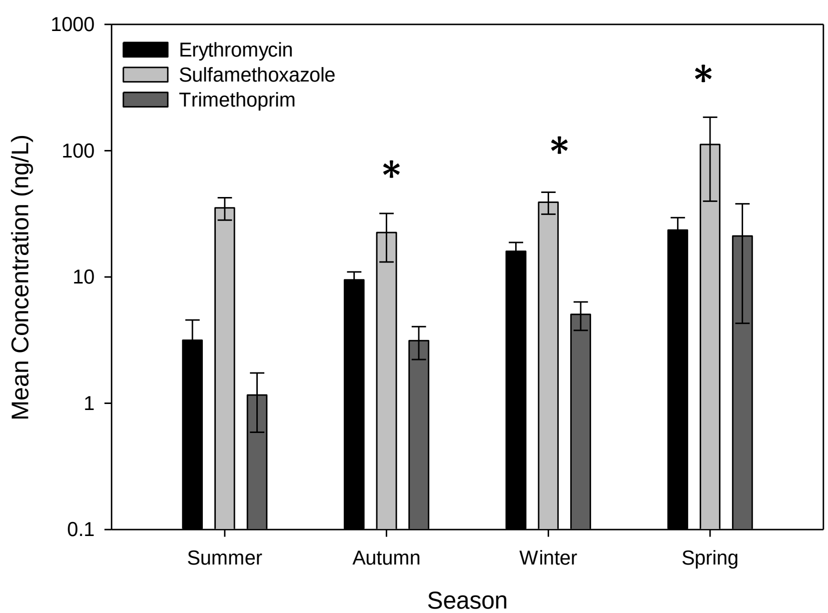

Figure 6. Mean concentration of antibiotics among seasons (ng/L) (±SE, *:p<0.05, N= 4 in summer and autumn and N=6 in winter and spring) in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

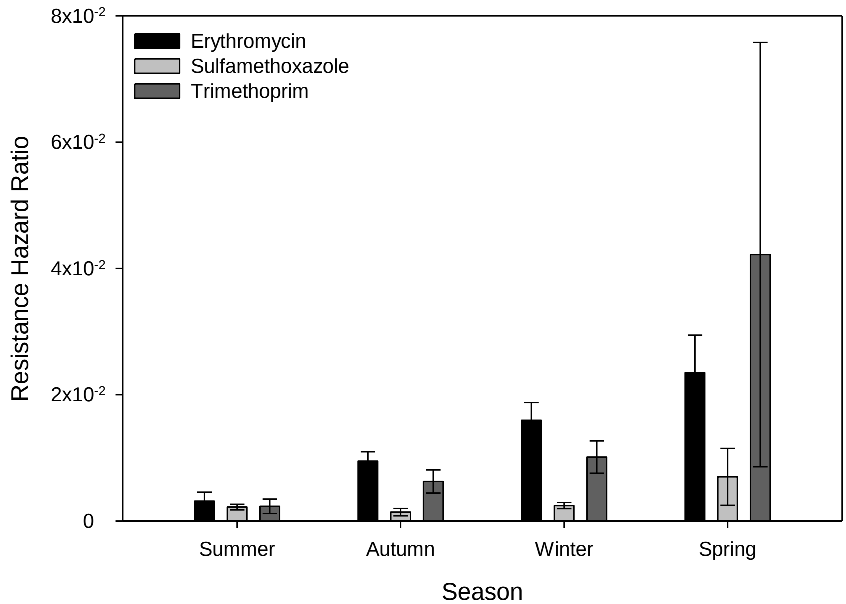

Figure 7. Resistance Hazard Ratios for antibiotics across seasons (Mean ± SE, N=4 for all compounds in summer and autumn and 6 in winter and spring) in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

Day of Week Variability of Effluent Water Quality

None of the monitored routine water quality parameters displayed significant differences between the Thursday and Sunday collection periods. Day of week analysis revealed no significant ($p > 0.05$) differences of any chemical between Thursday and Sunday samples during the 12-month sampling period. Analytes associated with drugs of abuse had similar concentrations on both days, with slightly higher concentrations of ketamine and methylphenidate detected on the weekday (Thursday) sampling days, and slightly higher concentrations of benzoylecgonine on weekends (Sunday; Figure 8).

Like the seasonal hazard observations, all THRs were less than 1 for all compounds on both weekdays and weekends prior to the addition of the recommended 1000-fold safety factor. After application of the safety factor, all THRs were greater than 1 except for acetaminophen, caffeine, and ketamine. RHRs were again lower than 1 for all antibiotics. THRs for the potential drugs of abuse ketamine and methylphenidate were higher on weekdays than on weekends (Figure 9). RHRs for all antibiotics were larger on weekends than during weekdays (Figure 10). THRs for the SSRIs, acetaminophen and diphenhydramine were not significantly different between weekend and weekday sampling events. Total THR was slightly higher on weekdays than on weekends.

Time of Day Variability of Effluent Water Quality

None of the monitored routine water quality parameters displayed significant differences between any collection periods at different times of the day. Comparing each sampling time from the higher temporal resolution sampling events (September, December, March, and June) yielded a few trends but limited statistically significant observations for PPCPs. Generally, concentrations across all categories remained fairly consistent throughout the day. Benzoylecgonine gradually decreased from 1:00 AM to 1:00 PM before peaking at 7:00 PM (Figure 11). The SSRI sertraline displayed significantly lower concentrations at 1:00 PM and 7:00 PM when compared to 1:00 AM (Figure 12).

Weekly Variability of Effluent Water Quality

None of the monitored routine water quality parameters displayed significant differences between the Thursday and Sunday collection periods during July. When the temporal resolution of the sampling effort was increased to examine daily variations over 7 consecutive days, similar results to the other daily observations were observed for PPCPs, with some key differences. Benzoylecgonine, ketamine, and methylphenidate concentrations in the effluent were within 5 ng/L during the summer quarterly sampling event and in the weeklong July sampling event. Both the antibiotic erythromycin and the anthropogenic tracer caffeine were significantly ($p < 0.05$) higher in the evenings than in the mornings (Figures 13 and 14, respectively). A complete list of detected analytes and their concentrations found in this study is provided in Table 3.

MDLs for the compounds listed in Table 3 are as follows: Acetaminophen = 3.47 ng/L August – January, 0.47 ng/L February – July; Amitriptyline = 5.3 ng/L; Benzoylecgonine = 0.05 ng/L August – January, 0.26 ng/L February – July; Caffeine = 4.43 ng/L August – January, 0.26 ng/L February – July; Carbamazepine = 0.27 ng/L August – January, 0.17 ng/L February – July; Diclofenac = 4.74 ng/L; Diltiazem = 0.24 ng/L; Diphenhydramine = 0.11 ng/L August – January, 0.08 ng/L February – July; Erythromycin = 0.16 ng/L; Fluoxetine = 2.39 ng/L; Ketamine = 0.07 ng/L; Methylphenidate = 0.14 ng/L; Norfluoxetine = 1.77 ng/L; Sertraline = 1.52 ng/L; Sucralose = 2.62 ng/L; Sulfamethoxazole = 0.06 ng/L; and Trimethoprim = 0.07 ng/L.

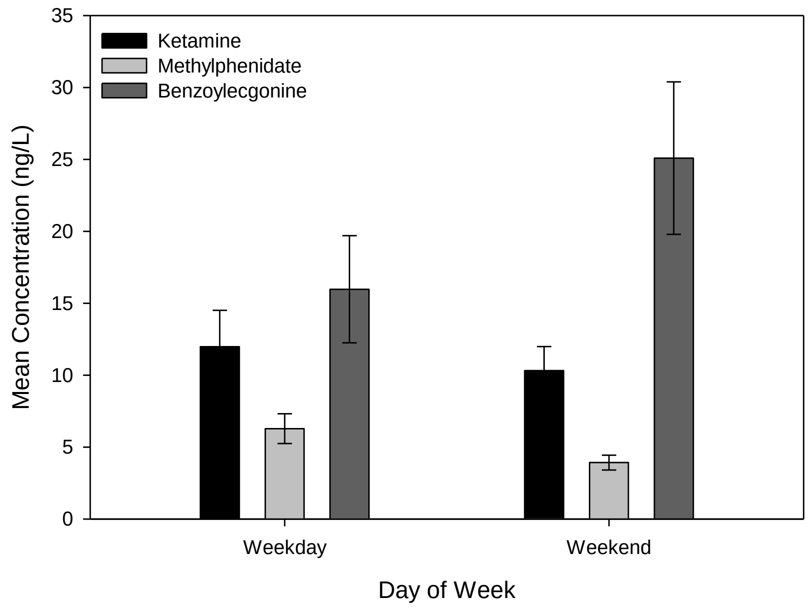

Figure 8. Mean concentrations of the cocaine metabolite benzoylecgonine and other drugs of abuse (Mean ± SE, N=10 for ketamine and 12 for methylphenidate and benzoylecgonine) in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

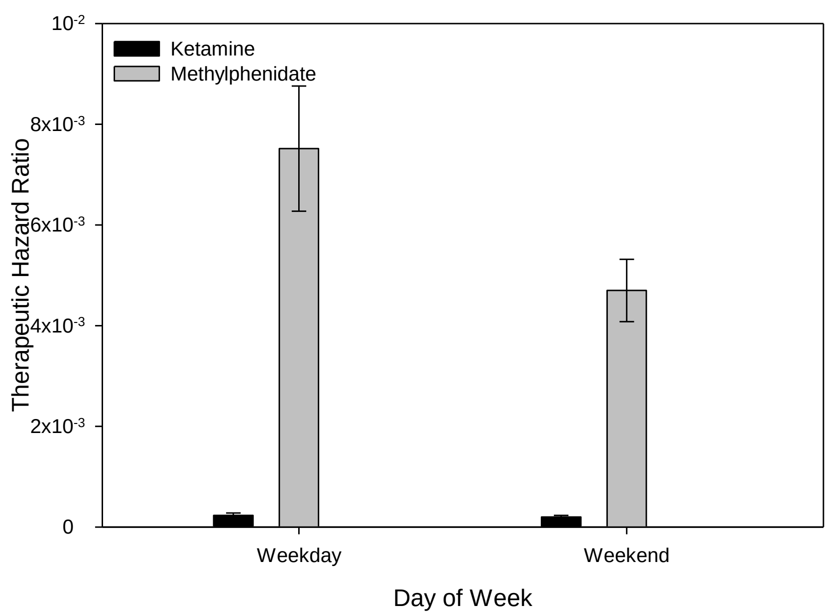

Figure 9. Therapeutic Hazard Ratios for drugs of abuse during weekdays and weekends (Mean ± SE, N=10 for ketamine and 12 for methylphenidate) in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

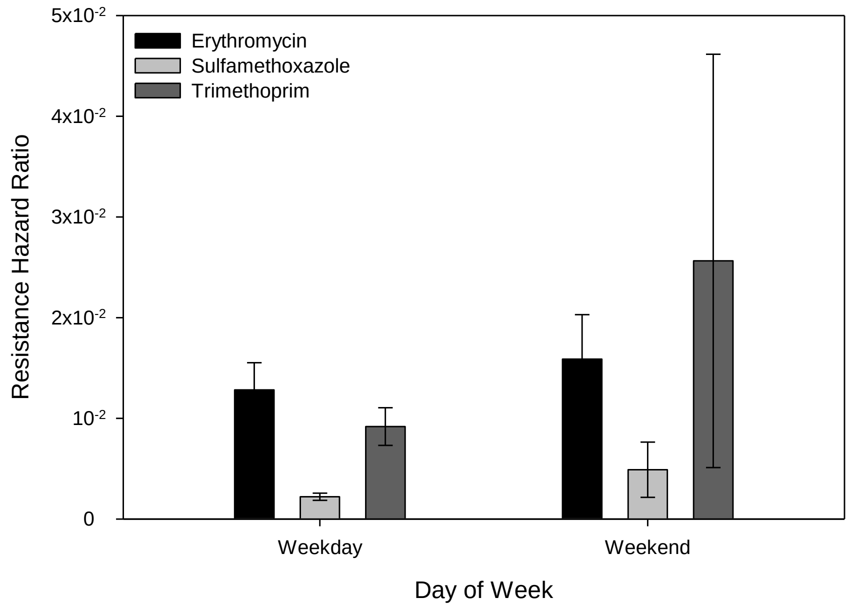

Figure 10. Resistance Hazard Ratios for antibiotics at different times of day (Mean ± SE, N=10) in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

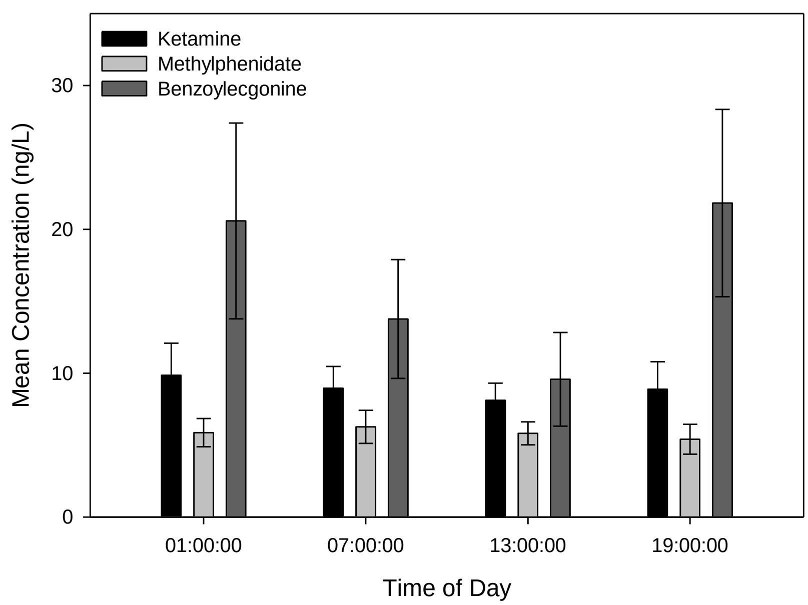

Figure 11. Mean concentrations of the cocaine metabolite benzoylecgonine and other drugs of abuse at different times of day (ng/L) (±SE, N= 6 for ketamine and 8 for all other compounds) in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

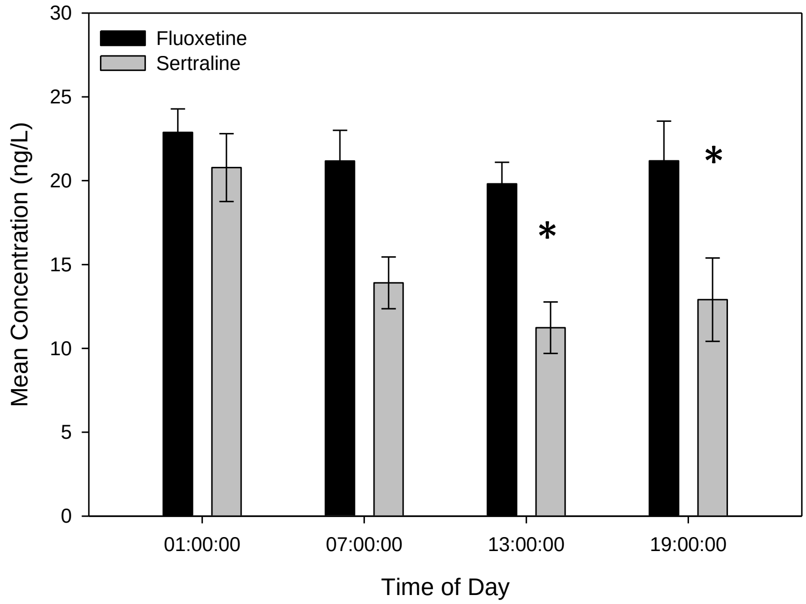

Figure 12. Mean concentration of the Selective Serotonin Reuptake Inhibitors fluoxetine and sertraline at different times of day (ng/L) (±SE, *:p<0.05, N=8) in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study.

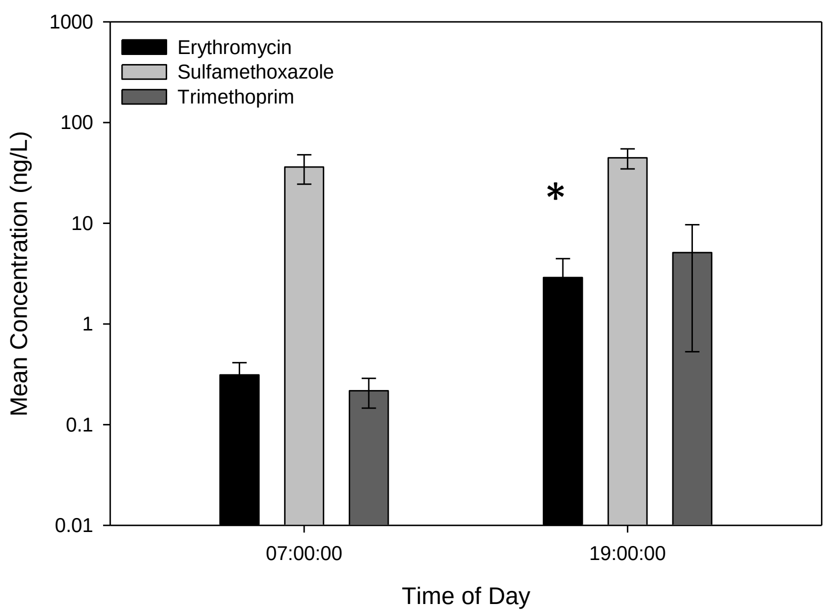

Figure 13. Mean concentration of antibiotics (ng/L) (±SE, *:p<0.05, N=7) during morning and evening in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a week long study.

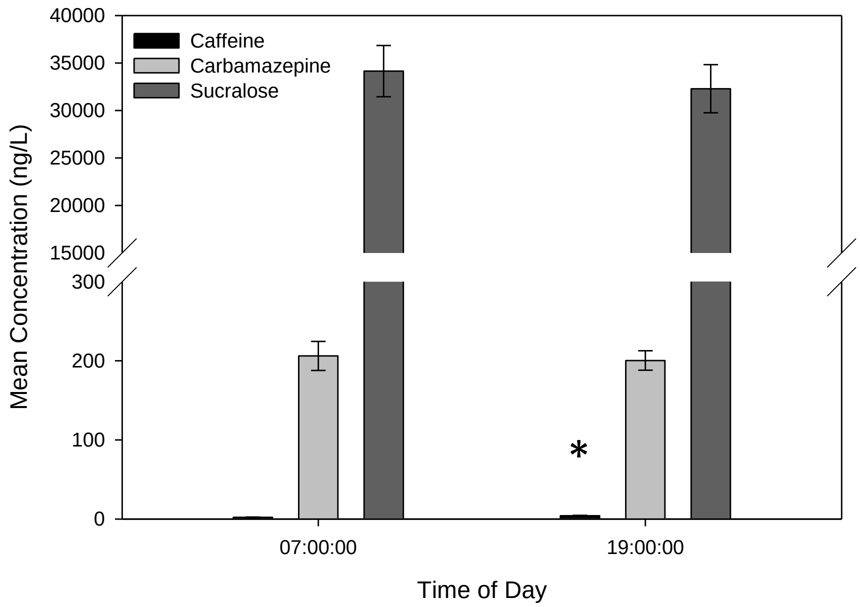

Figure 14. Mean concentration of anthropogenic tracers (ng/L) (±SE, *:p<0.05, N=7) during morning and evening in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a week long study.

Table 3. All concentrations of analytes in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study. ACE = Acetaminophen, AMI = Amitriptyline, BEN = Benzoylecgonine, CAF = Caffeine, CAR Carbamazepine, DIC = Diclofenac, DIL = Diltiazem, DIP =Diphenhydramine, ERY = Erythromycin, FLU = Fluoxetine, KET = Ketamine, MET = Methylphenidate, NOR = Norfluoxetine, SER = Sertraline, SUC = Sucralose, SUL = Sulfamethoxazole, TRI = Trimethoprim.

Date	Time	Rep.	ACE	AMI	BEN	CAF	CAR	DIC	DIL	DIP	ERY	FLU	KET	MET	NOR	SER	SUC	SUL	TRI
8/20/2015	1900	1	<3.47	N.D.	13.6	5.0	190	N.D.	N.D.	65.3	NA	25.5	NA	4.2	3.0	44.0	19000	NA	NA
		2	<3.47	N.D.	13.4	4.5	210	N.D.	N.D.	46.1	NA	22.5	NA	4.0	2.8	50.0	19000	NA	NA
8/23/2015	1900	1	<3.47	N.D.	4.3	7.4	170	N.D.	N.D.	1.3	NA	21.3	NA	4.2	4.5	20.0	17000	NA	NA
		2	<3.47	N.D.	4.1	20.4	170	N.D.	N.D.	1.3	NA	19.0	NA	4.2	2.4	25.0	17000	NA	NA
9/24/2015	0100	1	<3.47	N.D.	19.6	7.2	190	N.D.	N.D.	10.5	NA	28.1	NA	10.2	2.2	32.0	18000	NA	NA
		2	<3.47	N.D.	19.8	5.3	190	N.D.	N.D.	13.1	NA	28.6	NA	10.6	2.8	25.0	20000	NA	NA
9/24/2015	0700	1	<3.47	N.D.	17.7	5.1	180	N.D.	N.D.	2.4	NA	32.7	NA	12.7	2.5	21.0	20000	NA	NA
		2	<3.47	N.D.	17.5	6.0	190	N.D.	N.D.	2.3	NA	32.3	NA	13.0	2.9	21.0	18000	NA	NA
9/24/2015	1300	1	<3.47	N.D.	11.1	11.0	180	N.D.	N.D.	1.5	NA	25.4	NA	10.4	1.7	18.0	21000	NA	NA
		2	<3.47	N.D.	11.9	13.3	180	N.D.	N.D.	1.5	NA	23.0	NA	10.0	<1.77	17.0	18000	NA	NA
9/24/2015	1900	1	<3.47	N.D.	17.9	8.8	160	N.D.	N.D.	1.4	NA	25.8	NA	10.8	2.1	16.0	20000	NA	NA
		2	<3.47	N.D.	19.3	7.8	170	N.D.	N.D.	2.4	NA	28.0	NA	10.9	1.9	17.0	18000	NA	NA
9/27/2015	0100	1	<3.47	N.D.	31.1	5.2	170	N.D.	N.D.	3.2	NA	29.2	NA	9.5	1.9	18.0	17000	NA	NA
		2	<3.47	N.D.	30.1	4.8	160	N.D.	N.D.	2.7	NA	24.4	NA	8.2	2.0	16.0	18000	NA	NA
9/27/2015	0700	1	<3.47	N.D.	21.2	6.4	170	N.D.	N.D.	1.0	NA	20.0	NA	7.9	<1.77	12.0	18000	NA	NA
		2	<3.47	N.D.	20.7	3.9	170	N.D.	N.D.	1.2	NA	20.3	NA	7.5	1.7	8.5	21000	NA	NA
9/27/2015	1300	1	<3.47	N.D.	8.8	10.7	160	N.D.	N.D.	1.3	NA	24.1	NA	7.0	1.6	5.4	18000	NA	NA
		2	<3.47	N.D.	8.8	9.4	160	N.D.	N.D.	1.8	NA	20.7	NA	7.4	1.8	5.5	18000	NA	NA
9/27/2015	1900	1	<3.47	N.D.	34.1	5.1	180	N.D.	N.D.	2.2	NA	24.2	NA	7.9	2.2	12.0	17000	NA	NA
		2	<3.47	N.D.	33.9	5.6	180	N.D.	N.D.	1.8	NA	22.4	NA	7.7	2.2	9.0	17000	NA	NA
10/22/2015	1900	1	4.43	N.D.	14.8	6.4	220	N.D.	N.D.	2.4	5.4	23.7	18.9	12.0	2.5	15.0	23000	51.7	2.2
		2	5.10	N.D.	13.8	5.5	200	N.D.	N.D.	2.5	5.7	24.0	18.2	12.2	3.0	16.0	27000	49.1	2.6

Table 3. (continued)

Date	Time	Rep.	ACE	AMI	BEN	CAF	CAR	DIC	DIL	DIP	ERY	FLU	KET	MET	NOR	SER	SUC	SUL	TRI
10/25/2015	1900	1	<3.47	N.D.	38.1	4.6	40	N.D.	N.D.	4.4	11.5	15.4	12.4	2.2	3.0	24.0	8000	13.3	6.2
		2	<3.47	N.D.	32.9	4.6	35	N.D.	N.D.	4.3	10.7	14.8	10.7	2.0	2.0	23.0	8000	11.4	4.7
11/19/2015	1900	1	<3.47	N.D.	19.7	4.4	91	N.D.	N.D.	14.8	12.3	25.8	12.8	12.3	2.8	17.0	23000	11.6	3.6
		2	<3.47	N.D.	20.3	4.4	97	N.D.	N.D.	11.2	12.4	21.6	12.8	9.9	2.3	14.0	20000	13.7	3.4
11/22/2015	1900	1	<3.47	N.D.	46.1	4.4	120	N.D.	N.D.	11.8	8.8	16.5	16.9	3.8	1.7	8.8	19000	13.9	1.1
		2	<3.47	N.D.	45.5	4.4	120	N.D.	N.D.	NA	8.9	NA	16.9	NA	NA	NA	16000	15.0	1.2
12/17/2015	0100	1	<3.47	N.D.	24.4	4.4	110	N.D.	N.D.	24.8	10.7	24.5	7.2	5.9	3.0	21.0	21000	14.1	5.3
		2	<3.47	N.D.	24.5	5.1	110	N.D.	N.D.	28.7	10.9	18.6	8.0	5.7	2.2	17.0	21000	16.8	5.6
12/17/2015	0700	1	<3.47	N.D.	18.9	4.4	110	N.D.	N.D.	4.1	3.9	20.2	8.9	6.5	1.8	12.0	21000	12.9	1.7
		2	<3.47	N.D.	18.8	4.4	120	N.D.	N.D.	4.7	3.9	25.8	9.2	7.0	2.0	15.0	20000	12.8	1.8
12/17/2015	1300	1	<3.47	N.D.	21.8	4.9	110	N.D.	N.D.	55.9	19.4	21.6	7.8	5.6	2.2	14.0	17000	13.9	3.1
		2	<3.47	N.D.	21.8	4.9	110	N.D.	N.D.	56.8	19.1	20.2	7.7	5.4	2.0	11.0	21000	15.5	2.6
12/17/2015	1900	1	<3.47	N.D.	40.8	4.4	110	N.D.	N.D.	33.5	21.3	29.0	17.1	4.9	3.5	20.0	16000	18.4	10.2
		2	<3.47	N.D.	40.2	4.4	110	N.D.	N.D.	29.0	19.6	26.7	16.6	5.0	2.5	20.0	18000	15.5	9.5
12/20/2015	0100	1	4.03	N.D.	61.3	4.9	120	N.D.	N.D.	25.5	12.3	20.1	13.1	5.0	2.3	8.5	18000	18.8	3.7
		2	4.24	N.D.	60.5	6.8	130	N.D.	N.D.	26.6	13.6	19.7	12.7	5.2	2.3	11.0	17000	19.1	3.7
12/20/2015	0700	1	<3.47	N.D.	34.5	8.6	130	N.D.	N.D.	8.6	N.D.	19.2	15.4	5.4	2.1	7.2	18000	19.9	1.6
		2	<3.47	N.D.	36.2	5.5	140	N.D.	N.D.	6.9	N.D.	19.4	16.1	5.7	2.3	7.8	17000	19.3	1.0
12/20/2015	1300	1	4.38	N.D.	23.5	4.6	140	N.D.	N.D.	94.2	30.7	22.7	12.7	5.4	2.2	8.8	19000	27.2	4.5
		2	3.80	N.D.	25.7	4.1	140	N.D.	N.D.	90.7	32.7	22.3	13.6	5.3	2.1	6.8	17000	27.0	4.9
12/20/2015	1900	1	<3.47	N.D.	51.3	4.5	130	N.D.	N.D.	41.4	16.4	21.1	11.8	4.5	2.0	7.8	15000	18.7	3.1
		2	3.52	N.D.	52.2	4.9	130	N.D.	N.D.	43.9	18.7	20.0	11.2	4.7	2.7	6.8	18000	20.5	2.5
1/14/2016	1900	1	4.43	N.D.	28.8	4.4	130	N.D.	N.D.	52.2	24.8	28.3	13.1	9.1	2.4	13.0	29000	37.2	6.4
		2	5.28	N.D.	28.2	5.2	140	N.D.	N.D.	53.4	24.2	28.9	13.0	9.4	2.8	9.4	27000	35.9	5.9
1/17/2016	1900	1	<3.47	N.D.	29.5	5.9	140	N.D.	N.D.	19.6	14.7	25.3	12.9	7.8	2.1	12.0	22000	35.1	1.2
		2	5.35	N.D.	28.2	5.0	140	N.D.	N.D.	21.0	14.3	13.4	8.6	2.8	1.9	2.5	19000	46.8	0.2

Table 3. (continued)

Date	Time	Rep.	ACE	AMI	BEN	CAF	CAR	DIC	DIL	DIP	ERY	FLU	KET	MET	NOR	SER	SUC	SUL	TRI
2/18/2016	1900	1	4.80	<5.3	33.0	2.8	200	N.D.	<0.24	6.0	4.8	37.0	28.0	5.6	3.2	28.0	30000	59.0	6.0
		2	4.80	<5.3	33.0	8.6	230	N.D.	<0.24	6.2	3.6	32.0	31.0	5.6	2.8	23.0	37000	57.0	6.2
2/21/2016	1900	1	3.60	<5.3	44.0	2.5	240	N.D.	N.D.	11.0	15.0	32.0	20.0	4.7	1.9	17.0	24000	63.0	5.2
		2	3.70	<5.3	42.0	3.7	230	N.D.	N.D.	10.0	14.0	33.0	22.0	5.0	1.9	16.0	26000	62.0	4.4
3/17/2016	0100	1	10.00	17.0	15.0	7.7	170	40	11.00	120.0	38.0	24.0	19.0	6.0	2.8	21.0	21000	340.0	75.0
		2	19.00	20.0	15.0	20.0	150	34	12.00	120.0	34.0	25.0	20.0	6.5	2.6	23.0	28000	320.0	78.0
3/17/2016	0700	1	6.00	<5.3	8.0	9.8	160	N.D.	N.D.	12.0	10.0	19.0	7.9	6.7	2.0	12.0	25000	37.0	6.1
		2	5.00	<5.3	7.6	7.2	180	N.D.	N.D.	15.0	16.0	23.0	8.5	6.8	2.2	13.0	22000	39.0	6.4
3/17/2016	1300	1	4.90	<5.3	5.4	8.9	150	N.D.	N.D.	25.0	21.0	16.0	7.2	6.1	<1.77	12.0	20000	44.0	5.1
		2	4.80	<5.3	5.2	5.3	160	N.D.	N.D.	23.0	23.0	22.0	8.2	6.0	<1.77	13.0	19000	46.0	4.9
3/17/2016	1900	1	5.40	<5.3	14.0	6.6	140	N.D.	N.D.	35.0	27.0	27.0	8.2	5.5	<1.77	20.0	20000	42.0	8.1
		2	5.50	<5.3	14.0	4.7	150	N.D.	0.24	37.0	25.0	19.0	8.0	5.7	<1.77	13.0	18000	43.0	8.7
3/20/2016	0100	1	7.80	<5.3	11.0	7.1	170	N.D.	0.24	47.0	32.0	25.0	8.6	5.7	<1.77	25.0	41000	51.0	13.0
		2	19.00	<5.3	11.0	21.0	170	N.D.	0.27	49.0	33.0	24.0	7.8	5.7	<1.77	23.0	41000	51.0	13.0
3/20/2016	0700	1	7.40	<5.3	7.5	11.0	170	N.D.	<0.24	14.0	45.0	19.0	9.1	5.2	<1.77	16.0	35000	51.0	7.9
		2	9.10	<5.3	6.5	10.0	150	N.D.	N.D.	13.0	44.0	23.0	9.2	5.4	<1.77	18.0	33000	48.0	7.1
3/20/2016	1300	1	6.00	<5.3	3.4	14.0	170	N.D.	N.D.	33.0	70.0	20.0	9.8	5.5	<1.77	12.0	32000	65.0	3.7
		2	4.40	<5.3	3.3	8.0	150	N.D.	N.D.	31.0	64.0	21.0	7.9	5.5	<1.77	14.0	31000	59.0	3.4
3/20/2016	1900	1	4.30	<5.3	13.0	5.4	220	N.D.	<0.24	22.0	43.0	25.0	7.9	4.8	<1.77	11.0	27000	56.0	4.5
		2	4.30	<5.3	13.0	3.5	140	N.D.	N.D.	19.0	41.0	26.0	7.4	4.8	<1.77	7.3	23000	50.0	4.2
4/14/2016	1900	1	4.20	<5.3	2.8	2.4	400	N.D.	<0.24	6.8	13.0	23.0	6.5	3.9	<1.77	11.0	22000	66.0	2.5
		2	5.60	NA	2.5	2.8	320	N.D.	<0.24	5.9	12.0	NA	5.9	NA	NA	NA	28000	63.0	2.5
4/17/2016	1900	1	11.00	21.0	33.0	24.0	350	77	34.00	121.0	39.0	29.0	7.7	3.3	2.0	22.0	29000	510.0	102.0
		2	11.00	23.0	34.0	24.0	360	77	36.00	124.0	39.0	30.0	8.4	3.4	2.2	21.0	27000	430.0	108.0
5/19/2016	1900	1	6.20	<5.3	3.3	3.0	130	N.D.	0.25	13.0	15.0	9.9	3.7	1.2	<1.77	<1.52	23000	21.0	3.6
		2	5.20	<5.3	3.5	2.4	130	N.D.	N.D.	14.0	13.0	12.0	4.4	1.7	<1.77	1.7	20000	20.0	4.1

Table 3. (continued)

Date	Time	Rep.	ACE	AMI	BEN	CAF	CAR	DIC	DIL	DIP	ERY	FLU	KET	MET	NOR	SER	SUC	SUL	TRI
5/22/2016	1900	1	3.10	<5.3	1.6	1.6	340	N.D.	<0.24	6.7	7.3	17.0	6.4	2.6	<1.77	11.0	17000	21.0	2.3
		2	2.50	<5.3	1.8	1.2	340	N.D.	<0.24	6.5	7.5	16.0	6.1	2.5	<1.77	10.0	19000	19.0	2.6
6/16/2016	0100	1	6.80	<5.3	0.8	1.1	130	N.D.	N.D.	14.0	10.0	17.0	4.6	2.5	<1.77	22.0	22000	22.0	2.1
		2	7.30	<5.3	0.8	1.4	130	56	N.D.	15.0	15.0	26.0	5.3	2.6	1.9	28.0	23000	23.0	2.1
6/16/2016	0700	1	11.00	N.D.	1.0	1.7	160	230	<0.24	3.4	3.4	16.0	5.2	2.8	<1.77	19.0	24000	19.0	1.3
		2	9.00	N.D.	0.8	1.4	150	7.9	<0.24	3.2	3.3	19.0	4.7	2.9	<1.77	16.0	22000	19.0	1.1
6/16/2016	1300	1	8.50	N.D.	0.6	2.0	120	N.D.	<0.24	5.7	5.7	16.0	4.0	4.4	<1.77	15.0	21000	20.0	0.7
		2	10.00	N.D.	0.7	2.3	130	N.D.	<0.24	6.1	6.2	14.0	4.3	4.1	<1.77	15.0	21000	21.0	0.8
6/16/2016	1900	1	8.60	N.D.	1.1	3.1	120	240	N.D.	5.9	6.7	13.0	4.3	3.7	<1.77	21.0	20000	20.0	2.9
		2	8.10	N.D.	1.1	2.9	130	15	N.D.	6.2	8.0	14.0	4.9	3.7	<1.77	23.0	22000	22.0	2.8
6/19/2016	0100	1	19.00	<5.3	2.1	1.6	150	N.D.	N.D.	9.3	6.9	17.0	5.9	2.3	<1.77	22.0	30000	26.0	2.7
		2	20.00	<5.3	2.2	1.8	150	N.D.	N.D.	9.2	6.8	15.0	6.1	2.3	<1.77	20.0	31000	24.0	2.5
6/19/2016	0700	1	7.90	13.0	1.6	1.5	160	N.D.	<0.24	2.3	1.4	13.0	6.4	2.3	<1.77	12.0	25000	27.0	0.8
		2	7.80	N.D.	1.6	1.9	160	N.D.	<0.24	2.2	1.3	17.0	6.9	2.4	<1.77	12.0	30000	27.0	0.8
6/19/2016	1300	1	8.60	N.D.	0.7	2.2	150	N.D.	<0.24	3.4	3.9	15.0	7.1	2.3	<1.77	6.3	27000	37.0	0.5
		2	8.40	N.D.	0.7	2.3	150	N.D.	<0.24	3.4	4.0	13.0	7.1	2.6	<1.77	5.9	28000	35.0	0.4
6/19/2016	1900	1	8.30	N.D.	1.7	2.3	150	N.D.	<0.24	2.6	2.0	12.0	5.3	1.3	<1.77	2.0	20000	33.0	0.3
		2	9.50	N.D.	1.7	2.3	150	N.D.	0.79	3.3	1.7	5.8	3.9	0.5	N.D.	0.5	22000	39.0	1.4
7/25/2016	700	1	6.20	N.D.	1.5	4.4	210	N.D.	<0.24	2.0	N.D.	4.7	2.4	0.4	N.D.	<1.52	28000	110.0	<0.07
		2	5.50	N.D.	1.6	3.5	210	N.D.	<0.24	2.0	0.2	5.0	2.3	0.3	N.D.	N.D.	28000	94.0	<0.07
7/25/2016	1900	1	1.90	N.D.	1.7	2.4	230	N.D.	<0.24	2.6	1.4	27.0	11.0	3.6	<1.77	8.1	28000	47.0	0.8
		2	2.40	N.D.	1.7	3.1	300	N.D.	<0.24	2.1	1.3	26.0	11.0	3.6	<1.77	6.8	25000	48.0	1.0
7/26/2016	700	1	2.40	<5.3	1.1	1.8	210	N.D.	<0.24	1.4	0.4	25.0	9.6	3.6	<1.77	7.2	31000	17.0	0.2
		2	2.10	N.D.	1.0	1.8	200	N.D.	N.D.	1.5	0.2	23.0	10.0	3.3	<1.77	7.7	33000	16.0	0.1
7/26/2016	1900	1	2.10	<5.3	1.6	5.0	190	N.D.	<0.24	1.6	1.2	24.0	7.2	2.7	<1.77	6.7	33000	18.0	0.5
		2	3.10	<5.3	1.6	5.5	180	N.D.	<0.24	1.7	1.5	23.0	7.2	2.4	<1.77	6.7	26000	21.0	0.4

Table 3. (continued)

`Date	Time	Rep.	ACE	AMI	BEN	CAF	CAR	DIC	DIL	DIP	ERY	FLU	KET	MET	NOR	SER	SUC	SUL	TRI
7/27/2016	700	1	2.60	N.D.	1.0	1.7	250	N.D.	<0.24	1.7	0.9	25.0	8.0	3.0	<1.77	7.0	28000	20.0	0.3
		2	3.10	<5.3	1.0	2.0	250	N.D.	<0.24	1.7	0.9	24.0	7.7	2.9	<1.77	7.8	36000	18.0	0.3
7/27/2016	1900	1	6.20	N.D.	1.6	5.4	210	N.D.	<0.24	2.1	0.8	10.0	4.2	0.6	<1.77	<1.52	31000	26.0	0.1
		2	2.20	<5.3	1.7	4.3	210	N.D.	<0.24	1.6	0.5	24.0	7.6	2.4	<1.77	4.1	36000	27.0	0.1
7/28/2016	700	1	2.30	<5.3	1.3	1.7	250	N.D.	<0.24	1.7	N.D.	25.0	7.3	3.0	<1.77	7.2	NA	22.0	0.1
		2	2.70	<5.3	1.3	1.8	230	N.D.	<0.24	1.8	<0.16	24.0	6.8	3.1	<1.77	7.2	49000	24.0	0.1
7/28/2016	1900	1	2.00	N.D.	2.1	2.8	200	N.D.	<0.24	1.8	1.6	28.0	6.0	2.8	<1.77	10.0	28000	30.0	0.4
		2	2.00	<5.3	2.1	2.7	205	N.D.	<0.24	1.7	1.0	29.0	6.0	2.7	1.9	11.0	27000	29.0	0.3
7/29/2016	700	1	1.90	N.D.	1.6	1.4	230	15	<0.24	5.7	N.D.	27.0	7.8	3.2	<1.77	7.9	30000	31.0	0.3
		2	2.30	<5.3	1.7	2.0	200	N.D.	<0.24	5.8	0.6	28.0	8.1	3.3	<1.77	8.3	33000	31.0	0.3
7/29/2016	1900	1	2.10	N.D.	2.7	3.8	190	N.D.	<0.24	2.0	1.3	27.0	5.0	4.5	<1.77	10.0	28000	34.0	0.8
		2	2.60	<5.3	2.8	3.7	200	N.D.	<0.24	2.0	1.2	24.0	5.3	4.5	<1.77	11.0	33000	39.0	0.8
7/30/2016	700	1	2.40	N.D.	0.8	1.0	110	N.D.	<0.24	0.9	0.1	16.0	5.7	3.0	<1.77	<1.52	30000	17.0	<0.07
		2	1.50	N.D.	0.8	0.8	95	N.D.	<0.24	0.9	<0.16	20.0	6.0	3.4	<1.77	2.7	29000	15.0	<0.07
7/30/2016	1900	1	6.70	16.4	3.9	3.7	120	29	15.00	106.0	8.4	30.0	4.7	2.8	<1.77	11.6	50000	110.0	22.0
		2	11.00	18.2	7.2	8.4	200	61	29.00	200.0	16.0	36.0	8.8	2.8	<1.77	14.8	43000	87.0	43.0
7/31/2016	700	1	1.80	N.D.	5.5	2.2	240	N.D.	N.D.	7.3	0.2	29.0	7.4	2.8	<1.77	7.9	NA	45.0	0.6
		2	1.90	N.D.	5.4	2.1	200	N.D.	<0.24	6.3	0.6	26.0	6.7	2.7	<1.77	7.0	37000	45.0	0.5
7/31/2016	1900	1	3.80	<5.3	1.2	3.7	180	N.D.	N.D.	5.4	2.1	27.0	5.0	2.7	2.0	8.1	32000	56.0	0.6
		2	2.80	<5.3	1.2	2.9	190	N.D.	N.D.	5.2	2.1	25.0	4.9	3.0	<1.77	7.7	32000	53.0	0.6

Probabilistic Hazard Assessment

In an attempt to translate monitoring data into a probabilistic hazard framework, the mean concentrations of duplicates from every sampling event in this thesis were compiled to evaluate the likelihood of exceeding the THV with 1000 fold safety factor for seven compounds. Antibiotics were assessed by examining the probability of exceeding the estimated minimal selective concentration. For every compound, concentrations were ranked using the Weibull formula and plotted (Figures 15 and 16). Based on the data acquired over an entire year, the probability of caffeine, ketamine, erythromycin, sulfamethoxazole, and trimethoprim of exceeding their respective threshold in final effluent at this plant is nearly 0%. Sertraline and fluoxetine can be expected to exceed the THV with 1000 fold safety factor virtually all of the time (> 99 %). Methylphenidate and diphenhydramine can be expected to exceed the THV threshold around 98% and 95% of the time, respectively. Further details regarding each distribution can be found in Table 4. Because acetaminophen, amitriptyline, diclofenac, diltiazem, and norfluoxetine were only detected in less than 75% of all samplings dates, probabilistic hazard assessment was not performed. Similarly, probabilistic hazard assessment was not performed for the cocaine metabolite, benzoylecgonine.

Other Effluent Wastewater Concentrations

In order to place our findings in this thesis into the greater global literature, probabilistic methods were employed. Maximum concentrations in the literature for many common pharmaceuticals were compared to concentrations recorded in this study to determine how representative WMARSS is of other wastewater treatment plants (Figure 17). Maximum values were used for acetaminophen [55–61], caffeine [38,45,56,57,59,61–

64], carbamazepine [38,45,55–57,59,62,63], diclofenac [38,57,59–62,65], diphenhydramine, sulfamethoxazole [38,45,55–59,61,62,65,66], and trimethoprim [55,57–59,61,62,65,66] due to availability of data and an assumption of worst case scenarios. More information regarding the literature values can be found in Appendix B. The plot of diphenhydramine was modified from an existing figure from our research group [67]. So as to not skew the distribution of acetaminophen, only one half-MDL value was used for the no detects and <MDL values recorded in this study. Further details regarding distributions can be found in Table 5.

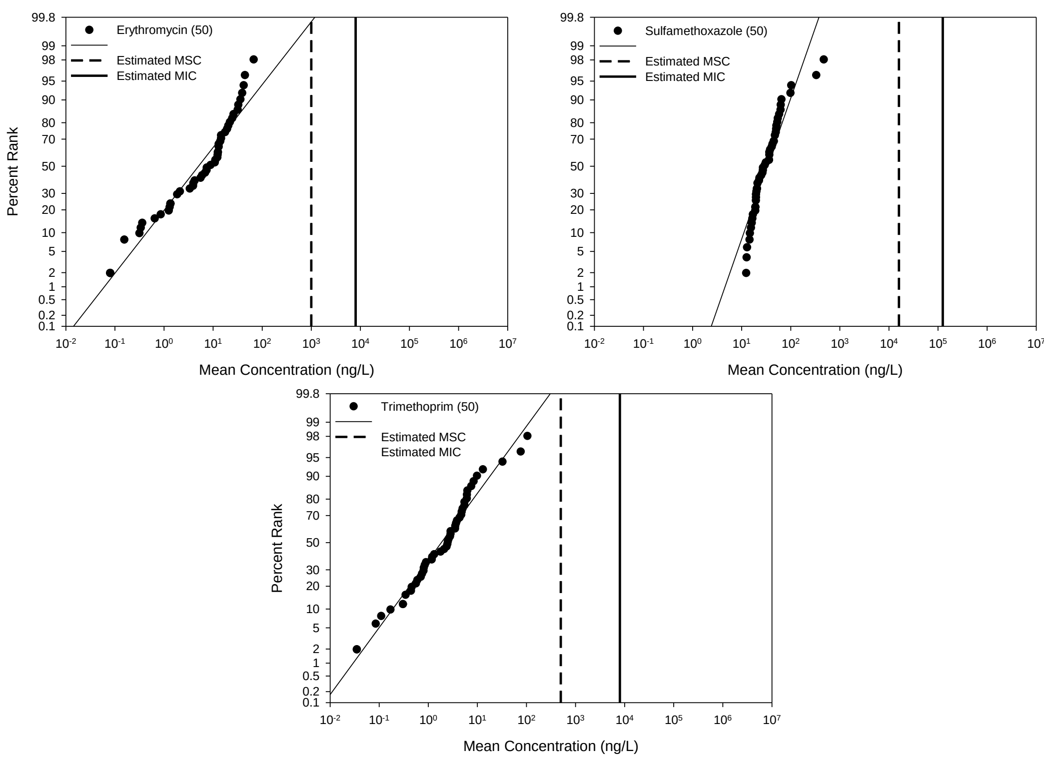

Figure 15. Probability distributions for selected antibiotics in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a year long study. Distributions are compared to estimated minimal selective concentrations (MSC, dashed line) and estimated minimal inhibitory concentrations (MIC, solid line).

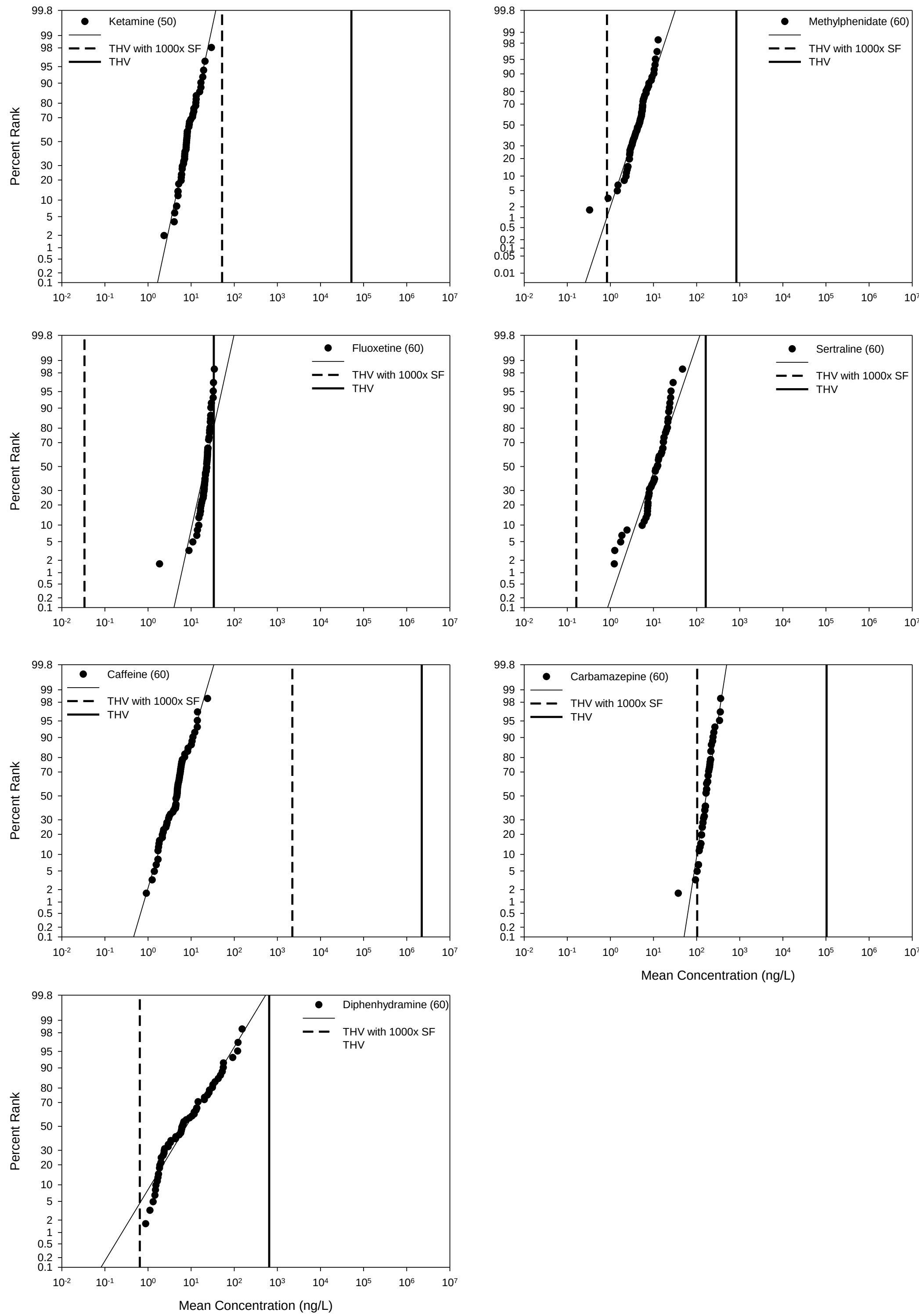

Figure 16. Probability distributions for selected PPCPs in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a year long study. Distributions are compared to THVs (solid line) and THVs with 1000 fold safety factor (solid line).

Table 4. List of compounds in which probability distributions were created, as well as values for regression lines, various centiles, and seasonal exceedances of hazard thresholds (THV with 1000 fold safety factor or estimated minimal selective concentration).

					Centile Value (ng/L)		Percent Exceedance			
Chemical	n	R^2	Slope	Intercept	1%	5%	Summer	Autumn	Winter	Spring
Caffeine	60	0.98	3.21	-2.02	0.80	1.31	0% (0/22)	0% (0/12)	0% (0/12)	0% (0/12)
Carbamazepine	60	0.89	6.04	-13.41	68.47	88.79	95.8% (23/24)	91.7% (11/12)	100% (12/12)	100% (12/12)
Ketamine	50	0.97	4.42	-4.07	2.48	3.53	0% (0/22)	0% (0/4)	0% (0/12)	0% (0/12)
Methylphenidate	60	0.92	3.28	-2.05	0.82	1.33	95.8% (23/24)	100% (12/12)	100% (12/12)	100% (12/12)
Fluoxetine	60	0.66	4.29	-5.67	6.03	8.69	100% (24/24)	100% (12/12)	100% (12/12)	100% (12/12)
Sertraline	60	0.88	2.79	-2.91	1.62	2.85	100% (24/24)	100% (12/12)	100% (12/12)	100% (12/12)
Diphenhydramine	60	0.96	1.56	-1.38	0.25	0.68	100% (24/24)	100% (12/12)	100% (12/12)	100% (12/12)
Erythromycin	50	0.94	1.21	-0.85	0.06	0.22	0% (0/22)	0% (0/4)	0% (0/12)	0% (0/12)
Sulfamethoxazole	50	0.87	2.72	-4.13	4.59	8.16	0% (0/22)	0% (0/4)	0% (0/12)	0% (0/12)
Trimethoprim	50	0.97	1.30	-0.34	0.03	0.10	0% (0/22)	0% (0/4)	0% (0/12)	0% (0/12)

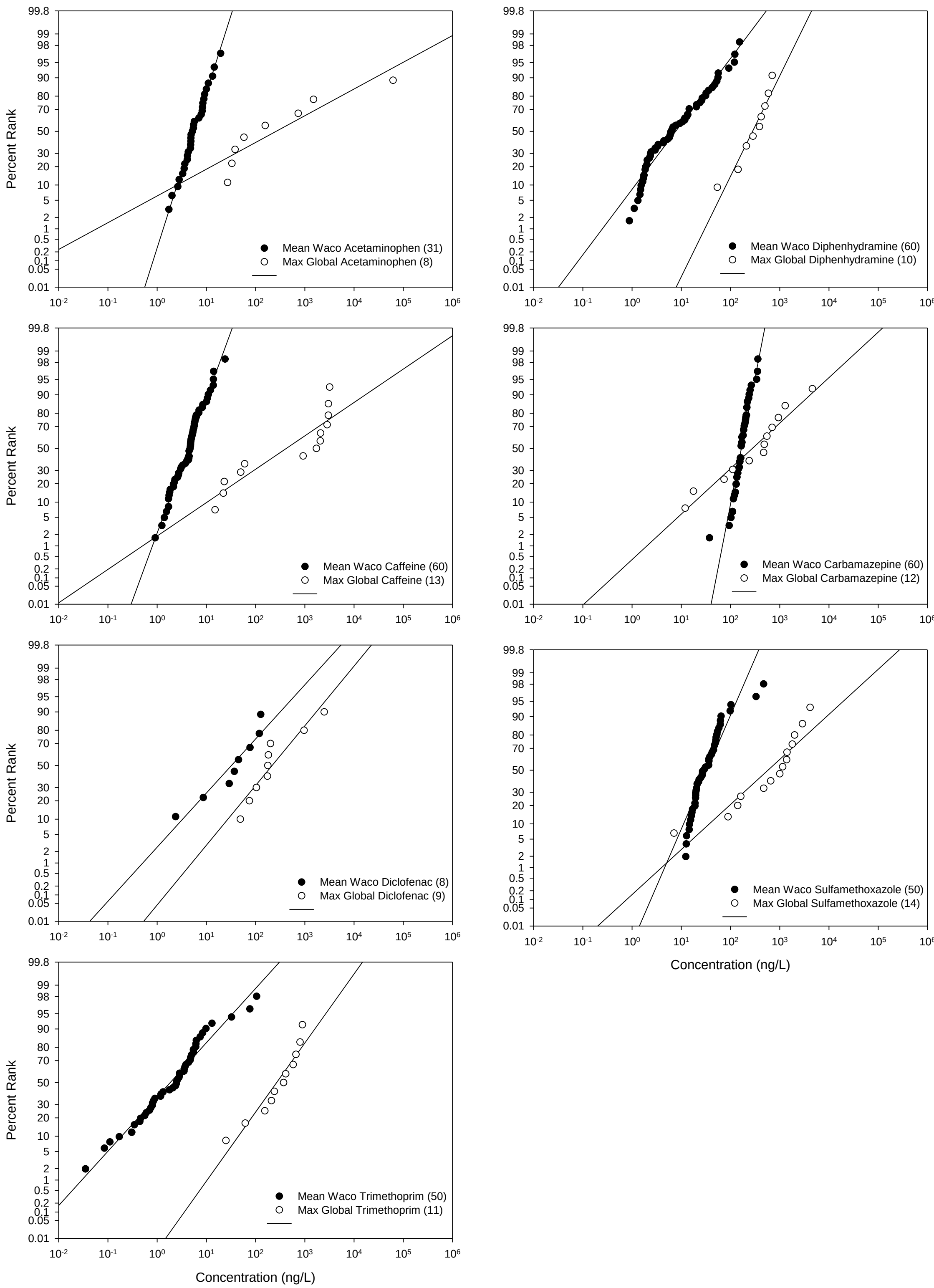

Figure 17. Probability distributions comparing representative global maximum literature values to effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a year long study.

Table 5. Representative sample of compounds from the literature in which probability distributions were created, as well as values for regression lines, and various centiles.

					Centile Value (ng/L)						
Chemical	n	R^2	Slope	Intercept	1%	5%	25%	50%	75%	95%	99%
Acetaminophen	8	0.84	0.64	-1.54	0.06	0.69	22.88	260.51	2965.85	98140.29	1145891.22
Caffeine	13	0.81	0.80	-2.09	0.51	3.64	59.98	420.69	2950.46	48629.78	348032.51
Carbamazepine	12	0.95	1.09	-2.65	2.00	8.49	66.38	277.21	1157.76	9052.01	38370.26
Diclofenac	9	0.87	1.43	-3.33	5.05	15.18	72.74	216.16	642.38	3078.30	9252.16
Sulfamethoxazole	14	0.86	1.08	-2.97	3.96	17.01	135.69	574.60	2433.23	19407.40	83425.20
Trimethoprim	11	0.91	1.65	-4.00	10.39	26.90	104.26	267.36	685.59	2657.28	6881.07

Discussion

WWTPs discharges represent the primary routes of pharmaceuticals introductions to aquatic systems [29]. Effluent concentrations can vary frequently to the point that different conclusions are drawn regarding potential adverse effects depending on when samples were collected [3]. Seasonal allergies, regional demographics and population shifts [4,5], temperature, dilution, live entertainment events [6], drug marketing and societal acceptance [7] are all factors that can influence long-term fluctuations in EIC. Short-term fluctuations can occur in a matter of minutes as influent can be thought of as individual compartments of sewage, randomly discharged from the flush of toilets throughout urban sewersheds, which flow together through sewer collection systems but do not consistently readily mix within different urban areas [8]. These small-scale variations within longer term periods indicate appropriate sampling approaches are imperative for effective environmental monitoring and decision-making. Subsequently, the goals of this research effort were to explore the variation of the occurrence and levels of pharmaceuticals at seasonal, weekly, and daily scales, and their corresponding hazards. In addition, I evaluated the summer critical monitoring period employed by regulatory agencies to determine if samples collected at this time are representative of the hazards that aquatic organisms face during other seasons.

Seasonal Variability of Effluent Water Quality

Most studies that investigate temporal variability do so from a seasonal perspective. Du et al. [50] recently studied seasonal variability of wastewater influent at a Texas WWTP. Building from this previous study, I conducted this thesis research at the same WWTP but instead analyzed EICs and associated hazards from effluent through time. My findings refuted my primary hypothesis, which stated concentrations of pharmaceuticals in effluent would not differ with season. However, low variability of acetaminophen across seasons in this study was similar to observations by Choi et al. [23]. Yu et al. and Hedgespeth et al. identified acetaminophen in different concentrations in different WWTPs, leading to conclusions that variation is due to regional usage patterns [4,28]. Regional usage could also explain that Stamatis and Konstantinou [25] observed lower concentrations in winter months, while Yu et al. and Hedgespeth et al. noticed increased concentrations in winter months. In the present study, the THR for acetaminophen exhibited similar behaviors, remaining low throughout the year.

When antibiotics were considered, erythromycin had significantly higher EICs in autumn, winter, and spring compared to summer, and trimethoprim, though not significantly different among seasons, demonstrated a similar trend of increasing ECIs from summer to spring. All antibiotics displayed increased RHRs over this same period, though it never reached or exceeded a threshold of 1 where resistance selection may be expected to begin. These observed concentrations are consistent with other studies that observed lowest concentrations in summer months [4,27,29,34,39,41,46]. Similar yearly peak concentrations for select antibiotics were found in winter and early spring in many other studies [4,25,28,29,33,34,38–40]. While generally this seems to be the case, some studies reported select antibiotics that deviated from this pattern [33,34,38]. Pereira et al. noted that loading of antibiotics was higher in summer than in spring in Portugal, but had lower removal efficiencies in spring [68], which could account for the patterns observed in the present thesis. For example, lower microbial activity in colder months may help explain the lower removal efficiency of some CECs [27]. Deceased treatment efficacy in colder winter months could explain significantly higher concentrations of ketamine and benzoylecgonine in autumn and winter months compared to summer, though a demographic shift over that time from students might also play a role [5]. Different treatment technologies undoubtedly have an influence on the final concentrations of CECs to reach the environment. Of the two daily studies that provided details on treatment technologies, one has less advanced treatment and displayed similar patterns as ours [19], while the other WWTP was more advanced than the current study system did not display any significant variability [18].

Concentrations of drugs of abuse have been known to correspond with local events [30]. The THR for ketamine was relatively constant throughout the year, while the THR for methylphenidate peaked in autumn and decreased gradually throughout the remaining seasons. Such elevated levels of methylphenidate are generally consistent with previous observations of this study location by Du et al (2014). However, the antihistamine diphenhydramine did not vary with season, which is contrary to evidence in the literature that showed antihistamines displaying significant seasonal variability [5,22]. The THR for diphenhydramine also remained stable throughout the year, and was below the threshold of 1 indicating low potential hazard. Total THR was higher in winter than in other seasons, and can most likely be attributed to lower degradation in colder months. Based on these results, conclusions made regarding effluent water quality hazards of antibiotics and drugs of abuse, and other pharmaceutical hazards of the effluent would be underestimated if samples were only collected during the TCEQ critical sampling period for surface water quality.

Day of Week Variability of Effluent Water Quality

My results indicated that there were no significant differences between weekday and weekend concentrations of CEC, in support of my hypothesis where differences were not expected. Ketamine and methylphenidate had slightly higher concentrations on Thursdays than on Sundays, and benzoylecgonine was found to have higher concentrations on weekend sampling events compared to weekdays. Benzoylecgonine concentrations are often monitored in influent [50,69,70], but also display similar trends in wastewater effluent [17,19] and have been attributed to temporal usage patterns of cocaine. Though drugs of abuse had a higher THR on weekdays and all antibiotics had a higher RHR on weekends, both ratios were below the threshold of 1 indicating that there are limited hazards posed to fish by these studied compounds. Total THR was higher on weekdays, and while below 1, the calculated value is limited by the number of target analytes. It is, however, important to note that there are undoubtedly other compounds contributing to the combined therapeutic hazards in this effluent, because the analyte list in the current study was limited to 23 analytes..

Time of Day Variability of Effluent Water Quality

Generally, the concentrations of all pharmaceuticals remained relatively constant throughout the day, in line with my hypothesis that concentrations would not vary at different times of day. The peak of benzoylecgonine at 7:00 PM and 1:00 AM followed by the gradual decline in concentration most likely corresponds to usage patterns of cocaine. Similar to observations made by Nelson et al. [46], a broad daily cycle of erythromycin, a more intense change in concentration of trimethoprim and sulfamethoxazole, and an absence of variation of carbamazepine and fluoxetine were recorded. This was the case even though the WWTP in the previous study by Nelson et al (26) employed more advanced wastewater treatment technology than in the present thesis. It is interesting to note that while the SSRI fluoxetine displayed no hourly variability, the SSRI sertraline did, which could also be a result of consumption patterns. A pattern of increased sucralose concentrations near meal times and an early evening spike in caffeine as noted by Anumol et al. [20] were not observed in the present study. Because only three previous studies in the literature attempted to characterize CEC variability in EICs at an hourly resolution, comparing such results from this study with these previous efforts is difficult. Future novel research in this area would be beneficial for understanding finer scale variations of CEC loading through sewage, from different sewersheds with cities, and subsequent influences on EICs.

Weekly Variability of Effluent Water Quality

I used a high-resolution weeklong sampling event during TCEQ's Critical Period to assess if differences in sampling times would yield different conclusions regarding effluent exposure of aquatic organisms to pharmaceuticals. Caffeine concentrations were higher in the effluent in the evenings than the mornings and can most likely be attributed to consumption patterns. This is contrary to findings reported by Anumol et al., which saw highest caffeine concentrations at 5:00 PM [20]. The antibiotic erythromycin was significantly higher at 7:00 PM than 7:00 AM, suggesting that samples collected during normal business hours would underestimate the hazard compared to sampling later in the day. The resolution of this sampling event was not high enough to determine if erythromycin displayed the same broad changes over 6-15 hours as seen in Nelson et al. [46].

Probabilistic Hazard Assessment

Of the seven compounds evaluated for exceedance of the THV with recommended safety factor and three antibiotics evaluated for resistance selection, five virtually cross this threshold throughout our year-long sampling event. The drug of abuse ketamine and the anthropogenic tracer caffeine were the lone compounds that were below the THV with safety factor year-round, and all antibiotics were predicted to be below the minimal selective concentration. However, the upper bounds of concentrations for erythromycin and trimethoprim approach the MSC. The upper bounds of concentrations for diphenhydramine and the SSRIs fluoxetine and sertraline approach the unadjusted THV. Given these results, further consideration is warranted regarding the potential adverse effects of these compounds in the aquatic environment.

Other Effluent Wastewater Concentrations

Employing probabilistic methods, I was able to relate the results of this study to concentrations of common pharmaceuticals in the literature. The maximum concentration for every compound except for carbamazepine (54.9%) was below the 50^{th} centile of maximum concentrations in the literature. In fact, acetaminophen and caffeine were both below the 25^{th} centile, and diphenhydramine and trimethoprim were just above at 26.4% and 25.2%, respectively. Based on these results it is reasonable to conclude that effluent from the Waco Metropolitan Area Regional Sewerage System has lower concentrations than a representative sample of other effluents found in the literature from around the world. This represents an initial review, and future efforts are required for a more extensive comparison.

Assumptions of Uncertainty Factors

The idea of uncertainty factors can be traced back to at least 1954, when Lehman and Fitzhugh proposed a 100-fold safety factor to humans from food additives [71]. This notion operates under the assumption that there is a safe dosage that will not cause observable, adverse effects, and that the distinction from a toxic dose would be readily apparent. Default uncertainty factors are typically factors of 10, which can be attributed to the fact that humans are approximately 10 times more sensitive to poisons than rats, and that when exposed to toxic substances, a sick human may be 10 times more vulnerable than a healthy human [71]. Lehman and Fitzhugh note that while they believe a 100-fold safety factor is appropriate, there is no scientific basis behind that number [71].

While uncertainty factors are necessary due to a paucity of data when it comes to extrapolating to other species, their accuracy can be improved. This is especially true when uncertainty is compounded by multiple extrapolations, as is the case in the calculation of THVs and MSCs in the present thesis. Because of these reasons there are benefits to data-derived uncertainty factors, one method of which is a probabilistic approach [72]. This method has the advantage of addressing the inherent variability of uncertainty factors as it deals with a range of values when calculating them [72]. Data-derived approaches to calculating uncertainty factors will be useful in future research for estimating hazard and risk as accurately as possible.

Regulatory Agencies

Regulatory agencies must prioritize spatial and temporal environmental surveillance and monitoring activities due to resource constraints. For example, in the State of Texas the TCEQ has established an index period (March 15^{th} – October 15^{th})

during which time surface water quality monitoring, including bioassessments of aquatic systems, should be conducted for regulatory purposes. Sampling during this period achieves many goals, most notable of which is that it ensures at least some samples are collected during the critical period (July 1st – September 30th), which is defined as the time when in-stream flows approach minimum levels and water reaches critical summer high temperatures. During this period, it is expected that dissolved oxygen will also be at its lowest levels [73]. Sampling during this critical period is intended to ensure that available resources are used most efficiently, based on an assumption that if criteria are met during these worst-case conditions, they will also be met at all other times of the year during regular flows, temperature, and dissolved oxygen concentrations. In arid and semi-arid regions like Texas, the concentration of down the drain chemicals and other wastewater contaminants have been shown to be highest when in-stream dilution of effluent discharge is at its lowest. In fact, effluent dominated and dependent systems likely represent worst case scenarios for aquatic exposures to pharmaceuticals and other down the drain chemicals in developed countries [74] because effective exposure duration is increased [75].

Conclusions

Based on the results in this study it is apparent that for some pharmaceuticals, temporal variations exist across many scales. Therefore, sampling at certain times of the year or at certain times of day has the potential to overestimate or, worse, underestimate the potential hazards posed by pharmaceuticals. In the present study, ketamine, benzoylecgonine, erythromycin, sertraline, and caffeine concentrations could be underestimated depending on when effluent samples were collected. Diverse factors that influence seasonal use patterns of pharmaceuticals [7], which significantly altered EICs in the present study through time, must be considered, particularly in urbanizing surface waters depending on effluent discharges for instream flows. Clearly, future efforts are needed to characterize the extent in which identified factors influence the variability of PPCPs in wastewater effluent, and to determine how the variability of exposure concentrations affects aquatic organisms.

APPENDICES

APPENDIX A

Measured Concentrations and Hazard Calculations

Table A.1. Measured concentrations of analytes in effluent from the Waco Metropolitan Area Regional Sewerage System, Waco, Texas, USA during a 1 year study, as well as Therapeutic Hazard Ratios (THR) and Resistance Hazard Ratios (RHR), and the Therapeutic Hazard Values (THV) and Minimal Selective Concentrations (MSC) used to calculate them, respectively. Estimated Minimal Inhibitory Concentrations (MIC) are also included for antibiotics. New THRs after the application of a 1000 fold safety factor to the THV are calculated here.

Caffeine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
June	Thursday	1900	3.1	2223339.097	1.3943E-06	0.001394299
June	Thursday	1900	2.9	2223339.097	1.30434E-06	0.001304344
June	Sunday	1900	2.3	2223339.097	1.03448E-06	0.00103448
June	Sunday	1900	2.3	2223339.097	1.03448E-06	0.00103448
July	Thursday	1900	2.8	2223339.097	1.25937E-06	0.001259367
July	Thursday	1900	2.7	2223339.097	1.21439E-06	0.00121439
July	Sunday	1900	3.7	2223339.097	1.66416E-06	0.001664164
July	Sunday	1900	2.9	2223339.097	1.30434E-06	0.001304344
Aug	Thursday	1900	5.018816284	2223339.097	2.25733E-06	0.002257333
Aug	Thursday	1900	4.48430701	2223339.097	2.01692E-06	0.002016924
Aug	Sunday	1900	7.408455106	2223339.097	3.33213E-06	0.00333213
Aug	Sunday	1900	20.42277632	2223339.097	9.18563E-06	0.009185633
Sept	Thursday	1900	8.795506789	2223339.097	3.95599E-06	0.00395599
Sept	Thursday	1900	7.77818469	2223339.097	3.49842E-06	0.003498425

Table A.1. (continued)

Caffeine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Sept	Sunday	1900	5.100470226	2223339.097	2.29406E-06	0.002294059
Sept	Sunday	1900	5.583403694	2223339.097	2.51127E-06	0.00251127
Oct	Thursday	1900	6.380298932	2223339.097	2.86969E-06	0.002869692
Oct	Thursday	1900	5.473935231	2223339.097	2.46203E-06	0.002462033
Oct	Sunday	1900	4.623079037	2223339.097	2.07934E-06	0.002079341
Oct	Sunday	1900	4.63683427	2223339.097	2.08553E-06	0.002085527
Nov	Thursday	1900	4.43	2223339.097	1.9925E-06	0.001992499
Nov	Thursday	1900	4.43	2223339.097	1.9925E-06	0.001992499
Nov	Sunday	1900	4.43	2223339.097	1.9925E-06	0.001992499
Nov	Sunday	1900	4.43	2223339.097	1.9925E-06	0.001992499
Dec	Thursday	1900	4.371072833	2223339.097	1.96599E-06	0.001965995
Dec	Thursday	1900	4.43	2223339.097	1.9925E-06	0.001992499
Dec	Sunday	1900	4.503964795	2223339.097	2.02577E-06	0.002025766
Dec	Sunday	1900	4.909143646	2223339.097	2.208E-06	0.002208005
Jan	Thursday	1900	4.43	2223339.097	1.9925E-06	0.001992499
Jan	Thursday	1900	5.163315333	2223339.097	2.32232E-06	0.002322325
Jan	Sunday	1900	5.874540253	2223339.097	2.64222E-06	0.002642215
Jan	Sunday	1900	4.95796232	2223339.097	2.22996E-06	0.002229962
Feb	Thursday	1900	2.8	2223339.097	1.25937E-06	0.001259367
Feb	Thursday	1900	8.6	2223339.097	3.86806E-06	0.003868056
Feb	Sunday	1900	2.5	2223339.097	1.12443E-06	0.001124435
Feb	Sunday	1900	3.7	2223339.097	1.66416E-06	0.001664164
March	Thursday	1900	6.6	2223339.097	2.96851E-06	0.002968508
March	Thursday	1900	4.7	2223339.097	2.11394E-06	0.002113938
March	Sunday	1900	5.4	2223339.097	2.42878E-06	0.002428779
March	Sunday	1900	3.5	2223339.097	1.57421E-06	0.001574209
April	Thursday	1900	2.4	2223339.097	1.07946E-06	0.001079457

Table A.1. (continued)

Caffeine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
April	Thursday	1900	2.8	2223339.097	1.25937E-06	0.001259367
April	Sunday	1900	24	2223339.097	1.07946E-05	0.010794575
April	Sunday	1900	24	2223339.097	1.07946E-05	0.010794575
May	Thursday	1900	3	2223339.097	1.34932E-06	0.001349322
May	Thursday	1900	2.4	2223339.097	1.07946E-06	0.001079457
May	Sunday	1900	1.6	2223339.097	7.19638E-07	0.000719638
May	Sunday	1900	1.2	2223339.097	5.39729E-07	0.000539729
Sept	Thursday	0100	7.224576443	2223339.097	3.24943E-06	0.003249426
Sept	Thursday	0100	5.288437323	2223339.097	2.3786E-06	0.002378601
Sept	Thursday	0700	5.084854904	2223339.097	2.28704E-06	0.002287035
Sept	Thursday	0700	6.012203761	2223339.097	2.70413E-06	0.002704133
Sept	Thursday	1300	11.01813201	2223339.097	4.95567E-06	0.004955669
Sept	Thursday	1300	13.27854697	2223339.097	5.97234E-06	0.005972344
Sept	Thursday	1900	8.795506789	2223339.097	3.95599E-06	0.00395599
Sept	Thursday	1900	7.77818469	2223339.097	3.49842E-06	0.003498425
Sept	Sunday	0100	5.17955321	2223339.097	2.32963E-06	0.002329628
Sept	Sunday	0100	4.842094899	2223339.097	2.17785E-06	0.002177848
Sept	Sunday	0700	6.37159958	2223339.097	2.86578E-06	0.002865779
Sept	Sunday	0700	3.927727174	2223339.097	1.76659E-06	0.001766589
Sept	Sunday	1300	10.74841626	2223339.097	4.83436E-06	0.004834358
Sept	Sunday	1300	9.431918482	2223339.097	4.24223E-06	0.004242231
Sept	Sunday	1900	5.100470226	2223339.097	2.29406E-06	0.002294059
Sept	Sunday	1900	5.583403694	2223339.097	2.51127E-06	0.00251127
Dec	Thursday	0100	4.43	2223339.097	1.9925E-06	0.001992499
Dec	Thursday	0100	5.121210509	2223339.097	2.30339E-06	0.002303387
Dec	Thursday	0700	4.43	2223339.097	1.9925E-06	0.001992499
Dec	Thursday	0700	4.43	2223339.097	1.9925E-06	0.001992499

Table A.1. (continued)

Caffeine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Dec	Thursday	1300	4.884788477	2223339.097	2.19705E-06	0.002197051
Dec	Thursday	1300	4.939773696	2223339.097	2.22178E-06	0.002221782
Dec	Thursday	1900	4.371072833	2223339.097	1.96599E-06	0.001965995
Dec	Thursday	1900	4.43	2223339.097	1.9925E-06	0.001992499
Dec	Sunday	0100	4.902104977	2223339.097	2.20484E-06	0.002204839
Dec	Sunday	0100	6.77619025	2223339.097	3.04775E-06	0.003047754
Dec	Sunday	0700	8.587655506	2223339.097	3.8625E-06	0.003862504
Dec	Sunday	0700	5.5047215	2223339.097	2.47588E-06	0.00247588
Dec	Sunday	1300	4.568040177	2223339.097	2.05459E-06	0.002054585
Dec	Sunday	1300	4.111474892	2223339.097	1.84923E-06	0.001849234
Dec	Sunday	1900	4.503964795	2223339.097	2.02577E-06	0.002025766
Dec	Sunday	1900	4.909143646	2223339.097	2.208E-06	0.002208005
March	Thursday	0100	7.7	2223339.097	3.46326E-06	0.003463259
March	Thursday	0100	20	2223339.097	8.99548E-06	0.008995479
March	Thursday	0700	9.8	2223339.097	4.40778E-06	0.004407785
March	Thursday	0700	7.2	2223339.097	3.23837E-06	0.003238372
March	Thursday	1300	8.9	2223339.097	4.00299E-06	0.004002988
March	Thursday	1300	5.3	2223339.097	2.3838E-06	0.002383802
March	Thursday	1900	6.6	2223339.097	2.96851E-06	0.002968508
March	Thursday	1900	4.7	2223339.097	2.11394E-06	0.002113938
March	Sunday	0100	7.1	2223339.097	3.1934E-06	0.003193395
March	Sunday	0100	21	2223339.097	9.44525E-06	0.009445253
March	Sunday	0700	11	2223339.097	4.94751E-06	0.004947513
March	Sunday	0700	10	2223339.097	4.49774E-06	0.004497739
March	Sunday	1300	14	2223339.097	6.29684E-06	0.006296835
March	Sunday	1300	8	2223339.097	3.59819E-06	0.003598192
March	Sunday	1900	5.4	2223339.097	2.42878E-06	0.002428779

Table A.1. (continued)

Caffeine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
March	Sunday	1900	3.5	2223339.097	1.57421E-06	0.001574209
June	Thursday	0100	1.1	2223339.097	4.94751E-07	0.000494751
June	Thursday	0100	1.4	2223339.097	6.29684E-07	0.000629684
June	Thursday	0700	1.7	2223339.097	7.64616E-07	0.000764616
June	Thursday	0700	1.4	2223339.097	6.29684E-07	0.000629684
June	Thursday	1300	2	2223339.097	8.99548E-07	0.000899548
June	Thursday	1300	2.3	2223339.097	1.03448E-06	0.00103448
June	Thursday	1900	3.1	2223339.097	1.3943E-06	0.001394299
June	Thursday	1900	2.9	2223339.097	1.30434E-06	0.001304344
June	Sunday	0100	1.6	2223339.097	7.19638E-07	0.000719638
June	Sunday	0100	1.8	2223339.097	8.09593E-07	0.000809593
June	Sunday	0700	1.5	2223339.097	6.74661E-07	0.000674661
June	Sunday	0700	1.9	2223339.097	8.5457E-07	0.00085457
June	Sunday	1300	2.2	2223339.097	9.89503E-07	0.000989503
June	Sunday	1300	2.3	2223339.097	1.03448E-06	0.00103448
June	Sunday	1900	2.3	2223339.097	1.03448E-06	0.00103448
June	Sunday	1900	2.3	2223339.097	1.03448E-06	0.00103448
Carbamazepine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
June	Thursday	1900	120	103063.716	0.001164328	1.164328288
June	Thursday	1900	130	103063.716	0.001261356	1.261355646
June	Sunday	1900	150	103063.716	0.00145541	1.45541036
June	Sunday	1900	150	103063.716	0.00145541	1.45541036
July	Thursday	1900	200	103063.716	0.001940547	1.940547147
July	Thursday	1900	205	103063.716	0.001989061	1.989060826
July	Sunday	1900	120	103063.716	0.001164328	1.164328288
July	Sunday	1900	200	103063.716	0.001940547	1.940547147

Table A.1. (continued)

Carbamazepine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Aug	Thursday	1900	190	103063.716	0.00184352	1.84351979
Aug	Thursday	1900	210	103063.716	0.002037575	2.037574505
Aug	Sunday	1900	170	103063.716	0.001649465	1.649465075
Aug	Sunday	1900	170	103063.716	0.001651728	1.651728303
Sept	Thursday	1900	160	103063.716	0.001552438	1.552437718
Sept	Thursday	1900	170	103063.716	0.001649465	1.649465075
Sept	Sunday	1900	180	103063.716	0.001746492	1.746492432
Sept	Sunday	1900	180	103063.716	0.001746492	1.746492432
Oct	Thursday	1900	220	103063.716	0.002134602	2.134601862
Oct	Thursday	1900	200	103063.716	0.001940547	1.940547147
Oct	Sunday	1900	40	103063.716	0.000388109	0.388109429
Oct	Sunday	1900	35	103063.716	0.000339596	0.339595751
Nov	Thursday	1900	91	103063.716	0.000882949	0.882948952
Nov	Thursday	1900	97	103063.716	0.000941165	0.941165366
Nov	Sunday	1900	120	103063.716	0.001164328	1.164328288
Nov	Sunday	1900	120	103063.716	0.001164328	1.164328288
Dec	Thursday	1900	110	103063.716	0.001067301	1.067300931
Dec	Thursday	1900	110	103063.716	0.001067301	1.067300931
Dec	Sunday	1900	130	103063.716	0.001261356	1.261355646
Dec	Sunday	1900	130	103063.716	0.001261356	1.261355646
Jan	Thursday	1900	130	103063.716	0.001261356	1.261355646
Jan	Thursday	1900	140	103063.716	0.001358383	1.358383003
Jan	Sunday	1900	140	103063.716	0.001358383	1.358383003
Jan	Sunday	1900	140	103063.716	0.001358383	1.358383003
Feb	Thursday	1900	200	103063.716	0.001940547	1.940547147
Feb	Thursday	1900	230	103063.716	0.002231629	2.231629219
Feb	Sunday	1900	240	103063.716	0.002328657	2.328656577

Table A.1. (continued)

Carbamazepine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Feb	Sunday	1900	230	103063.716	0.002231629	2.231629219
March	Thursday	1900	140	103063.716	0.001358383	1.358383003
March	Thursday	1900	150	103063.716	0.00145541	1.45541036
March	Sunday	1900	220	103063.716	0.002134602	2.134601862
March	Sunday	1900	140	103063.716	0.001358383	1.358383003
April	Thursday	1900	400	103063.716	0.003881094	3.881094294
April	Thursday	1900	320	103063.716	0.003104875	3.104875436
April	Sunday	1900	350	103063.716	0.003395958	3.395957508
April	Sunday	1900	360	103063.716	0.003492985	3.492984865
May	Thursday	1900	130	103063.716	0.001261356	1.261355646
May	Thursday	1900	130	103063.716	0.001261356	1.261355646
May	Sunday	1900	340	103063.716	0.00329893	3.29893015
May	Sunday	1900	340	103063.716	0.00329893	3.29893015
Sept	Thursday	0100	190	103063.716	0.00184352	1.84351979
Sept	Thursday	0100	190	103063.716	0.00184352	1.84351979
Sept	Thursday	0700	180	103063.716	0.001746492	1.746492432
Sept	Thursday	0700	190	103063.716	0.00184352	1.84351979
Sept	Thursday	1300	180	103063.716	0.001746492	1.746492432
Sept	Thursday	1300	180	103063.716	0.001746492	1.746492432
Sept	Thursday	1900	160	103063.716	0.001552438	1.552437718
Sept	Thursday	1900	170	103063.716	0.001649465	1.649465075
Sept	Sunday	0100	170	103063.716	0.001649465	1.649465075
Sept	Sunday	0100	160	103063.716	0.001552438	1.552437718
Sept	Sunday	0700	170	103063.716	0.001649465	1.649465075
Sept	Sunday	0700	170	103063.716	0.001649465	1.649465075
Sept	Sunday	1300	160	103063.716	0.001552438	1.552437718
Sept	Sunday	1300	160	103063.716	0.001552438	1.552437718

Table A.1. (continued)

Carbamazepine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Sept	Sunday	1900	180	103063.716	0.001746492	1.746492432
Sept	Sunday	1900	180	103063.716	0.001746492	1.746492432
Dec	Thursday	0100	110	103063.716	0.001067301	1.067300931
Dec	Thursday	0100	110	103063.716	0.001067301	1.067300931
Dec	Thursday	0700	110	103063.716	0.001067301	1.067300931
Dec	Thursday	0700	120	103063.716	0.001164328	1.164328288
Dec	Thursday	1300	110	103063.716	0.001067301	1.067300931
Dec	Thursday	1300	110	103063.716	0.001067301	1.067300931
Dec	Thursday	1900	110	103063.716	0.001067301	1.067300931
Dec	Thursday	1900	110	103063.716	0.001067301	1.067300931
Dec	Sunday	0100	120	103063.716	0.001164328	1.164328288
Dec	Sunday	0100	130	103063.716	0.001261356	1.261355646
Dec	Sunday	0700	130	103063.716	0.001261356	1.261355646
Dec	Sunday	0700	140	103063.716	0.001358383	1.358383003
Dec	Sunday	1300	140	103063.716	0.001358383	1.358383003
Dec	Sunday	1300	140	103063.716	0.001358383	1.358383003
Dec	Sunday	1900	130	103063.716	0.001261356	1.261355646
Dec	Sunday	1900	130	103063.716	0.001261356	1.261355646
March	Thursday	0100	170	103063.716	0.001649465	1.649465075
March	Thursday	0100	150	103063.716	0.00145541	1.45541036
March	Thursday	0700	160	103063.716	0.001552438	1.552437718
March	Thursday	0700	180	103063.716	0.001746492	1.746492432
March	Thursday	1300	150	103063.716	0.00145541	1.45541036
March	Thursday	1300	160	103063.716	0.001552438	1.552437718
March	Thursday	1900	140	103063.716	0.001358383	1.358383003
March	Thursday	1900	150	103063.716	0.00145541	1.45541036
March	Sunday	0100	170	103063.716	0.001649465	1.649465075

Table A.1. (continued)

Carbamazepine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
March	Sunday	0100	170	103063.716	0.001649465	1.649465075
March	Sunday	0700	170	103063.716	0.001649465	1.649465075
March	Sunday	0700	150	103063.716	0.00145541	1.45541036
March	Sunday	1300	170	103063.716	0.001649465	1.649465075
March	Sunday	1300	150	103063.716	0.00145541	1.45541036
March	Sunday	1900	220	103063.716	0.002134602	2.134601862
March	Sunday	1900	140	103063.716	0.001358383	1.358383003
June	Thursday	0100	130	103063.716	0.001261356	1.261355646
June	Thursday	0100	130	103063.716	0.001261356	1.261355646
June	Thursday	0700	160	103063.716	0.001552438	1.552437718
June	Thursday	0700	150	103063.716	0.00145541	1.45541036
June	Thursday	1300	120	103063.716	0.001164328	1.164328288
June	Thursday	1300	130	103063.716	0.001261356	1.261355646
June	Thursday	1900	120	103063.716	0.001164328	1.164328288
June	Thursday	1900	130	103063.716	0.001261356	1.261355646
June	Sunday	0100	150	103063.716	0.00145541	1.45541036
June	Sunday	0100	150	103063.716	0.00145541	1.45541036
June	Sunday	0700	160	103063.716	0.001552438	1.552437718
June	Sunday	0700	160	103063.716	0.001552438	1.552437718
June	Sunday	1300	150	103063.716	0.00145541	1.45541036
June	Sunday	1300	150	103063.716	0.00145541	1.45541036
June	Sunday	1900	150	103063.716	0.00145541	1.45541036
June	Sunday	1900	150	103063.716	0.00145541	1.45541036
Ketamine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
June	Thursday	1900	4.3	52182.12664	8.24037E-05	0.082403694
June	Thursday	1900	4.9	52182.12664	9.39019E-05	0.093901884

Table A.1. (continued)

Ketamine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
June	Sunday	1900	5.3	52182.12664	0.000101567	0.101567344
June	Sunday	1900	3.9	52182.12664	7.47382E-05	0.074738234
July	Thursday	1900	6	52182.12664	0.000114982	0.114981899
July	Thursday	1900	6	52182.12664	0.000114982	0.114981899
July	Sunday	1900	5	52182.12664	9.58182E-05	0.095818249
July	Sunday	1900	4.9	52182.12664	9.39019E-05	0.093901884
Aug	Thursday	1900	N/A	52182.12664	N/A	N/A
Aug	Thursday	1900	N/A	52182.12664	N/A	N/A
Aug	Sunday	1900	N/A	52182.12664	N/A	N/A
Aug	Sunday	1900	N/A	52182.12664	N/A	N/A
Sept	Thursday	1900	N/A	52182.12664	N/A	N/A
Sept	Thursday	1900	N/A	52182.12664	N/A	N/A
Sept	Sunday	1900	N/A	52182.12664	N/A	N/A
Sept	Sunday	1900	N/A	52182.12664	N/A	N/A
Oct	Thursday	1900	18.9364	52182.12664	0.000362891	0.362890538
Oct	Thursday	1900	18.2246	52182.12664	0.00034925	0.349249852
Oct	Sunday	1900	12.3825	52182.12664	0.000237294	0.237293893
Oct	Sunday	1900	10.6884	52182.12664	0.000204829	0.204828754
Nov	Thursday	1900	12.779	52182.12664	0.000244892	0.244892281
Nov	Thursday	1900	12.7961	52182.12664	0.00024522	0.245219979
Nov	Sunday	1900	16.873	52182.12664	0.000323348	0.323348263
Nov	Sunday	1900	16.8841	52182.12664	0.000323561	0.323560979
Dec	Thursday	1900	17.1287	52182.12664	0.000328248	0.328248408
Dec	Thursday	1900	16.5802	52182.12664	0.000317737	0.317737146
Dec	Sunday	1900	11.7546	52182.12664	0.000225261	0.225261038
Dec	Sunday	1900	11.2385	52182.12664	0.000215371	0.215370678
Jan	Thursday	1900	13.1228	52182.12664	0.000251481	0.251480743

Table A.1. (continued)

Ketamine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Jan	Thursday	1900	13.0213	52182.12664	0.000249536	0.249535633
Jan	Sunday	1900	12.8819	52182.12664	0.000246864	0.24686422
Jan	Sunday	1900	8.6457	52182.12664	0.000165683	0.165683167
Feb	Thursday	1900	28	52182.12664	0.000536582	0.536582194
Feb	Thursday	1900	31	52182.12664	0.000594073	0.594073143
Feb	Sunday	1900	20	52182.12664	0.000383273	0.383272996
Feb	Sunday	1900	22	52182.12664	0.0004216	0.421600295
March	Thursday	1900	8.2	52182.12664	0.000157142	0.157141928
March	Thursday	1900	8	52182.12664	0.000153309	0.153309198
March	Sunday	1900	7.9	52182.12664	0.000151393	0.151392833
March	Sunday	1900	7.4	52182.12664	0.000141811	0.141811008
April	Thursday	1900	6.5	52182.12664	0.000124564	0.124563724
April	Thursday	1900	5.9	52182.12664	0.000113066	0.113065534
April	Sunday	1900	7.7	52182.12664	0.00014756	0.147560103
April	Sunday	1900	8.4	52182.12664	0.000160975	0.160974658
May	Thursday	1900	3.7	52182.12664	7.09055E-05	0.070905504
May	Thursday	1900	4.4	52182.12664	8.43201E-05	0.084320059
May	Sunday	1900	6.4	52182.12664	0.000122647	0.122647359
May	Sunday	1900	6.1	52182.12664	0.000116898	0.116898264
Sept	Thursday	0100	N/A	52182.12664	N/A	N/A
Sept	Thursday	0100	N/A	52182.12664	N/A	N/A
Sept	Thursday	0700	N/A	52182.12664	N/A	N/A
Sept	Thursday	0700	N/A	52182.12664	N/A	N/A
Sept	Thursday	1300	N/A	52182.12664	N/A	N/A
Sept	Thursday	1300	N/A	52182.12664	N/A	N/A
Sept	Thursday	1900	N/A	52182.12664	N/A	N/A
Sept	Thursday	1900	N/A	52182.12664	N/A	N/A

Table A.1. (continued)

Ketamine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Sept	Sunday	0100	N/A	52182.12664	N/A	N/A
Sept	Sunday	0100	N/A	52182.12664	N/A	N/A
Sept	Sunday	0700	N/A	52182.12664	N/A	N/A
Sept	Sunday	0700	N/A	52182.12664	N/A	N/A
Sept	Sunday	1300	N/A	52182.12664	N/A	N/A
Sept	Sunday	1300	N/A	52182.12664	N/A	N/A
Sept	Sunday	1900	N/A	52182.12664	N/A	N/A
Sept	Sunday	1900	N/A	52182.12664	N/A	N/A
Dec	Thursday	0100	7.2139	52182.12664	0.000138245	0.138244653
Dec	Thursday	0100	8.0073	52182.12664	0.000153449	0.153449093
Dec	Thursday	0700	8.9285	52182.12664	0.000171103	0.171102647
Dec	Thursday	0700	9.168	52182.12664	0.000175692	0.175692341
Dec	Thursday	1300	7.8336	52182.12664	0.00015012	0.150120367
Dec	Thursday	1300	7.7318	52182.12664	0.00014817	0.148169507
Dec	Thursday	1900	17.1287	52182.12664	0.000328248	0.328248408
Dec	Thursday	1900	16.5802	52182.12664	0.000317737	0.317737146
Dec	Sunday	0100	13.0764	52182.12664	0.000250592	0.25059155
Dec	Sunday	0100	12.7083	52182.12664	0.000243537	0.243537411
Dec	Sunday	0700	15.4287	52182.12664	0.00029567	0.295670203
Dec	Sunday	0700	16.0508	52182.12664	0.000307592	0.30759191
Dec	Sunday	1300	12.6898	52182.12664	0.000243183	0.243182883
Dec	Sunday	1300	13.5523	52182.12664	0.000259712	0.259711531
Dec	Sunday	1900	11.7546	52182.12664	0.000225261	0.225261038
Dec	Sunday	1900	11.2385	52182.12664	0.000215371	0.215370678
March	Thursday	0100	19	52182.12664	0.000364109	0.364109346
March	Thursday	0100	20	52182.12664	0.000383273	0.383272996
March	Thursday	0700	7.9	52182.12664	0.000151393	0.151392833

Table A.1. (continued)

Ketamine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
March	Thursday	0700	8.5	52182.12664	0.000162891	0.162891023
March	Thursday	1300	7.2	52182.12664	0.000137978	0.137978278
March	Thursday	1300	8.2	52182.12664	0.000157142	0.157141928
March	Thursday	1900	8.2	52182.12664	0.000157142	0.157141928
March	Thursday	1900	8	52182.12664	0.000153309	0.153309198
March	Sunday	0100	8.6	52182.12664	0.000164807	0.164807388
March	Sunday	0100	7.8	52182.12664	0.000149476	0.149476468
March	Sunday	0700	9.1	52182.12664	0.000174389	0.174389213
March	Sunday	0700	9.2	52182.12664	0.000176306	0.176305578
March	Sunday	1300	9.8	52182.12664	0.000187804	0.187803768
March	Sunday	1300	7.9	52182.12664	0.000151393	0.151392833
March	Sunday	1900	7.9	52182.12664	0.000151393	0.151392833
March	Sunday	1900	7.4	52182.12664	0.000141811	0.141811008
June	Thursday	0100	4.6	52182.12664	8.81528E-05	0.088152789
June	Thursday	0100	5.3	52182.12664	0.000101567	0.101567344
June	Thursday	0700	5.2	52182.12664	9.9651E-05	0.099650979
June	Thursday	0700	4.7	52182.12664	9.00692E-05	0.090069154
June	Thursday	1300	4	52182.12664	7.66546E-05	0.076654599
June	Thursday	1300	4.3	52182.12664	8.24037E-05	0.082403694
June	Thursday	1900	4.3	52182.12664	8.24037E-05	0.082403694
June	Thursday	1900	4.9	52182.12664	9.39019E-05	0.093901884
June	Sunday	0100	5.9	52182.12664	0.000113066	0.113065534
June	Sunday	0100	6.1	52182.12664	0.000116898	0.116898264
June	Sunday	0700	6.4	52182.12664	0.000122647	0.122647359
June	Sunday	0700	6.9	52182.12664	0.000132229	0.132229184
June	Sunday	1300	7.1	52182.12664	0.000136062	0.136061913
June	Sunday	1300	7.1	52182.12664	0.000136062	0.136061913

Table A.1. (continued)

Ketamine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
June	Sunday	1900	5.3	52182.12664	0.000101567	0.101567344
June	Sunday	1900	3.9	52182.12664	7.47382E-05	0.074738234

Diphenhydramine						
Month	Day	Time	Water Concentration (ng/L)	THV (ng/L)	THR	THR Safety Factor 1000
June	Thursday	1900	5.9	646.5010754	0.009126048	9.126048239
June	Thursday	1900	6.2	646.5010754	0.009590085	9.59008459
June	Sunday	1900	2.6	646.5010754	0.004021648	4.021648376
June	Sunday	1900	3.3	646.5010754	0.0051044	5.104399862
July	Thursday	1900	1.8	646.5010754	0.002784218	2.784218107
July	Thursday	1900	1.7	646.5010754	0.002629539	2.629539323
July	Sunday	1900	5.4	646.5010754	0.008352654	8.35265432
July	Sunday	1900	5.2	646.5010754	0.008043297	8.043296753
Aug	Thursday	1900	65.311	646.5010754	0.10102226	101.0222604
Aug	Thursday	1900	46.1442	646.5010754	0.071375287	71.37528731
Aug	Sunday	1900	1.3481	646.5010754	0.002085225	2.085224683
Aug	Sunday	1900	1.2805	646.5010754	0.001980662	1.980661825
Sept	Thursday	1900	1.3848	646.5010754	0.002141992	2.141991797
Sept	Thursday	1900	2.3745	646.5010754	0.003672848	3.672847719
Sept	Sunday	1900	2.2099	646.5010754	0.003418246	3.418246441
Sept	Sunday	1900	1.8475	646.5010754	0.002857691	2.857690529
Oct	Thursday	1900	2.3757	646.5010754	0.003674704	3.674703864
Oct	Thursday	1900	2.4971	646.5010754	0.003862484	3.862483908
Oct	Sunday	1900	4.4239	646.5010754	0.006842835	6.842834712
Oct	Sunday	1900	4.2957	646.5010754	0.006644537	6.644536512
Nov	Thursday	1900	14.7994	646.5010754	0.022891532	22.89153192
Nov	Thursday	1900	11.2374	646.5010754	0.017381874	17.38187364
Nov	Sunday	1900	11.7981	646.5010754	0.018249158	18.24915758

Table A.1. (continued)

Diphenhydramine						
Month	Day	Time	Water Concentration (ng/L)	THV (ng/L)	THR	THR Safety Factor 1000
Nov	Sunday	1900	N/A	646.5010754	N/A	N/A
Dec	Thursday	1900	33.4658	646.5010754	0.051764492	51.7644924
Dec	Thursday	1900	28.9942	646.5010754	0.044847876	44.84787591
Dec	Sunday	1900	41.4442	646.5010754	0.064105384	64.10538448
Dec	Sunday	1900	43.8877	646.5010754	0.067884961	67.88496056
Jan	Thursday	1900	52.2441	646.5010754	0.080810538	80.81053844
Jan	Thursday	1900	53.3697	646.5010754	0.082551603	82.55160283
Jan	Sunday	1900	19.6271	646.5010754	0.03035896	30.35895956
Jan	Sunday	1900	21.0327	646.5010754	0.032533125	32.53312454
Feb	Thursday	1900	6	646.5010754	0.009280727	9.280727022
Feb	Thursday	1900	6.2	646.5010754	0.009590085	9.59008459
Feb	Sunday	1900	11	646.5010754	0.017014666	17.01466621
Feb	Sunday	1900	10	646.5010754	0.015467878	15.46787837
March	Thursday	1900	35	646.5010754	0.054137574	54.1375743
March	Thursday	1900	37	646.5010754	0.05723115	57.23114997
March	Sunday	1900	22	646.5010754	0.034029332	34.02933242
March	Sunday	1900	19	646.5010754	0.029388969	29.3889689
April	Thursday	1900	6.8	646.5010754	0.010518157	10.51815729
April	Thursday	1900	5.9	646.5010754	0.009126048	9.126048239
April	Sunday	1900	121	646.5010754	0.187161328	187.1613283
April	Sunday	1900	124	646.5010754	0.191801692	191.8016918
May	Thursday	1900	13	646.5010754	0.020108242	20.10824188
May	Thursday	1900	14	646.5010754	0.02165503	21.65502972
May	Sunday	1900	6.7	646.5010754	0.010363479	10.36347851
May	Sunday	1900	6.5	646.5010754	0.010054121	10.05412094
Sept	Thursday	0100	10.5121	646.5010754	0.016259988	16.25998842
Sept	Thursday	0100	13.0722	646.5010754	0.02021992	20.21991996

Table A.1. (continued)

Diphenhydramine						
Month	Day	Time	Water Concentration (ng/L)	THV (ng/L)	THR	THR Safety Factor 1000
Sept	Thursday	0700	2.4259	646.5010754	0.003752353	3.752352614
Sept	Thursday	0700	2.3232	646.5010754	0.003593498	3.593497503
Sept	Thursday	1300	1.4874	646.5010754	0.002300692	2.300692229
Sept	Thursday	1300	1.4941	646.5010754	0.002311056	2.311055707
Sept	Thursday	1900	1.3848	646.5010754	0.002141992	2.141991797
Sept	Thursday	1900	2.3745	646.5010754	0.003672848	3.672847719
Sept	Sunday	0100	3.1837	646.5010754	0.004924508	4.924508437
Sept	Sunday	0100	2.7119	646.5010754	0.004194734	4.194733935
Sept	Sunday	0700	1.0488	646.5010754	0.001622271	1.622271084
Sept	Sunday	0700	1.1743	646.5010754	0.001816393	1.816392957
Sept	Sunday	1300	1.3042	646.5010754	0.002017321	2.017320697
Sept	Sunday	1300	1.7543	646.5010754	0.00271353	2.713529903
Sept	Sunday	1900	2.2099	646.5010754	0.003418246	3.418246441
Sept	Sunday	1900	1.8475	646.5010754	0.002857691	2.857690529
Dec	Thursday	0100	24.8055	646.5010754	0.038368846	38.36884569
Dec	Thursday	0100	28.6527	646.5010754	0.044319648	44.31964786
Dec	Thursday	0700	4.1169	646.5010754	0.006367971	6.367970846
Dec	Thursday	0700	4.722	646.5010754	0.007303932	7.303932167
Dec	Thursday	1300	55.8679	646.5010754	0.086415788	86.4157882
Dec	Thursday	1300	56.8428	646.5010754	0.087923752	87.92375166
Dec	Thursday	1900	33.4658	646.5010754	0.051764492	51.7644924
Dec	Thursday	1900	28.9942	646.5010754	0.044847876	44.84787591
Dec	Sunday	0100	25.5044	646.5010754	0.039449896	39.44989571
Dec	Sunday	0100	26.5592	646.5010754	0.041081448	41.08144752
Dec	Sunday	0700	8.59	646.5010754	0.013286908	13.28690752
Dec	Sunday	0700	6.8731	646.5010754	0.010631227	10.63122748
Dec	Sunday	1300	94.2329	646.5010754	0.145758304	145.7583036

Table A.1. (continued)

Diphenhydramine						
Month	Day	Time	Water Concentration (ng/L)	THV (ng/L)	THR	THR Safety Factor 1000
Dec	Sunday	1300	90.6638	646.5010754	0.140237663	140.2376631
Dec	Sunday	1900	41.4442	646.5010754	0.064105384	64.10538448
Dec	Sunday	1900	43.8877	646.5010754	0.067884961	67.88496056
March	Thursday	0100	120	646.5010754	0.18561454	185.6145404
March	Thursday	0100	120	646.5010754	0.18561454	185.6145404
March	Thursday	0700	12	646.5010754	0.018561454	18.56145404
March	Thursday	0700	15	646.5010754	0.023201818	23.20181756
March	Thursday	1300	25	646.5010754	0.038669696	38.66969593
March	Thursday	1300	23	646.5010754	0.03557612	35.57612025
March	Thursday	1900	35	646.5010754	0.054137574	54.1375743
March	Thursday	1900	37	646.5010754	0.05723115	57.23114997
March	Sunday	0100	47	646.5010754	0.072699028	72.69902834
March	Sunday	0100	49	646.5010754	0.075792604	75.79260402
March	Sunday	0700	14	646.5010754	0.02165503	21.65502972
March	Sunday	0700	13	646.5010754	0.020108242	20.10824188
March	Sunday	1300	33	646.5010754	0.051043999	51.04399862
March	Sunday	1300	31	646.5010754	0.047950423	47.95042295
March	Sunday	1900	22	646.5010754	0.034029332	34.02933242
March	Sunday	1900	19	646.5010754	0.029388969	29.3889689
June	Thursday	0100	14	646.5010754	0.02165503	21.65502972
June	Thursday	0100	15	646.5010754	0.023201818	23.20181756
June	Thursday	0700	3.4	646.5010754	0.005259079	5.259078646
June	Thursday	0700	3.2	646.5010754	0.004949721	4.949721079
June	Thursday	1300	5.7	646.5010754	0.008816691	8.816690671
June	Thursday	1300	6.1	646.5010754	0.009435406	9.435405806
June	Thursday	1900	5.9	646.5010754	0.009126048	9.126048239
June	Thursday	1900	6.2	646.5010754	0.009590085	9.59008459

Table A.1. (continued)

Diphenhydramine						
Month	Day	Time	Water Concentration (ng/L)	THV (ng/L)	THR	THR Safety Factor 1000
June	Sunday	0100	9.3	646.5010754	0.014385127	14.38512688
June	Sunday	0100	9.2	646.5010754	0.014230448	14.2304481
June	Sunday	0700	2.3	646.5010754	0.003557612	3.557612025
June	Sunday	0700	2.2	646.5010754	0.003402933	3.402933242
June	Sunday	1300	3.4	646.5010754	0.005259079	5.259078646
June	Sunday	1300	3.4	646.5010754	0.005259079	5.259078646
June	Sunday	1900	2.6	646.5010754	0.004021648	4.021648376
June	Sunday	1900	3.3	646.5010754	0.0051044	5.104399862

Fluoxetine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
June	Thursday	1900	13	33.54440296	0.387546024	387.5460242
June	Thursday	1900	14	33.54440296	0.417357257	417.3572568
June	Sunday	1900	12	33.54440296	0.357734792	357.7347916
June	Sunday	1900	5.8	33.54440296	0.172905149	172.9051493
July	Thursday	1900	28	33.54440296	0.834714514	834.7145137
July	Thursday	1900	29	33.54440296	0.864525746	864.5257463
July	Sunday	1900	27	33.54440296	0.804903281	804.9032811
July	Sunday	1900	25	33.54440296	0.745280816	745.2808158
Aug	Thursday	1900	25.4926	33.54440296	0.759965829	759.965829
Aug	Thursday	1900	22.4986	33.54440296	0.670710998	670.7109985
Aug	Sunday	1900	21.3216	33.54440296	0.635623178	635.6231777
Aug	Sunday	1900	18.969	33.54440296	0.565489272	565.4892718
Sept	Thursday	1900	25.7625	33.54440296	0.768011881	768.0118807
Sept	Thursday	1900	27.9616	33.54440296	0.833569762	833.5697623
Sept	Sunday	1900	24.2032	33.54440296	0.721527226	721.5272256
Sept	Sunday	1900	22.4075	33.54440296	0.667995195	667.9951952
Oct	Thursday	1900	23.7301	33.54440296	0.707423531	707.4235315

Table A.1. (continued)

Fluoxetine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Oct	Thursday	1900	23.957	33.54440296	0.7141877	714.1877002
Oct	Sunday	1900	15.4338	33.54440296	0.460100602	460.1006022
Oct	Sunday	1900	14.8222	33.54440296	0.441868052	441.8680523
Nov	Thursday	1900	25.7581	33.54440296	0.767880711	767.8807112
Nov	Thursday	1900	21.5508	33.54440296	0.642455912	642.4559122
Nov	Sunday	1900	16.5328	33.54440296	0.492863147	492.8631469
Nov	Sunday	1900	N/A	33.54440296	N/A	N/A
Dec	Thursday	1900	28.9951	33.54440296	0.864379671	864.3796713
Dec	Thursday	1900	26.7013	33.54440296	0.795998666	795.9986659
Dec	Sunday	1900	21.1497	33.54440296	0.630498627	630.4986268
Dec	Sunday	1900	19.9937	33.54440296	0.596036842	596.0368419
Jan	Thursday	1900	28.3364	33.54440296	0.844743012	844.7430123
Jan	Thursday	1900	28.9497	33.54440296	0.863026241	863.0262413
Jan	Sunday	1900	25.2666	33.54440296	0.75322849	753.2284904
Jan	Sunday	1900	13.3548	33.54440296	0.39812305	398.1230495
Feb	Thursday	1900	37	33.54440296	1.103015607	1103.015607
Feb	Thursday	1900	32	33.54440296	0.953959444	953.9594442
Feb	Sunday	1900	32	33.54440296	0.953959444	953.9594442
Feb	Sunday	1900	33	33.54440296	0.983770677	983.7706768
March	Thursday	1900	27	33.54440296	0.804903281	804.9032811
March	Thursday	1900	19	33.54440296	0.56641342	566.41342
March	Sunday	1900	25	33.54440296	0.745280816	745.2808158
March	Sunday	1900	26	33.54440296	0.775092048	775.0920484
April	Thursday	1900	23	33.54440296	0.685658351	685.6583505
April	Thursday	1900	N/A	33.54440296	N/A	N/A
April	Sunday	1900	29	33.54440296	0.864525746	864.5257463
April	Sunday	1900	30	33.54440296	0.894336979	894.3369789

Table A.1. (continued)

Fluoxetine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
May	Thursday	1900	9.9	33.54440296	0.295131203	295.1312031
May	Thursday	1900	12	33.54440296	0.357734792	357.7347916
May	Sunday	1900	17	33.54440296	0.506790955	506.7909547
May	Sunday	1900	16	33.54440296	0.476979722	476.9797221
Sept	Thursday	0100	28.0647	33.54440296	0.8366433	836.6433004
Sept	Thursday	0100	28.5556	33.54440296	0.851277635	851.2776345
Sept	Thursday	0700	32.6711	33.54440296	0.973965762	973.9657624
Sept	Thursday	0700	32.2532	33.54440296	0.961507648	961.5076483
Sept	Thursday	1300	25.4015	33.54440296	0.757250026	757.2500257
Sept	Thursday	1300	23.0164	33.54440296	0.686147255	686.1472547
Sept	Thursday	1900	25.7625	33.54440296	0.768011881	768.0118807
Sept	Thursday	1900	27.9616	33.54440296	0.833569762	833.5697623
Sept	Sunday	0100	29.1796	33.54440296	0.869879844	869.8798437
Sept	Sunday	0100	24.383	33.54440296	0.726887285	726.8872853
Sept	Sunday	0700	19.96	33.54440296	0.595032203	595.0322033
Sept	Sunday	0700	20.3227	33.54440296	0.605844737	605.8447374
Sept	Sunday	1300	24.0974	33.54440296	0.718373197	718.3731972
Sept	Sunday	1300	20.6999	33.54440296	0.617089534	617.0895343
Sept	Sunday	1900	24.2032	33.54440296	0.721527226	721.5272256
Sept	Sunday	1900	22.4075	33.54440296	0.667995195	667.9951952
Dec	Thursday	0100	24.5281	33.54440296	0.731212895	731.2128951
Dec	Thursday	0100	18.5614	33.54440296	0.553338213	553.3382134
Dec	Thursday	0700	20.2216	33.54440296	0.602830822	602.8308218
Dec	Thursday	0700	25.7916	33.54440296	0.768879388	768.8793875
Dec	Thursday	1300	21.5731	33.54440296	0.643120703	643.1207027
Dec	Thursday	1300	20.1607	33.54440296	0.601015318	601.0153177
Dec	Thursday	1900	28.9951	33.54440296	0.864379671	864.3796713

Table A.1. (continued)

Fluoxetine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Dec	Thursday	1900	26.7013	33.54440296	0.795998666	795.9986659
Dec	Sunday	0100	20.1135	33.54440296	0.599608228	599.6082275
Dec	Sunday	0100	19.7179	33.54440296	0.587814904	587.8149039
Dec	Sunday	0700	19.1825	33.54440296	0.57185397	571.85397
Dec	Sunday	0700	19.4442	33.54440296	0.57965557	579.6555695
Dec	Sunday	1300	22.6692	33.54440296	0.675796795	675.7967948
Dec	Sunday	1300	22.3351	33.54440296	0.665836862	665.8368619
Dec	Sunday	1900	21.1497	33.54440296	0.630498627	630.4986268
Dec	Sunday	1900	19.9937	33.54440296	0.596036842	596.0368419
March	Thursday	0100	24	33.54440296	0.715469583	715.4695832
March	Thursday	0100	25	33.54440296	0.745280816	745.2808158
March	Thursday	0700	19	33.54440296	0.56641342	566.41342
March	Thursday	0700	23	33.54440296	0.685658351	685.6583505
March	Thursday	1300	16	33.54440296	0.476979722	476.9797221
March	Thursday	1300	22	33.54440296	0.655847118	655.8471179
March	Thursday	1900	27	33.54440296	0.804903281	804.9032811
March	Thursday	1900	19	33.54440296	0.56641342	566.41342
March	Sunday	0100	25	33.54440296	0.745280816	745.2808158
March	Sunday	0100	24	33.54440296	0.715469583	715.4695832
March	Sunday	0700	19	33.54440296	0.56641342	566.41342
March	Sunday	0700	23	33.54440296	0.685658351	685.6583505
March	Sunday	1300	20	33.54440296	0.596224653	596.2246526
March	Sunday	1300	21	33.54440296	0.626035885	626.0358853
March	Sunday	1900	25	33.54440296	0.745280816	745.2808158
March	Sunday	1900	26	33.54440296	0.775092048	775.0920484
June	Thursday	0100	17	33.54440296	0.506790955	506.7909547
June	Thursday	0100	26	33.54440296	0.775092048	775.0920484

Table A.1. (continued)

Fluoxetine						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
June	Thursday	0700	16	33.54440296	0.476979722	476.9797221
June	Thursday	0700	19	33.54440296	0.56641342	566.41342
June	Thursday	1300	16	33.54440296	0.476979722	476.9797221
June	Thursday	1300	14	33.54440296	0.417357257	417.3572568
June	Thursday	1900	13	33.54440296	0.387546024	387.5460242
June	Thursday	1900	14	33.54440296	0.417357257	417.3572568
June	Sunday	0100	17	33.54440296	0.506790955	506.7909547
June	Sunday	0100	15	33.54440296	0.447168489	447.1684895
June	Sunday	0700	13	33.54440296	0.387546024	387.5460242
June	Sunday	0700	17	33.54440296	0.506790955	506.7909547
June	Sunday	1300	15	33.54440296	0.447168489	447.1684895
June	Sunday	1300	13	33.54440296	0.387546024	387.5460242
June	Sunday	1900	12	33.54440296	0.357734792	357.7347916
June	Sunday	1900	5.8	33.54440296	0.172905149	172.9051493
Methylphenidate						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
June	Thursday	1900	3.7	835.1628976	0.004430273	4.430273436
June	Thursday	1900	3.7	835.1628976	0.004430273	4.430273436
June	Sunday	1900	1.3	835.1628976	0.001556583	1.556582559
June	Sunday	1900	0.47	835.1628976	0.000562764	0.562764464
July	Thursday	1900	2.8	835.1628976	0.003352639	3.352639357
July	Thursday	1900	2.7	835.1628976	0.003232902	3.232902237
July	Sunday	1900	2.7	835.1628976	0.003232902	3.232902237
July	Sunday	1900	3	835.1628976	0.003592114	3.592113597
Aug	Thursday	1900	4.1915	835.1628976	0.005018781	5.018781381
Aug	Thursday	1900	4.0047	835.1628976	0.004795112	4.795112441
Aug	Sunday	1900	4.2134	835.1628976	0.005045004	5.04500381

Table A.1. (continued)

Methylphenidate						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Aug	Sunday	1900	4.1864	835.1628976	0.005012675	5.012674787
Sept	Thursday	1900	10.8283	835.1628976	0.012965495	12.96549455
Sept	Thursday	1900	10.8906	835.1628976	0.013040091	13.04009078
Sept	Sunday	1900	7.9433	835.1628976	0.009511079	9.511078645
Sept	Sunday	1900	7.6946	835.1628976	0.009213292	9.213292428
Oct	Thursday	1900	12.0161	835.1628976	0.014387732	14.38773206
Oct	Thursday	1900	12.1707	835.1628976	0.014572846	14.57284565
Oct	Sunday	1900	2.2219	835.1628976	0.002660439	2.660439067
Oct	Sunday	1900	1.9624	835.1628976	0.002349721	2.349721241
Nov	Thursday	1900	12.3157	835.1628976	0.014746464	14.74646448
Nov	Thursday	1900	9.8519	835.1628976	0.011796381	11.79638132
Nov	Sunday	1900	3.7987	835.1628976	0.004548454	4.548453974
Nov	Sunday	1900	N/A	835.1628976	N/A	N/A
Dec	Thursday	1900	4.9191	835.1628976	0.005889989	5.889988665
Dec	Thursday	1900	5.0056	835.1628976	0.005993561	5.993561274
Dec	Sunday	1900	4.5378	835.1628976	0.005433431	5.433431027
Dec	Sunday	1900	4.708	835.1628976	0.005637224	5.637223605
Jan	Thursday	1900	9.1099	835.1628976	0.010907932	10.90793189
Jan	Thursday	1900	9.3883	835.1628976	0.01124128	11.24128003
Jan	Sunday	1900	7.7585	835.1628976	0.009289804	9.289804447
Jan	Sunday	1900	2.7599	835.1628976	0.003304625	3.304624772
Feb	Thursday	1900	5.6	835.1628976	0.006705279	6.705278714
Feb	Thursday	1900	5.6	835.1628976	0.006705279	6.705278714
Feb	Sunday	1900	4.7	835.1628976	0.005627645	5.627644635
Feb	Sunday	1900	5	835.1628976	0.005986856	5.986855995
March	Thursday	1900	5.5	835.1628976	0.006585542	6.585541594
March	Thursday	1900	5.7	835.1628976	0.006825016	6.825015834

Table A.1. (continued)

Methylphenidate						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
March	Sunday	1900	4.8	835.1628976	0.005747382	5.747381755
March	Sunday	1900	4.8	835.1628976	0.005747382	5.747381755
April	Thursday	1900	3.9	835.1628976	0.004669748	4.669747676
April	Thursday	1900	N/A	835.1628976	N/A	N/A
April	Sunday	1900	3.3	835.1628976	0.003951325	3.951324957
April	Sunday	1900	3.4	835.1628976	0.004071062	4.071062077
May	Thursday	1900	1.2	835.1628976	0.001436845	1.436845439
May	Thursday	1900	1.7	835.1628976	0.002035531	2.035531038
May	Sunday	1900	2.6	835.1628976	0.003113165	3.113165117
May	Sunday	1900	2.5	835.1628976	0.002993428	2.993427997
Sept	Thursday	0100	10.1541	835.1628976	0.012158227	12.15822689
Sept	Thursday	0100	10.6176	835.1628976	0.012713208	12.71320844
Sept	Thursday	0700	12.6729	835.1628976	0.015174165	15.17416547
Sept	Thursday	0700	12.9695	835.1628976	0.015529306	15.52930577
Sept	Thursday	1300	10.3906	835.1628976	0.012441405	12.44140518
Sept	Thursday	1300	10.0487	835.1628976	0.012032024	12.03202397
Sept	Thursday	1900	10.8283	835.1628976	0.012965495	12.96549455
Sept	Thursday	1900	10.8906	835.1628976	0.013040091	13.04009078
Sept	Sunday	0100	9.4758	835.1628976	0.01134605	11.34605001
Sept	Sunday	0100	8.2203	835.1628976	0.00984275	9.842750467
Sept	Sunday	0700	7.8864	835.1628976	0.009442948	9.442948224
Sept	Sunday	0700	7.529	835.1628976	0.009015008	9.015007757
Sept	Sunday	1300	7.0437	835.1628976	0.008433924	8.433923514
Sept	Sunday	1300	7.4435	835.1628976	0.008912633	8.91263252
Sept	Sunday	1900	7.9433	835.1628976	0.009511079	9.511078645
Sept	Sunday	1900	7.6946	835.1628976	0.009213292	9.213292428
Dec	Thursday	0100	5.9338	835.1628976	0.007104961	7.104961221

Table A.1. (continued)

Methylphenidate						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Dec	Thursday	0100	5.6634	835.1628976	0.006781192	6.781192048
Dec	Thursday	0700	6.5156	835.1628976	0.007801592	7.801591784
Dec	Thursday	0700	6.9522	835.1628976	0.008324364	8.32436405
Dec	Thursday	1300	5.5974	835.1628976	0.006702166	6.702165549
Dec	Thursday	1300	5.4096	835.1628976	0.006477299	6.477299238
Dec	Thursday	1900	4.9191	835.1628976	0.005889989	5.889988665
Dec	Thursday	1900	5.0056	835.1628976	0.005993561	5.993561274
Dec	Sunday	0100	5.0308	835.1628976	0.006023735	6.023735028
Dec	Sunday	0100	5.172	835.1628976	0.006192804	6.192803841
Dec	Sunday	0700	5.4412	835.1628976	0.006515136	6.515136168
Dec	Sunday	0700	5.7363	835.1628976	0.00686848	6.868480409
Dec	Sunday	1300	5.3531	835.1628976	0.006409648	6.409647765
Dec	Sunday	1300	5.2609	835.1628976	0.00629925	6.299250141
Dec	Sunday	1900	4.5378	835.1628976	0.005433431	5.433431027
Dec	Sunday	1900	4.708	835.1628976	0.005637224	5.637223605
March	Thursday	0100	6	835.1628976	0.007184227	7.184227194
March	Thursday	0100	6.5	835.1628976	0.007782913	7.782912793
March	Thursday	0700	6.7	835.1628976	0.008022387	8.022387033
March	Thursday	0700	6.8	835.1628976	0.008142124	8.142124153
March	Thursday	1300	6.1	835.1628976	0.007303964	7.303964314
March	Thursday	1300	6	835.1628976	0.007184227	7.184227194
March	Thursday	1900	5.5	835.1628976	0.006585542	6.585541594
March	Thursday	1900	5.7	835.1628976	0.006825016	6.825015834
March	Sunday	0100	5.7	835.1628976	0.006825016	6.825015834
March	Sunday	0100	5.7	835.1628976	0.006825016	6.825015834
March	Sunday	0700	5.2	835.1628976	0.00622633	6.226330235
March	Sunday	0700	5.4	835.1628976	0.006465804	6.465804474

Table A.1. (continued)

Methylphenidate						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
March	Sunday	1300	5.5	835.1628976	0.006585542	6.585541594
March	Sunday	1300	5.5	835.1628976	0.006585542	6.585541594
March	Sunday	1900	4.8	835.1628976	0.005747382	5.747381755
March	Sunday	1900	4.8	835.1628976	0.005747382	5.747381755
June	Thursday	0100	2.5	835.1628976	0.002993428	2.993427997
June	Thursday	0100	2.6	835.1628976	0.003113165	3.113165117
June	Thursday	0700	2.8	835.1628976	0.003352639	3.352639357
June	Thursday	0700	2.9	835.1628976	0.003472376	3.472376477
June	Thursday	1300	4.4	835.1628976	0.005268433	5.268433276
June	Thursday	1300	4.1	835.1628976	0.004909222	4.909221916
June	Thursday	1900	3.7	835.1628976	0.004430273	4.430273436
June	Thursday	1900	3.7	835.1628976	0.004430273	4.430273436
June	Sunday	0100	2.3	835.1628976	0.002753954	2.753953758
June	Sunday	0100	2.3	835.1628976	0.002753954	2.753953758
June	Sunday	0700	2.3	835.1628976	0.002753954	2.753953758
June	Sunday	0700	2.4	835.1628976	0.002873691	2.873690878
June	Sunday	1300	2.3	835.1628976	0.002753954	2.753953758
June	Sunday	1300	2.6	835.1628976	0.003113165	3.113165117
June	Sunday	1900	1.3	835.1628976	0.001556583	1.556582559
June	Sunday	1900	0.47	835.1628976	0.000562764	0.562764464
Sertraline						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
June	Thursday	1900	21	162.3423405	0.129356272	129.3562723
June	Thursday	1900	23	162.3423405	0.141675917	141.6759173
June	Sunday	1900	2	162.3423405	0.012319645	12.31964498
June	Sunday	1900	0.53	162.3423405	0.003264706	3.26470592
July	Thursday	1900	10	162.3423405	0.061598225	61.59822491

Table A.1. (continued)

Sertraline						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
July	Thursday	1900	11	162.3423405	0.067758047	67.7580474
July	Sunday	1900	8.1	162.3423405	0.049894562	49.89456218
July	Sunday	1900	7.7	162.3423405	0.047430633	47.43063318
Aug	Thursday	1900	44	162.3423405	0.27103219	271.0321896
Aug	Thursday	1900	50	162.3423405	0.307991125	307.9911246
Aug	Sunday	1900	20	162.3423405	0.12319645	123.1964498
Aug	Sunday	1900	25	162.3423405	0.153995562	153.9955623
Sept	Thursday	1900	16	162.3423405	0.09855716	98.55715986
Sept	Thursday	1900	17	162.3423405	0.104716982	104.7169824
Sept	Sunday	1900	12	162.3423405	0.07391787	73.9178699
Sept	Sunday	1900	9	162.3423405	0.055438402	55.43840242
Oct	Thursday	1900	15	162.3423405	0.092397337	92.39733737
Oct	Thursday	1900	16	162.3423405	0.09855716	98.55715986
Oct	Sunday	1900	24.0039	162.3423405	0.147859763	147.8597631
Oct	Sunday	1900	23	162.3423405	0.141675917	141.6759173
Nov	Thursday	1900	17	162.3423405	0.104716982	104.7169824
Nov	Thursday	1900	14	162.3423405	0.086237515	86.23751488
Nov	Sunday	1900	8.8	162.3423405	0.054206438	54.20643792
Nov	Sunday	1900	N/A	162.3423405	N/A	N/A
Dec	Thursday	1900	20	162.3423405	0.12319645	123.1964498
Dec	Thursday	1900	20	162.3423405	0.12319645	123.1964498
Dec	Sunday	1900	7.8	162.3423405	0.048046615	48.04661543
Dec	Sunday	1900	6.8	162.3423405	0.041886793	41.88679294
Jan	Thursday	1900	13	162.3423405	0.080077692	80.07769239
Jan	Thursday	1900	9.4	162.3423405	0.057902331	57.90233142
Jan	Sunday	1900	12	162.3423405	0.07391787	73.9178699
Jan	Sunday	1900	2.5	162.3423405	0.015399556	15.39955623

Table A.1. (continued)

Sertraline						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Feb	Thursday	1900	28	162.3423405	0.17247503	172.4750298
Feb	Thursday	1900	23	162.3423405	0.141675917	141.6759173
Feb	Sunday	1900	17	162.3423405	0.104716982	104.7169824
Feb	Sunday	1900	16	162.3423405	0.09855716	98.55715986
March	Thursday	1900	20	162.3423405	0.12319645	123.1964498
March	Thursday	1900	13	162.3423405	0.080077692	80.07769239
March	Sunday	1900	11	162.3423405	0.067758047	67.7580474
March	Sunday	1900	7.3	162.3423405	0.044966704	44.96670419
April	Thursday	1900	11	162.3423405	0.067758047	67.7580474
April	Thursday	1900	N/A	162.3423405	N/A	N/A
April	Sunday	1900	22	162.3423405	0.135516095	135.5160948
April	Sunday	1900	21	162.3423405	0.129356272	129.3562723
May	Thursday	1900	0.76	162.3423405	0.004681465	4.681465093
May	Thursday	1900	1.7	162.3423405	0.010471698	10.47169824
May	Sunday	1900	11	162.3423405	0.067758047	67.7580474
May	Sunday	1900	10	162.3423405	0.061598225	61.59822491
Sept	Thursday	0100	32	162.3423405	0.19711432	197.1143197
Sept	Thursday	0100	25	162.3423405	0.153995562	153.9955623
Sept	Thursday	0700	21	162.3423405	0.129356272	129.3562723
Sept	Thursday	0700	21	162.3423405	0.129356272	129.3562723
Sept	Thursday	1300	18	162.3423405	0.110876805	110.8768048
Sept	Thursday	1300	17	162.3423405	0.104716982	104.7169824
Sept	Thursday	1900	16	162.3423405	0.09855716	98.55715986
Sept	Thursday	1900	17	162.3423405	0.104716982	104.7169824
Sept	Sunday	0100	18	162.3423405	0.110876805	110.8768048
Sept	Sunday	0100	16	162.3423405	0.09855716	98.55715986
Sept	Sunday	0700	12	162.3423405	0.07391787	73.9178699

Table A.1. (continued)

Sertraline						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
Sept	Sunday	0700	8.5	162.3423405	0.052358491	52.35849118
Sept	Sunday	1300	5.4	162.3423405	0.033263041	33.26304145
Sept	Sunday	1300	5.5	162.3423405	0.033879024	33.8790237
Sept	Sunday	1900	12	162.3423405	0.07391787	73.9178699
Sept	Sunday	1900	9	162.3423405	0.055438402	55.43840242
Dec	Thursday	0100	21	162.3423405	0.129356272	129.3562723
Dec	Thursday	0100	17	162.3423405	0.104716982	104.7169824
Dec	Thursday	0700	12	162.3423405	0.07391787	73.9178699
Dec	Thursday	0700	15	162.3423405	0.092397337	92.39733737
Dec	Thursday	1300	14	162.3423405	0.086237515	86.23751488
Dec	Thursday	1300	11	162.3423405	0.067758047	67.7580474
Dec	Thursday	1900	20	162.3423405	0.12319645	123.1964498
Dec	Thursday	1900	20	162.3423405	0.12319645	123.1964498
Dec	Sunday	0100	8.5	162.3423405	0.052358491	52.35849118
Dec	Sunday	0100	11	162.3423405	0.067758047	67.7580474
Dec	Sunday	0700	7.2	162.3423405	0.044350722	44.35072194
Dec	Sunday	0700	7.8	162.3423405	0.048046615	48.04661543
Dec	Sunday	1300	8.8	162.3423405	0.054206438	54.20643792
Dec	Sunday	1300	6.8	162.3423405	0.041886793	41.88679294
Dec	Sunday	1900	7.8	162.3423405	0.048046615	48.04661543
Dec	Sunday	1900	6.8	162.3423405	0.041886793	41.88679294
March	Thursday	0100	21	162.3423405	0.129356272	129.3562723
March	Thursday	0100	23	162.3423405	0.141675917	141.6759173
March	Thursday	0700	12	162.3423405	0.07391787	73.9178699
March	Thursday	0700	13	162.3423405	0.080077692	80.07769239
March	Thursday	1300	12	162.3423405	0.07391787	73.9178699
March	Thursday	1300	13	162.3423405	0.080077692	80.07769239

Table A.1. (continued)

Sertraline						
Month	Day	Time	Water Concentration (ng/L)	THV	THR	THR Safety Factor 1000
March	Thursday	1900	20	162.3423405	0.12319645	123.1964498
March	Thursday	1900	13	162.3423405	0.080077692	80.07769239
March	Sunday	0100	25	162.3423405	0.153995562	153.9955623
March	Sunday	0100	23	162.3423405	0.141675917	141.6759173
March	Sunday	0700	16	162.3423405	0.09855716	98.55715986
March	Sunday	0700	18	162.3423405	0.110876805	110.8768048
March	Sunday	1300	12	162.3423405	0.07391787	73.9178699
March	Sunday	1300	14	162.3423405	0.086237515	86.23751488
March	Sunday	1900	11	162.3423405	0.067758047	67.7580474
March	Sunday	1900	7.3	162.3423405	0.044966704	44.96670419
June	Thursday	0100	22	162.3423405	0.135516095	135.5160948
June	Thursday	0100	28	162.3423405	0.17247503	172.4750298
June	Thursday	0700	19	162.3423405	0.117036627	117.0366273
June	Thursday	0700	16	162.3423405	0.09855716	98.55715986
June	Thursday	1300	15	162.3423405	0.092397337	92.39733737
June	Thursday	1300	15	162.3423405	0.092397337	92.39733737
June	Thursday	1900	21	162.3423405	0.129356272	129.3562723
June	Thursday	1900	23	162.3423405	0.141675917	141.6759173
June	Sunday	0100	22	162.3423405	0.135516095	135.5160948
June	Sunday	0100	20	162.3423405	0.12319645	123.1964498
June	Sunday	0700	12	162.3423405	0.07391787	73.9178699
June	Sunday	0700	12	162.3423405	0.07391787	73.9178699
June	Sunday	1300	6.3	162.3423405	0.038806882	38.8068817
June	Sunday	1300	5.9	162.3423405	0.036342953	36.3429527
June	Sunday	1900	2	162.3423405	0.012319645	12.31964498
June	Sunday	1900	0.53	162.3423405	0.003264706	3.26470592

Table A.1. (continued)

Erythromycin						
Month	Day	Time	Water Concentration (ng/L)	MSC (ng/L)	MIC (ng/L)	RHR
June	Thursday	1900	6.7	1000	8000	0.0067
June	Thursday	1900	8	1000	8000	0.008
June	Sunday	1900	2	1000	8000	0.002
June	Sunday	1900	1.7	1000	8000	0.0017
July	Thursday	1900	1.6	1000	8000	0.0016
July	Thursday	1900	1	1000	8000	0.001
July	Sunday	1900	2.1	1000	8000	0.0021
July	Sunday	1900	2.1	1000	8000	0.0021
Aug	Thursday	1900	N/A	1000	8000	N/A
Aug	Thursday	1900	N/A	1000	8000	N/A
Aug	Sunday	1900	N/A	1000	8000	N/A
Aug	Sunday	1900	N/A	1000	8000	N/A
Sept	Thursday	1900	N/A	1000	8000	N/A
Sept	Thursday	1900	N/A	1000	8000	N/A
Sept	Sunday	1900	N/A	1000	8000	N/A
Sept	Sunday	1900	N/A	1000	8000	N/A
Oct	Thursday	1900	5.3547	1000	8000	0.0053547
Oct	Thursday	1900	5.7185	1000	8000	0.0057185
Oct	Sunday	1900	11.4762	1000	8000	0.0114762
Oct	Sunday	1900	10.7169	1000	8000	0.0107169
Nov	Thursday	1900	12.3331	1000	8000	0.0123331
Nov	Thursday	1900	12.3919	1000	8000	0.0123919
Nov	Sunday	1900	8.8076	1000	8000	0.0088076
Nov	Sunday	1900	8.9314	1000	8000	0.0089314
Dec	Thursday	1900	21.2649	1000	8000	0.0212649
Dec	Thursday	1900	19.5849	1000	8000	0.0195849
Dec	Sunday	1900	16.3696	1000	8000	0.0163696

Table A.1. (continued)

Erythromycin						
Month	Day	Time	Water Concentration (ng/L)	MSC (ng/L)	MIC (ng/L)	RHR
Dec	Sunday	1900	18.6624	1000	8000	0.0186624
Jan	Thursday	1900	24.7571	1000	8000	0.0247571
Jan	Thursday	1900	24.2049	1000	8000	0.0242049
Jan	Sunday	1900	14.7258	1000	8000	0.0147258
Jan	Sunday	1900	14.3193	1000	8000	0.0143193
Feb	Thursday	1900	4.8	1000	8000	0.0048
Feb	Thursday	1900	3.6	1000	8000	0.0036
Feb	Sunday	1900	15	1000	8000	0.015
Feb	Sunday	1900	14	1000	8000	0.014
March	Thursday	1900	27	1000	8000	0.027
March	Thursday	1900	25	1000	8000	0.025
March	Sunday	1900	43	1000	8000	0.043
March	Sunday	1900	41	1000	8000	0.041
April	Thursday	1900	13	1000	8000	0.013
April	Thursday	1900	12	1000	8000	0.012
April	Sunday	1900	39	1000	8000	0.039
April	Sunday	1900	39	1000	8000	0.039
May	Thursday	1900	15	1000	8000	0.015
May	Thursday	1900	13	1000	8000	0.013
May	Sunday	1900	7.3	1000	8000	0.0073
May	Sunday	1900	7.5	1000	8000	0.0075

Sulfamethoxazole						
Month	Day	Time	Water Concentration (ng/L)	MSC (ng/L)	MIC (ng/L)	RHR
June	Thursday	1900	20	16000	125000	0.00125
June	Thursday	1900	22	16000	125000	0.001375
June	Sunday	1900	33	16000	125000	0.0020625
June	Sunday	1900	39	16000	125000	0.0024375

Table A.1. (continued)

Sulfamethoxazole						
Month	Day	Time	Water Concentration (ng/L)	MSC (ng/L)	MIC (ng/L)	RHR
July	Thursday	1900	30	16000	125000	0.001875
July	Thursday	1900	29	16000	125000	0.0018125
July	Sunday	1900	56	16000	125000	0.0035
July	Sunday	1900	53	16000	125000	0.0033125
Aug	Thursday	1900	N/A	16000	125000	N/A
Aug	Thursday	1900	N/A	16000	125000	N/A
Aug	Sunday	1900	N/A	16000	125000	N/A
Aug	Sunday	1900	N/A	16000	125000	N/A
Sept	Thursday	1900	N/A	16000	125000	N/A
Sept	Thursday	1900	N/A	16000	125000	N/A
Sept	Sunday	1900	N/A	16000	125000	N/A
Sept	Sunday	1900	N/A	16000	125000	N/A
Oct	Thursday	1900	51.6784	16000	125000	0.0032299
Oct	Thursday	1900	49.0826	16000	125000	0.003067663
Oct	Sunday	1900	13.3161	16000	125000	0.000832256
Oct	Sunday	1900	11.4143	16000	125000	0.000713394
Nov	Thursday	1900	11.5667	16000	125000	0.000722919
Nov	Thursday	1900	13.6691	16000	125000	0.000854319
Nov	Sunday	1900	13.9106	16000	125000	0.000869413
Nov	Sunday	1900	15.0062	16000	125000	0.000937888
Dec	Thursday	1900	18.3821	16000	125000	0.001148881
Dec	Thursday	1900	15.4918	16000	125000	0.000968238
Dec	Sunday	1900	18.6721	16000	125000	0.001167006
Dec	Sunday	1900	20.4622	16000	125000	0.001278888
Jan	Thursday	1900	37.2156	16000	125000	0.002325975
Jan	Thursday	1900	35.9007	16000	125000	0.002243794
Jan	Sunday	1900	35.0635	16000	125000	0.002191469

Table A.1. (continued)

Sulfamethoxazole						
Month	Day	Time	Water Concentration (ng/L)	MSC (ng/L)	MIC (ng/L)	RHR
Jan	Sunday	1900	46.7865	16000	125000	0.002924156
Feb	Thursday	1900	59	16000	125000	0.0036875
Feb	Thursday	1900	57	16000	125000	0.0035625
Feb	Sunday	1900	63	16000	125000	0.0039375
Feb	Sunday	1900	62	16000	125000	0.003875
March	Thursday	1900	42	16000	125000	0.002625
March	Thursday	1900	43	16000	125000	0.0026875
March	Sunday	1900	56	16000	125000	0.0035
March	Sunday	1900	50	16000	125000	0.003125
April	Thursday	1900	66	16000	125000	0.004125
April	Thursday	1900	63	16000	125000	0.0039375
April	Sunday	1900	510	16000	125000	0.031875
April	Sunday	1900	430	16000	125000	0.026875
May	Thursday	1900	21	16000	125000	0.0013125
May	Thursday	1900	20	16000	125000	0.00125
May	Sunday	1900	21	16000	125000	0.0013125
May	Sunday	1900	19	16000	125000	0.0011875
Trimethoprim						
Month	Day	Time	Water Concentration (ng/L)	MSC (ng/L)	MIC (ng/L)	RHR
June	Thursday	1900	2.9	500	8000	0.0058
June	Thursday	1900	2.8	500	8000	0.0056
June	Sunday	1900	0.3	500	8000	0.0006
June	Sunday	1900	1.4	500	8000	0.0028
July	Thursday	1900	0.35	500	8000	0.0007
July	Thursday	1900	0.34	500	8000	0.00068
July	Sunday	1900	0.6	500	8000	0.0012
July	Sunday	1900	0.6	500	8000	0.0012

Table A.1. (continued)

Trimethoprim						
Month	Day	Time	Water Concentration (ng/L)	MSC (ng/L)	MIC (ng/L)	RHR
Aug	Thursday	1900	N/A	500	8000	N/A
Aug	Thursday	1900	N/A	500	8000	N/A
Aug	Sunday	1900	N/A	500	8000	N/A
Aug	Sunday	1900	N/A	500	8000	N/A
Sept	Thursday	1900	N/A	500	8000	N/A
Sept	Thursday	1900	N/A	500	8000	N/A
Sept	Sunday	1900	N/A	500	8000	N/A
Sept	Sunday	1900	N/A	500	8000	N/A
Oct	Thursday	1900	2.165	500	8000	0.00433
Oct	Thursday	1900	2.5606	500	8000	0.0051212
Oct	Sunday	1900	6.1674	500	8000	0.0123348
Oct	Sunday	1900	4.7292	500	8000	0.0094584
Nov	Thursday	1900	3.5895	500	8000	0.007179
Nov	Thursday	1900	3.4467	500	8000	0.0068934
Nov	Sunday	1900	1.1406	500	8000	0.0022812
Nov	Sunday	1900	1.2135	500	8000	0.002427
Dec	Thursday	1900	10.1812	500	8000	0.0203624
Dec	Thursday	1900	9.4731	500	8000	0.0189462
Dec	Sunday	1900	3.0945	500	8000	0.006189
Dec	Sunday	1900	2.4559	500	8000	0.0049118
Jan	Thursday	1900	6.4106	500	8000	0.0128212
Jan	Thursday	1900	5.8555	500	8000	0.011711
Jan	Sunday	1900	1.2093	500	8000	0.0024186
Jan	Sunday	1900	0.1973	500	8000	0.0003946
Feb	Thursday	1900	6	500	8000	0.012
Feb	Thursday	1900	6.2	500	8000	0.0124
Feb	Sunday	1900	5.2	500	8000	0.0104

Table A.1. (continued)

Trimethoprim						
Month	Day	Time	Water Concentration (ng/L)	MSC (ng/L)	MIC (ng/L)	RHR
Feb	Sunday	1900	4.4	500	8000	0.0088
March	Thursday	1900	8.1	500	8000	0.0162
March	Thursday	1900	8.7	500	8000	0.0174
March	Sunday	1900	4.5	500	8000	0.009
March	Sunday	1900	4.2	500	8000	0.0084
April	Thursday	1900	2.5	500	8000	0.005
April	Thursday	1900	2.5	500	8000	0.005
April	Sunday	1900	102	500	8000	0.204
April	Sunday	1900	108	500	8000	0.216
May	Thursday	1900	3.6	500	8000	0.0072
May	Thursday	1900	4.1	500	8000	0.0082
May	Sunday	1900	2.3	500	8000	0.0046
May	Sunday	1900	2.6	500	8000	0.0052

APPENDIX B

Measured Maximum Concentrations from Relevant Literature

Table B.1. Measured maximum concentrations of analytes (ng/L) in effluent from the literature. Multiple concentrations for a compound within a study resulted from measurements at different wastewater treatment plants.

Author	Location	Acetaminophen	Caffeine	Carbamazepine	Diclofenac	Sulfamethoxazole	Trimethoprim
Behera *et al.* (2011)	Asia	27	60	74	49	162	154
Chiffre *et al.* (2016)	Europe	—	—	—	965.7; 2476.3	655.7; 1380.4	61.6; 241.2
Guerra *et al.* (2014)	North America	62,000	—	—	—	1800	580
Hirsch *et al.* (1999)	Europe	—	—	—	—	2000	660
Kostich *et al.* (2014)	North America	1500	—	240	—	2900; 1000	370; 210
Loos *et al.* (2013)	Europe	—	3002	4609	174	1691; 1147	800
Mohapatra *et al.* (2016)	North America	58; 33	923; 15	941; 485	104; 75	4145; 1406	894; 410
Nam *et al.* (2014)	Asia	38.3	22.1	17.7	—	7.1	—
Santos *et al.* (2007)	Europe	—	2060; 3200; 2840; 3010	550; 1290; 700;470	—	—	—

Table B.1. (continued)

Author	Location	Acetaminophen	Caffeine	Carbamazepine	Diclofenac	Sulfamethoxazole	Trimethoprim
Spongberg and Witter (2008)	North America	–	23.1	111.2	177.1	472.4	–
Tewari *et al.* (2013)	Asia	734	1720	–	182	89	25
Wilkinson *et al.* (2016)	Europe	157	–	–	201	–	–
Yang *et al.* (2011)	North America	–	50	12	–	140	–
Yao *et al.* (2016)	Asia	–	2095	–	–	–	–

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