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REGIONAL MONITORING
PROGRAM FOR WATER QUALITY
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DRAFT REPORT

Screening of Pharmaceuticals in San Francisco Bay Wastewater

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Executive Summary

Previous studies have shown that pharmaceuticals are widely detected in San Francisco Bay, and some compounds occasionally approach levels of concern for wildlife. In 2016 and 2017, seven wastewater treatment facilities located throughout the Bay Area voluntarily collected wastewater samples and funded analyses for 104 pharmaceutical compounds. This dataset represents the most comprehensive analysis of pharmaceuticals in wastewater to date in this region. On behalf of the Regional Monitoring Program for Water Quality in San Francisco Bay (RMP), the complete dataset was reviewed utilizing RMP quality assurance methods. An analysis of influent and effluent information is summarized in this report, and is intended to inform future monitoring recommendations for the Bay.

Influent and effluent concentration ranges measured were generally within the same order of magnitude as other US studies, with a few exceptions for effluent. Effluent concentrations were generally significantly lower than influent concentrations, though estimated removal efficiency varied by pharmaceutical, and in some cases, by treatment type. These removal efficiencies were generally consistent with those reported in other studies in the US. Pharmaceuticals detected at the highest concentrations and with the highest frequencies in effluent were commonly used drugs, including treatments for diabetes and high blood pressure, antibiotics, diuretics, and anticonvulsants.

For pharmaceuticals detected in discharged effluent, screening exercises were conducted to determine which might be appropriate candidates for further examination and potential monitoring in the Bay. First, a review of the scientific literature was conducted to assess available ecotoxicity thresholds for individual pharmaceuticals. Effluent concentrations were compared to these ecotoxicity values, as were Bay water concentrations from previous studies.

A hydrodynamic Bay model was then used to estimate the potential dilution of these effluent discharges in different subembayments, assuming that the median concentrations discharged by participating facilities are typical of municipal wastewater plants in the Bay Area. Estimated pharmaceutical concentrations in Bay water calculated by this model are considered at the high-end of the range of possible concentrations in the Bay because further reduction of discharged contaminants, through processes such as degradation and partitioning to sediment, were not considered.

Pharmaceuticals with previously measured or predicted Bay water concentrations in the range of ecotoxicity thresholds are recommended for further evaluation and may warrant monitoring in the Bay. The 17 compounds that are prioritized for further evaluation are: the antibiotics azithromycin, ciprofloxacin, clarithromycin, erythromycin, ofloxacin, and sulfamethoxazole; the antidepressants amitriptyline, fluoxetine, and sertraline; the anti-convulsant carbamazepine; the painkillers codeine, oxycodone, and ibuprofen; the antihistamine diphenhydramine; the antidiabetic drug metformin; and treatments for high blood pressure metoprolol and propanolol (Table 4). Results from this study indicate dilution alone may not be sufficient to reduce effluent-derived concentrations in surface water below ecotoxicity thresholds.

1. Introduction

Pharmaceuticals are detected frequently in US waterways, suggesting concern for impacts to exposed aquatic life. Laboratory studies indicate fish exposed to antidepressant medications at environmentally relevant doses exhibit behavioral changes that affect survival and reproduction (e.g., Brodin et al., 2013; Weinberger and Klaper, 2014). Antibiotic medications, designed specifically to kill organisms, may disrupt bacterial communities and essential functions (e.g., Näslund et al. 2008), impart broader antibiotic resistance (e.g., Rizzo et al., 2013), and are often toxic to algal species (e.g., Ferrari et al., 2004). Other pharmaceutical compounds have significant endocrine disrupting effects on aquatic species (e.g., Niemuth and Klaper, 2015). Pharmaceuticals typically enter the waste stream through excretion and flushing of unused medicines, suggesting the primary pathway for Bay contamination is via treated wastewater.

The RMP has assessed Bay pharmaceutical pollution in two previous special studies. In the first study, surface water from the Lower South Bay and influent and effluent from two tertiary wastewater treatment plants in the Lower South Bay were collected in 2006 and analyzed for 39 pharmaceutical and personal care products (Harrold et al., 2009). A subsequent study utilized novel analytical methods to analyze for 104 pharmaceutical and personal care products in San Francisco Bay surface water, sediment, and mussels collected in 2009-2010 (Klosterhaus et al., 2013). An additional, independent study examined pharmaceuticals and other contaminants in Bay water samples collected from shoreline locations in 2010 (Nödler et al., 2014). Finally, the City of San Jose has conducted a separate study in 2008-2009 to investigate the presence and removal efficiency of pharmaceuticals in the San Jose/Santa Clara Water Pollution Control Plant. This study and the first RMP study are the only available studies of pharmaceuticals in wastewater for the Bay.

Based on these studies and available ecotoxicity data, pharmaceuticals are currently considered an emerging contaminant of low concern for the Bay, as current levels suggest minimal impacts to aquatic life (Sutton et al. 2017). However, continuing examination of pharmaceuticals is recommended for two reasons: 1) the ever-growing Bay Area population is likely to discharge more and more of this class of contaminants into the Bay; and 2) the ever-expanding array of chemicals that can be analyzed by academic or commercial laboratories allows for an increasingly comprehensive evaluation of pharmaceutical risks to the Bay.

Additionally, increasing policy focus on proper pharmaceutical prescription, use, and disposal is occurring at the federal, state, and local levels, suggesting that current evaluation of pharmaceuticals in the Bay may be useful for policy-makers to evaluate management actions that may affect concentrations in the Bay. Additionally, the California State Water Resources Control Board's monitoring priorities for constituents of emerging concern (Tadesse, 2016) includes a few pharmaceutical compounds recommended for monitoring in wastewater effluent and stormwater runoff.

Within this context, seven wastewater treatment facilities located throughout the Bay Area volunteered to collect wastewater samples and have them analyzed for pharmaceutical compounds. These combined results provide the most comprehensive analysis of pharmaceuticals in wastewater in the Bay Area to date. Subsequently, the RMP funded a special study to leverage the existing dataset, by providing a comprehensive data quality review and

interpretation, while maintaining anonymity of participants. This technical report summarizes the results of this special study and provides recommendations for future study.

2. Methods

Seven anonymous wastewater treatment facilities chose to participate in the study. These plants were located throughout the Bay Area and represented a large range in flow rates. Five plants utilized secondary treatment of final effluent, and two plants utilized tertiary treatment. The participants in this study were volunteers, rather than selected to be representative of the region; as such, the dataset may not be fully representative of Bay-wide wastewater treatment plants.

The sampling design varied by facility. This variation included sampling procedures, sampling frequency, sampling date, and matrices collected. Final effluent was collected at all seven facilities, six of which also collected influent samples. Some of the facilities collected partially treated effluent, recycled water, and reverse osmosis concentrate. Field blanks and field duplicates were collected at some of the facilities to provide quality assurance samples for all participants. Most of the samples were collected as 24-hour composites, while samples at two of the facilities were collected as grab samples. The differences in collection method at each of the plants may have introduced additional variables affecting the measurements. A summary of the samples collected is provided in Table A-1 in the Appendix.

Samples were shipped to SGS AXYS and analyzed using AXYS Method MLA-075, which uses high performance liquid chromatography coupled to a triple quadrupole mass spectrometer. Sampled were filtered and analyzed as dissolved water samples, and spiked with surrogate standards before solid phase extraction. Samples were spiked with recovery standards before analysis by LC/ESI-MS/MS. The target analyte list included 104 compounds (Lists 1, 3, 4, and 5 of MLA-075). A description of the laboratory analytical method is provided in the Appendix.

SFEI staff reviewed the complete dataset utilizing RMP QAPP methods (Yee et al., 2017), and data were censored if accuracy and precision did not meet QAPP criteria. Compliant and qualified data are included in the data analysis, while censored data are excluded. A summary of the data quality review is provided in the Appendix.

2.1 Calculations

Weighted median

Weighted median influent and effluent concentrations were calculated. For this calculation, each sample result is weighted by the influent or effluent daily flow rate at the plant during the day of sampling divided by the number of sample results for that plant. For example, an effluent sample result from a plant that had collected two effluent samples, on a day that had a daily flow rate of 20 million gallons per day (mgd), would be weighted by a factor of 10 (20 mgd / 2 samples = 10). This means sample results from larger plants have greater weight, allowing for the calculated weighted median to be more representative of effluent flows into the Bay. All influent and effluent samples collected, including grab and 24-hour composites, were used to calculate the weighted median concentration. Including measurements from grab samples in the weighted median calculation did not change the calculated median by more than a factor of two, except for three compounds in effluent (cocaine, enalapril, gemfibrozil).

Per capita influent loads

Also calculated from 24-hour composite influent measurements (5 plants) was the range of per capita influent loads, using service area populations provided by the facilities and the following equation:

Per capita influent loads [mg/capita/day] *= 24-hour composite influent concentration [ng/L] * plant daily influent flow rate [10^6 L/day] / population served [capita] / [10^6 ng/mg]*.

Removal efficiency

Removal efficiency was calculated based on the difference in concentration of the parent compound in the influent and effluent at each plant.

Removal efficiency [%] *= (Influent Conc. [ng/L] - Effluent Conc. [ng/L]) / Influent Conc. [ng/L]*.

Removal efficiency was further categorized as high (80-100% removal), moderate (50-80% removal), or low (<50% removal). Removal efficiency was not calculated for about 30% of the compounds because either influent concentrations were below detection limits or concentrations were censored.

Samples were not collected to account for hydraulic residence time at the plant, a source of uncertainty in estimates of removal efficiency. Since wastewater can take several hours to transit through the plant, the effluent did not represent the same parcel of water in the corresponding influent sample used to calculate removal efficiency. Negative removal efficiency results are also possible, particularly in cases where metabolites are converted back to parent compounds as a consequence of biological activity during treatment.

In cases where several samples were collected on different days from the same plant during the same month, a removal efficiency was calculated using the median influent and effluent concentration from the plant. If samples were collected during different months from the same plant, a removal efficiency was calculated for each pair of influent and effluent collected during the same month. The removal efficiencies ranges reported includes different removal efficiencies calculated for different months from the same plant. If the contaminant was detected in the influent, but not in the effluent, a minimum removal efficiency was calculated using the MDL of the effluent. If the contaminant was not detected in the influent, then no removal efficiency was calculated.

Ratio of effluent concentration relative to ecotoxicity threshold

A common risk screening approach is to compare surface water concentrations to ecotoxicity thresholds such as a predicted no effects concentration (PNEC), a protective threshold for wildlife. Ratios of observed water concentrations and ecotoxicity thresholds can be used to prioritize contaminants; a ratio above one suggests potential for risks to wildlife.

In this study, ambient waters were not sampled, and so maximum and median effluent concentrations were compared to ecotoxicity thresholds, and a ratio was calculated. Literature

review for ecotoxicity thresholds was prioritized for compounds detected in effluent, and ecotoxicity values are reported for all compounds with median effluent detections above 200 ng/L. When several different PNEC values were found, the lowest value was used. When PNEC values were not found, the lowest available effects concentration is shown (e.g., lowest observable effect concentration [LOEC]). Effluent concentrations will be significantly diluted in the Bay; an effluent-based ratio above one does not indicate risk, but relative ratios may be useful to prioritize compounds of concern and suggest whether further evaluation is needed.

2.2 Modeling dilution of pharmaceuticals discharged to Bay

A Bay hydrodynamic dilution spreadsheet model has been developed as a screening tool to approximate the dilution of persistent and water soluble contaminants discharged into the Bay (Holleman et al., 2017; Lin et al., 2018). This spreadsheet model condenses runs from the full San Francisco Bay hydrodynamic model to evaluate how direct discharges from 34 wastewater treatment plants, 5 refineries, a single representative concentration for stormwater, and a representative concentration for the Delta are diluted in the Bay. The model predicts ambient water concentrations in each subembayment based on contributions from these inputs.

Modeled concentrations in the Bay are considered conservative (e.g., worst case scenario), because the model does not include degradation processes, sorption to sediment, and exchange with the atmosphere, which can significantly reduce concentrations of many contaminants in Bay waters. For CECs that are relatively persistent and water-soluble, the spreadsheet provides a reasonable approximation of ambient water concentrations, and can be used to screen for contaminants that may merit further monitoring.

This dilution spreadsheet model was used to estimate whether wastewater effluent discharges that are above ecotoxicity thresholds are likely to remain above threshold when diluted in ambient water. For this calculation, we assumed that the median effluent concentration from this study was constant and representative of all 34 wastewater treatment plant discharges in the Bay. This assumption does not account for differences among plants, or potential temporal variations in pharmaceutical concentrations. Nevertheless, this assumption is considered an appropriate starting point to provide a rough estimate of the potential for pharmaceuticals discharged into the Bay to reach levels greater than toxicity thresholds, based on the available data. Zero pharmaceutical load was specified for the refineries, Delta, and stormwater discharges.

3. Results and Discussion

3.1 Influent

Table 1: Summary of Influent

Table 1 summarizes the concentrations and per capita loads measured in influent samples. In general, influent concentrations among the six wastewater treatment plants ranged within a factor of three, and eight chemicals (diltiazem and metabolite, sulfamethoxazole, diphenhydramine, diltiazem, trimethroprim, meprobamate, thiabendazole) varied by more than a factor of 10. Ranges of influent loads calculated on a per capita basis typically showed a somewhat lower degree of variation than concentration ranges, suggesting service population is an important

factor contributing to influent loads and concentrations. As expected from a screening study, there were a large number of non-detects; 16 of 104 compounds were always below method detection limits in influent samples.

The top ten pharmaceutical compounds detected in influent based on median influent concentration were:

- Metformin (anti-diabetic)
- Caffeine (stimulant)
- Acetaminophen (painkiller)
- Ibuprofen (painkiller) and metabolite (2-hydroxy-ibuprofen)
- Naproxen (painkiller)
- Valsartan (high blood pressure – cardiovascular)
- Atenolol (high blood pressure –cardiovascular)
- Gemfibrozil (cholesterol-lowering – cardiovascular)
- Furosemide (diuretic)
- Cotinine (nicotine metabolite)

A subset of several pharmaceuticals was detected at very high relative concentrations. Median concentrations of metformin and the sum of the top three over-the-counter painkillers (acetaminophen, ibuprofen and metabolite, naproxen) exceeded median concentrations of caffeine (82,500 ng/L). Calculated median per capita influent loads were also greater than caffeine loads. Additionally, 18 different antibiotics were detected in influent samples, with sulfamethoxazole, azithromycin, trimethroprim, and ciprofloxacin all detected at concentrations greater than 1000 ng/L. The influent concentrations of these commonly used drugs are consistent with those reported in other wastewater studies globally (Luo et al., 2014; Tran et al., 2018).

Table 1: Influent pharmaceutical concentrations for six Bay Area wastewater treatment facilities.

Class	Pharmaceuticals	Common Brand Name	Influent Conc. (ng/L)	Per Capita Influent Load (mg/capita/day)[1]
			Weighted Median (Min - Max)	Weighted Median (Min - Max)
Painkiller	Acetaminophen	Tylenol, Paracetamol	66,600 (44,800 - 110,000)	19 (15 - 25)
Asthma treatment	Albuterol	ProAir HFA, Proventil HFA	17.1 (11.8 - 25.8)	0.005 (0.004 - 0.006)
Anti-anxiety (CNS)	Alprazolam	Xanax	2.02 (ND - 4.12)	0.001 (ND - 0.001)
Anti-depressant (CNS)	Amitriptyline		14.25 (ND - 48.5)	0.005 (0.003 - 0.02)
Anti-depressant (CNS)	Amlodipine	Norvasc	27.25 (ND - 60.5)	0.009 (0.005 - 0.02)
Stimulant	Amphetamine	Adderall	(458 - 598)[2]	(0.15 - 0.17)
High blood pressure (cardiovascular)	Atenolol	Tenormin	3,570 (2,280 - 4,490)	1 (0.7 - 1)
Cholesterol-lowering (cardiovascular)	Atorvastatin	Lipitor	244 (98.7 - 298)	0.07 (0.02 - 0.1)
Antibiotic	Azithromycin	Zithromax, AzaSite	890 (690 - 1,540)	0.3 (0.1 - 0.4)
Cocaine metabolite	Benzoylecgonine		866 (353 - 2,830)	0.3 (0.2 - 0.6)
Parkinson's disease treatment (CNS)	Benztropine	Cogentin	3.9 (ND - 11.9)	ND (ND - 0.002)
Coricosteroid	Betamethasone	Betaloan, Diprolene AF	ND	NA
Plastic additive	Bisphenol A		ND	NA
Stimulant	Caffeine		82,500 (62,350 - 165,000)	22 (17 - 34)
Antibiotic (veterinary)	Carbadox		ND	NA
Anti-convulsant (CNS)	Carbamazepine	Tegretol, Carbatrol, Epitol	189 (129 - 389)	0.05 (0.04 - 0.07)
Antibiotic	Cefotaxime	Claforan	NR	NA
Gastric Issues	Cimetidine	Heartburn Relief	175 (104 - 354)	0.04 (0.02 - 0.07)
Antibiotic	Ciprofloxacin	Cetraxal, Ciloxan	378 (239 - 1,290)	0.09 (0.06 - 0.3)
Antibiotic	Clarithromycin	Biaxin	427 (130 - 648)	0.1 (0 - 0.2)
Antibiotic	Clinafloxacin		ND	NA
High blood pressure (cardiovascular)	Clonidine	Catapres, Kapvay	ND	NA
Antibiotic	Cloxacillin		NR	NA
Recreational drug	Cocaine		357 (164 - 814)	0.09 (0.06 - 0.2)
Painkiller	Codeine		175 (95 - 349)	0.05 (0.03 - 0.1)
Nicotine metabolite	Cotinine		998 (633 - 1,850)	0.3 (0.2 - 0.4)
High blood pressure (cardiovascular)	Dehydronifedipine	Procardia, Adalat CC	6.2 (ND - 13.6)	0.002 (0.001 - 0.004)
High blood pressure (cardiovascular)	Desmethyldiltiazem		55 (2.3 - 107)	0.01 (0.01 - 0.03)
Anti-anxiety (CNS)	Diazepam	Valium, Diastat	2.5 (ND - 4.2)	0.001 (ND - 0.001)
Insect repellent (DEET)	Diethyl-3-methyl-benzamide, N,N-		660 (304 - 2,700)	0.3 (0.1 - 0.9)
Immuno-tag	Digoxigenin		ND	NA
High blood pressure (cardiovascular)	Digoxin	Lanoxin, Digox	46.8 (ND - 108)	0.01 (ND - 0.03)
High blood pressure (cardiovascular)	Diltiazem	Cardizem, Tiazac, Cartia	179 (22 - 273)	0.05 (0.04 - 0.07)
Stimulant	Dimethylxanthine, 1,7-		NR	NA
Antihistamine (CNS)	Diphenhydramine	Benadryl, Banophen	486 (81 - 1,120)	0.2 (0.1 - 0.4)
High blood pressure (cardiovascular)	Enalapril	Vasotec	14.8 (11 - 26)	0.004 (0.002 - 0.006)
Antibiotic (veterinary)	Enrofloxacin	Baytril	ND	NA
Antibiotic	Erythromycin-H2O	Ery-tab, Erygel, Eryc	67 (30 - 109)	0.02 (ND - 0.03)
Antibiotic	Flumequine		ND	NA
Corticosteroid	Fluocinonide	Vanos	ND	NA
Anti-depressant (CNS)	Fluoxetine	Prozac, Sarafem	28 (ND - 64)	0.008 (0.003 - 0.02)
Corticosteroid	Fluticasone propionate	Flonase, Cutivate	ND (ND - 70)	ND (ND - 0.006)
Diuretic	Furosemide	Lasix	1,590 (736 - 2,620)	0.4 (0.2 - 0.6)

Class	Pharmaceuticals	Common Brand Name	Influent Conc. (ng/L)	Per Capita Influent Load (mg/capita/day)[1]
			Weighted Median (Min - Max)	Weighted Median (Min - Max)
Cholesterol-lowering (cardiovascular)	Gemfibrozil	Lopid	1,460 (397 - 2,480)	0.4 (0.3 - 0.7)
Anti-diabetic	Glipizide	Glucotrol	33.5 (ND - 70.6)	0.009 (ND - 0.01)
Anti-diabetic	Glyburide	Glynase	ND (ND - 16)	ND (ND - 0.003)
Diuretic	Hydrochlorothiazide	Microzide	734 (214 - 1,070)	0.2 (0.1 - 0.3)
Painkiller	Hydrocodone	Norco, Vicodin[3]	78 (36 - 306)	0.02 (0.01 - 0.1)
Corticosteroid	Hydrocortisone	Alat-Cort, Cortizone 10	291 (ND - 415)	0.08 (ND - 0.1)
Anti-depressant (CNS)	Hydroxy-amitriptyline, 10-		15.2 (3.84 - 34.6)	0.004 (0.004 - 0.01)
Painkiller	Hydroxy-ibuprofen, 2-		38,400 (19,300 - 81,000)	10 (6 - 13)
Painkiller	Ibuprofen	Advil	15,200 (9,665 - 21,350)	4 (3 - 6)
Antibiotic	Lincomycin	Lincocin	18.8 (ND - 34.8)	0.006 (ND - 0.01)
Antibiotic	Lomefloxacin	Maxaquin, Okacyn, Uniquin	ND	NA
Anti-anxiety (CNS)	Meprobamate	Miltown, Equanil	185 (51 - 551)	0.05 (0.02 - 0.1)
Anti-diabetic	Metformin	Glumetza, Glucophage	146,000 (72,800 - 157,000)	36 (24 - 43)
Coricosteroid	Methylprednisolone	Medrol, ReadySharp	ND (ND - 164)	ND
High blood pressure (cardiovascular)	Metoprolol	Lopressor, Toprol X	530 (228 - 877)	0.2 (0.1 - 0.2)
Antibiotic	Miconazole	Zeasorb, Micatin	7.3 (ND - 40)	0.002 (ND - 0.01)
Painkiller	Naproxen	Aleve, Naprosyn	10,800 (6,585 - 18,600)	3 (2 - 5)
Antibiotic	Norfloxacin	Noroxin	ND (ND - 85)	ND (ND - 0.02)
Anti-depressant (CNS)	Norfluoxetine		7.8 (ND - 31)	0.002 (0.002 - 0.01)
Birth control (hormone)	Norgestimate	Ortho Tri-Cyclen, Previfem	ND	NA
High blood pressure (cardiovascular)	Norverapamil		1.04 (ND - 8.01)	0.0003 (ND - 0.002)
Antibiotic	Ofloxacin	Ocuflox, Floxin	225 (27.8 - 538)	0.05 (0.03 - 0.2)
Antibiotic (veterinary)	Ormetoprim	Primor	ND	NA
Antibiotic	Oxacillin	Bactocill	NR	NA
Antibiotic	Oxolinic Acid		ND	NA
Painkiller	Oxycodone	Oxycontin, Roxicodone	40.3 (34.2 - 175)	0.01 (0.01 - 0.04)
Anti-depressant (CNS)	Paroxetine	Paxil, Pexeva, Brisdelle	ND	NA
Antibiotic	Penicillin G	Pfizerpen	NR	NA
Antibiotic	Penicillin V	Veetids, Apocillin	ND (ND - 33)	ND
Coricosteroid	Prednisolone	Omnipred, Pediapred	ND (ND - 113)	ND (ND - 0.02)
Coricosteroid	Prednisone	Deltasone, Rayos	NR	NA
Antihistamine	Promethazine	Phenergan, Phenadoz	1.33 (ND - 13.9)	0.0004 (ND - 0.001)
Painkiller	Propoxyphene	Darvon, Dolene	ND (ND - 5.38)	ND (ND - 0.002)
High blood pressure (cardiovascular)	Propranolol	Hemangeol, Inderal XL	42.7 (ND - 113)	0.01 (0.01 - 0.04)
Treat ulcers	Ranitidine	Zantac, Heartburn Relief	NR	NA
Antibiotic	Roxithromycin		14 (ND - 37)	0.004 (ND - 0.01)
Antibiotic	Sarafloxacin		ND	NA
Anti-depressant (CNS)	Sertraline	Zoloft	33 (16 - 77)	0.01 (0.003 - 0.03)
Cholesterol-lowering (cardiovascular)	Simvastatin	Zocor, FloLipid	ND	NA
Antibiotic	Sulfachloropyridazine		ND	NA
Antibiotic	Sulfadiazine	Lantrisul, Neotrizine	ND (ND - 35.9)	ND (ND - 0.01)
Antibiotic	Sulfadimethoxine	Albon, Di-Methox	ND (ND - 5.4)	ND (ND - 0.002)
Antibiotic	Sulfamerazine		ND (ND - 8.7)	ND (ND - 0.002)
Antibiotic	Sulfamethazine		ND (ND - 7.05)	ND (ND - 0.001)

Class	Pharmaceuticals	Common Brand Name	Influent Conc. (ng/L)	Per Capita Influent Load (mg/capita/day)[1]
			Weighted Median (Min - Max)	Weighted Median (Min - Max)
Antibiotic	Sulfamethizole		ND (ND - 3.21)	ND (ND - 0.0008)
Antibiotic	Sulfamethoxazole	Bactrim, Sulfatrim	875 (365 - 3,570)	0.3 (0.1 - 0.4)
Antibiotic	Sulfanilamide	AVC Vaginal	66 (ND - 120)	0.02 (ND - 0.03)
Antibiotic	Sulfathiazole		ND (ND - 12)	ND (ND - 0.003)
Asthma treatment	Theophylline	Theo-24, Elixophylline	NR	NA
Antibiotic (fungicide)	Thiabendazole	Mintezol, Tresaderm	34.8 (22.5 - 245)	0.009 (0.006 - 0.07)
Hormone	Trenbolone		ND	NA
Hormone	Trenbolone acetate		ND (ND - 8.15)	ND (ND - 0.0005)
Diuretic	Triamterene	Dyrenium	110 (37 - 243)	0.03 (0.02 - 0.06)
Antimicrobial	Triclocarban		86.5 (31.7 - 142)	0.02 (0.02 - 0.05)
Antimicrobial	Triclosan		511 (405 - 1,930)	0.2 (0.1 - 0.2)
Antibiotic	Trimethoprim	Primsol	431 (109 - 1,390)	0.1 (0.1 - 0.2)
Antibiotic (veterinary)	Tylosin		ND	NA
High blood pressure (cardiovascular)	Valsartan	Diovan	4,410 (1,710 - 9,940)	1 (0 - 2)
High blood pressure (cardiovascular)	Verapamil	Verelan, Calan	9.3 (ND - 59.4)	0.003 (0.001 - 0.02)
Antibiotic	Virginiamycin M1		ND	NA
Anticoagulant	Warfarin	Coumadin, Jantoven	ND (ND - 7.18)	ND (ND - 0.002)

ND = non-detect

NR = not reported by lab or censored after QA

NA = not applicable

CNS = Central nervous system

[1]Load calculated only for plants where at 24-hour influent composite was collected

[2]Greater than 50% data censored

[3]Combination with acetaminophen

3.2 Effluent

3.2.1 Effluent concentrations

Table 2: Summary of Effluent

Table 2 summarizes the range of concentrations for pharmaceuticals measured in effluent samples, detection frequency in effluent samples, along with a qualitative characterization of estimated removal efficiencies. While effluent concentrations for individual pharmaceuticals among the seven wastewater treatment plants generally varied within a factor of four, there were some pharmaceuticals with effluent concentration ranges that spanned more than an order of magnitude due to large differences in removal efficiency. As expected from a screening study, there were a large number of non-detects; 27 of 104 compounds were always below method detection limits in effluent samples.

The top ten pharmaceutical compounds detected in effluent based on median effluent concentration were:

- Metformin (anti-diabetic)
- Valsartan (high blood pressure)
- Furosemide (diuretic)
- Hydrochlorothiazide (diuretic)
- Sulfamethoxazole (antibiotic)
- Azithromycin (antibiotic)
- Metoprolol (high blood pressure – cardiovascular)
- Atenolol (high blood pressure – cardiovascular)
- Ofloxacin (antibiotic)
- Carbamazepine (anti-convulsant – central nervous system agent)

Generally, effluent concentrations of measured pharmaceuticals seem well within the range of reported effluent concentrations in North America and Europe (Blair et al., 2013; Luo et al., 2014; Tran et al., 2018). Metformin (anti-diabetic), which was detected at the highest concentration in effluent, is widely observed to be one of the highest concentration pharmaceuticals in wastewater effluent and surface waters in the U.S. and Europe (e.g. Blair et al., 2013; Oosterhuis et al., 2013). Median Bay Area effluent concentrations of metformin are comparable to effluent concentrations measured in the Great Lakes region, although maximum concentrations are an order of magnitude higher than wastewater effluent studies reported in the Great Lakes, Netherlands, and Germany (Blair et al., 2013; Oosterhuis et al., 2013; Scheurer et al., 2012). The high influent and effluent concentrations of metformin may indicate widespread use of metformin in the service population.

3.2.2 Removal efficiencies

Table 2 also includes characterization of removal efficiencies of pharmaceuticals based on influent and effluent samples collected at each plant. Removal efficiency varied by plant and drug, but in general, effluent concentrations were significantly lower than influent. Median metformin (anti-diabetic) concentrations in effluent decreased by two orders of magnitude, while the painkillers ibuprofen and acetaminophen are reduced by at least three orders of magnitude

(below MDL) when compared to influent concentrations. The level of variation in removal efficiency among plants and among different classes of contaminants is consistent with observations in the literature (Melvin and Leusch, 2016; Petrie et al., 2015). Figure 1 summarizes some key examples of pharmaceuticals with a range of removal efficiencies.

Of the 65 compounds where removal efficiencies were calculated, about 10% of the compounds had low removal efficiency across all seven plants, 30% had high removal efficiency, and the remaining 60% ranged between low and high removal efficiency. Some key examples of pharmaceuticals in the high removal efficiency class are commonly used drugs, including caffeine, ibuprofen, and acetaminophen.

Compounds in the low removal category include a wide variety of drugs, such as carbamazepine (anti-convulsant) and metoprolol (high blood pressure - cardiovascular); both of these compounds were detected in 100% of the final effluent samples at concentrations in the hundreds of ng/L range. The low removal efficiencies for these two compounds are consistent with findings from other studies (Luo et al., 2014; Petrie et al., 2015; Tran et al., 2018).

Most pharmaceutical compounds had high variability in calculated removal efficiencies across plants (ranging from low to high; this included gemfibrozil (cholesterol-lowering drug) and atenolol (high blood pressure). Both of these compounds had higher removal efficiencies in the tertiary treatment plants compared to the secondary treatment plants. Some of the variation in removal efficiency may be due sampling periods that did not account for hydraulic residence time.

Removal as calculated in this study does not necessarily mean complete degradation. In some cases, removal often means partitioning to biosolids, which is an important issue relating to use or disposal of this waste stream (but a topic that is beyond the scope of this study).

Table 2: Effluent pharmaceutical concentrations and estimated removal efficiencies for seven Bay Area wastewater treatment facilities.

Class	Pharmaceuticals	Effluent Concentrations (ng/L)			Detection Frequency	Removal Efficiency[1,2]
		Weighted Median	Min	Max		
Painkiller	Acetaminophen	ND	ND	66.7	29%	H
Asthma treatment	Albuterol	14.2	6.7	27.5	100%	L
Anti-anxiety (CNS)	Alprazolam	2.7	1.8	4.9	100%	L
Anti-depressant (CNS)	Amitriptyline	13.0	5.9	27.0	100%	L,M
Anti-depressant (CNS)	Amlodipine	5.7	ND	24.1	86%	L,M,H[2]
Stimulant	Amphetamine	NA[3]	ND	27.9	NA[3]	H[3,5]
High blood pressure (cardiovascular	Atenolol	438	120	2,640	100%	L,M,H[2]
Cholesterol-lowering (cardiovascula	Atorvastatin	14.2	ND	128	100%	M,H
Antibiotic	Azithromycin	544	37	787	100%	L,M,H
Cocaine metabolite	Benzoylecgonine	NA[3]	61.5	336	NA[3]	M,H
Parkinson's disease treatment (CNS	Benztropine	ND	ND	0.7	29%	H
Coricosteroid	Betamethasone	ND	ND	ND	0%	NA
Plastic additive	Bisphenol A	ND	ND	ND	0%	NA
Stimulant	Caffeine	ND	ND	13,000	86%	H
Antibiotic (veterinary)	Carbadox	ND	ND	ND	0%	NA
Anti-convulsant (CNS)	Carbamazepine	209	157	276	100%	L
Antibiotic	Cefotaxime	NR[3]	NR	NR	NA	NA
Gastric Issues	Cimetidine	ND	ND	139	43%	L,M,H
Antibiotic	Ciprofloxacin	119	ND	286	100%	M,H
Antibiotic	Clarithromycin	155	27.6	417	100%	L,M,H
Antibiotic	Clinafloxacin	ND	ND	ND	0%	NA
High blood pressure (cardiovascular	Clonidine	ND	ND	ND	0%	NA
Antibiotic	Cloxacillin	NR[3]	NR	NR	NA	NA
Recreational drug	Cocaine	1.7	ND	59.2	100%	M,H
Painkiller	Codeine	148	ND	262	86%	L
Nicotine metabolite	Cotinine	36.2	14.7	555	100%	M,H
High blood pressure (cardiovascular	Dehydronifedipine	11.8	6.8	23.0	100%	L
High blood pressure (cardiovascular	Desmethyldiltiazem	45.7	22.4	73.2	100%	L,M
Anti-anxiety (CNS)	Diazepam	1.6	ND	3.5	83%	L
Insect repellent (DEET)	Diethyl-3-methyl-benzamide, N,N-	156	ND	1,880	100%	L,M,H
Immuno-tag	Digoxigenin	ND	ND	ND	0%	NA
High blood pressure (cardiovascular	Digoxin	ND	ND	ND	0%	H[5]

Class	Pharmaceuticals	Effluent Concentrations (ng/L)			Detection Frequency	Removal Efficiency[1,2]
		Weighted Median	Min	Max		
High blood pressure (cardiovascular	Diltiazem	132	83	217	100%	L
Stimulant	Dimethylxanthine, 1,7-	NR[3]	NR	NR	NA	NA
Antihistamine (CNS)	Diphenhydramine	145	82.4	955	100%	L,M,H[2]
High blood pressure (cardiovascular	Enalapril	ND	ND	13.5	43%	L,H
Antibiotic (veterinary)	Enrofloxacin	ND	ND	7.0	29%	NA
Antibiotic	Erythromycin-H2O	45.3	25.3	79.3	100%	L,M
Antibiotic	Flumequine	ND	ND	ND	0%	NA
Corticosteroid	Fluocinonide	ND	ND	ND	0%	NA
Anti-depressant (CNS)	Fluoxetine	26.8	14.5	91.2	100%	L,M
Corticosteroid	Fluticasone propionate	ND	ND	7.6	29%	M[4],H
Diuretic	Furosemide	737	206	1,360	100%	L,M,H
Cholesterol-lowering (cardiovascula	Gemfibrozil	15.6	5.2	2,050	100%	L,H[2]
Anti-diabetic	Glipizide	13.9	ND	66.0	71%	L,M
Anti-diabetic	Glyburide	7.1	ND	14.4	71%	L,M
Diuretic	Hydrochlorothiazide	570	245	965	100%	L
Painkiller	Hydrocodone	61.1	ND	207	100%	L
Corticosteroid	Hydrocortisone	ND	ND	ND	0%	M[4]
Anti-depressant (CNS)	Hydroxy-amitriptyline, 10-	15.0	ND	41.4	83%	L,H
Painkiller	Hydroxy-ibuprofen, 2-	ND	ND	5,920	57%	H
Painkiller	Ibuprofen	ND	ND	1,330	43%	H
Antibiotic	Lincomycin	ND	ND	7.4	14%	M
Antibiotic	Lomefloxacin	ND	ND	ND	0%	NA
Anti-anxiety (CNS)	Meprobamate	195	82.2	959	100%	L
Anti-diabetic	Metformin	2,780	320	96,900	100%	L,H
Coricosteroid	Methylprednisolone	ND	ND	ND	0%	H[5]
High blood pressure (cardiovascular	Metoprolol	499	350	751	100%	L
Antibiotic	Miconazole	3.2	ND	4.0	71%	M,H
Painkiller	Naproxen	31.1	14.2	2,340	100%	M,H
Antibiotic	Norfloxacin	ND	ND	ND	0%	NA
Anti-depressant (CNS)	Norfluoxetine	4.5	ND	11.8	86%	L,M
Birth control (hormone)	Norgestimate	ND	ND	ND	0%	NA
High blood pressure (cardiovascula	Norverapamil	4.5	2.2	11.9	100%	L
Antibiotic	Ofloxacin	256	70	363	100%	L,M

Class	Pharmaceuticals	Effluent Concentrations (ng/L)			Detection Frequency	Removal Efficiency[1,2]
		Weighted Median	Min	Max		
Antibiotic (veterinary)	Ormetoprim	ND	ND	ND	0%	NA
Antibiotic	Oxacillin	NR[3]	NR	NR	NA	NA
Antibiotic	Oxolinic Acid	ND	ND	5.5	14%	NA
Painkiller	Oxycodone	46.2	27.4	80.6	100%	L,M
Anti-depressant (CNS)	Paroxetine	ND	ND	6.1	43%	NA
Antibiotic	Penicillin G	NR[3]	NR	NR	NA	NA
Antibiotic	Penicillin V	ND	ND	ND	0%	M[5]
Coricosteroid	Prednisolone	ND	ND	ND	0%	H[5]
Coricosteroid	Prednisone	ND	ND	ND	0%	NA
Antihistamine	Promethazine	ND	ND	ND	0%	M[5]
Painkiller	Propoxyphene	0.4	ND	15.8	57%	M[5]
High blood pressure (cardiovascular	Propranolol	46.3	31.9	106	100%	L
Treat ulcers	Ranitidine	NR[3]	NR	NR	NA	NA
Antibiotic	Roxithromycin	3.7	ND	25.2	83%	L,M
Antibiotic	Sarafloxacin	ND	ND	ND	0%	NA
Anti-depressant (CNS)	Sertraline	22.3	9.6	51.6	100%	L,M
Cholesterol-lowering (cardiovascula	Simvastatin	ND	ND	ND	0%	NA
Antibiotic	Sulfachloropyridazine	ND	ND	ND	0%	NA
Antibiotic	Sulfadiazine	7.6	ND	13.0	33%	L,M[5]
Antibiotic	Sulfadimethoxine	ND	ND	22.3	14%	H[5]
Antibiotic	Sulfamerazine	ND	ND	ND	0%	H[5]
Antibiotic	Sulfamethazine	ND	ND	ND	0%	L[4,5]
Antibiotic	Sulfamethizole	ND	ND	ND	0%	L[4,5]
Antibiotic	Sulfamethoxazole	501	192	731	100%	L,M,H
Antibiotic	Sulfanilamide	69	ND	158	60%	L[5]
Antibiotic	Sulfathiazole	ND	ND	5.4	29%	M[5]
Asthma treatment	Theophylline	NR[3]	NR	NR	NA	NA
Antibiotic (fungicide)	Thiabendazole	46.2	25.0	72.0	100%	L,M
Hormone	Trenbolone	ND	ND	ND	0%	NA
Hormone	Trenbolone acetate	ND	ND	2.2	14%	L,M,H
Diuretic	Triamterene	119	102	211	100%	L
Antimicrobial	Triclocarban	11.1	8.1	47.6	100%	L,M,H
Antimicrobial	Triclosan	ND	ND	245	43%	L,M,H[2]

Class	Pharmaceuticals	Effluent Concentrations (ng/L)			Detection Frequency	Removal Efficiency[1,2]
		Weighted Median	Min	Max		
Antibiotic	Trimethoprim	178	39.2	568	100%	L,M,H[2]
Antibiotic (veterinary)	Tylosin	ND	ND	56.2	33%	NA
High blood pressure (cardiovascular	Valsartan	453	ND	4,020	100%	L,M,H[2]
High blood pressure (cardiovascular	Verapamil	13.8	8.7	45.4	100%	L
Antibiotic	Virginiamycin M1	ND	ND	ND	0%	NA
Anticoagulant	Warfarin	ND	ND	4.7	14%	M[4,5]

ND = non-detect

NR = not reported by lab or censored after QA

NA = not applicable, insufficient data for calculation

CNS = Central nervous system

[1] L = low removal efficiency (<50%), M = moderate removal efficiency (50-80%), H = high removal efficiency (>80%)

[2] Higher removal efficiency at tertiary treatment facilities compared to secondary treatment facilities (p<10%).

[3] >50% of data censored

[4] Minimum removal efficiency calculated assuming effluent at method detection limits.

[5] Removal efficiency calculations limited to 1 or 2 facilities with detections in influent.

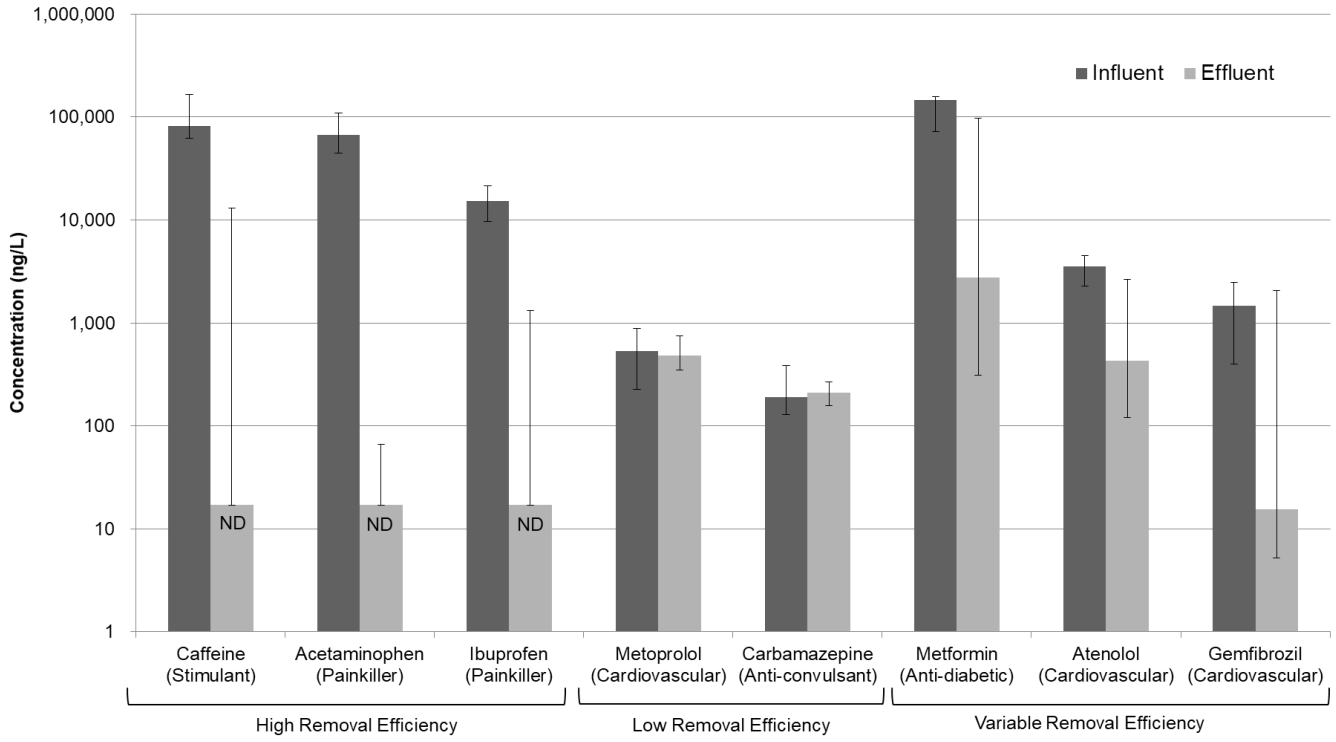

Figure 1. Weighted median influent and effluent concentrations of key pharmaceuticals illustrating a range of removal efficiencies across different pharmaceuticals and wastewater treatment plants. Concentrations are presented using a logarithmic scale given the wide range in values. Error bars represent minimum and maximum values detected in influent and effluent. Weighted median concentrations of caffeine, acetaminophen, and ibuprofen were below detection limits and are shown at values of half the method detection limit.

3.2.2 Temporal trends based on available data

Pharmaceuticals present in wastewater effluent can vary due to a changing population, usage, water consumption patterns, weather conditions, persistence, and efficacy of wastewater treatment processes. Loads of pharmaceuticals entering wastewater treatment plants are expected to increase from a growing and aging population in the San Francisco Bay Area. Between 2010 and 2040, the Bay Area population is projected to increase by 2 million people, and people over 65 are expected to double to 20% of the population (MTC, 2017). Globally, the World Health Organization reports increasing use of pharmaceuticals across all income groups (Hoebert et al. 2011). As a result, the RMP's CEC Strategy recommends periodic monitoring of this contaminant class (Sutton et al., 2017). Reductions in inputs, should they occur, would depend on source control, including more prudent use of pharmaceuticals and improved disposal practices.

Previous wastewater effluent data available for comparison are from samples collected in 2006 and 2008-2009 from two Lower South Bay wastewater treatment plants. In part because these samples were collected as grab samples near peak flow, it is challenging to detect temporal changes.

Nevertheless, concentrations of sulfamethoxazole (antibiotic) in final effluent at the two plants appear to an order of magnitude higher in 2016-2017 relative to 2006, which may suggest increase in use. Erythromycin-H_2O (antibiotic) concentrations appear to have decreased in 2016-2017 (25 - 54 ng/L) relative to 2006 (average 200 ng/L) and 2009 (average 169 ng/L). These differences may be due to changing prescription and usage of antibiotics. Triclocarban (antimicrobial) effluent concentrations seem to have decreased from 2009 (average 145 ng/L) to 2016-2017 (average 11 ng/L).

Metformin (anti-diabetic) results from 2006 (Harrold et al., 2009) were censored due to poor surrogate recoveries, therefore changes in effluent concentrations cannot be observed. However, increase in use of these drugs is expected to continue with an increase in populations diagnosed with and treated for diabetes (CDC, 2017; Rowley et al., 2017).

3.3 Effluent Concentrations Relative to Ecotoxicity Thresholds

3.3.1 Comparison of effluent concentrations to ecotoxicity thresholds

Table 3: Effluent Concentrations Relative to Ecotoxicity Thresholds

As a first step to screen the pharmaceuticals detected in effluent to see which may merit further examination, the ratios of both median and maximum effluent levels relative to available ecotoxicity thresholds were calculated and summarized in Table 3. Of the 48 compounds where a ratio was calculated based on available ecotoxicity information and detections in effluent, nineteen pharmaceuticals had a maximum concentration ratio greater than one. Fifteen pharmaceuticals had a median concentration ratio greater than one, including painkillers (codeine, oxycodone), antibiotics (azithromycin, ciprofloxacin, clarithromycin, ofloxacin, sulfamethoxazole), treatments for diabetes (metformin) and high blood pressure (metoprolol, propranolol), the antihistamine diphenhydramine, and central nervous system agents used to treat depression, anxiety, and seizures (amitriptyline, carbamazepine, fluoxetine, sertraline). Figure 2 summarizes ratios calculated between the median effluent concentration and ecotoxicity threshold for these fifteen pharmaceuticals.

Of note, ecotoxicity thresholds reviewed here are based on exposure to a single compound, and the presence of pharmaceutical mixtures discharged to the Bay presents the potential for synergistic or antagonistic effects among compounds. Therefore, actual risks to Bay aquatic life may be greater from the additive effects of pharmaceuticals that impact organisms through similar modes of action.

Table 3: Effluent pharmaceutical concentrations relative to ecotoxicity thresholds

Class	Pharmaceutical	Effluent Median	Effluent Max	Environmental Threshold (ng/L)	Ratio (Median/Threshold)	Ratio (Max/Threshold)	Reference
Painkiller	Acetaminophen	ND	66.7	1,000	NA	0.07	PNEC Verlicchi et al. 2012[1]
Asthma treatment	Albuterol	14.15	27.5	NA	NA	NA	
Anti-anxiety (CNS)	Alprazolam	2.69	4.89	NA	NA	NA	
Anti-depressant (CNS)	Amitriptyline	13	27	4.1	3.2	6.6	PNEC Minguez et al. 2016[2]
Anti-depressant (CNS)	Amlodipine	5.68	24.1	10,000	0.0006	0.002	LOEC WikiPharma
Stimulant	Amphetamine	ND	27.9	NA	NA	NA	
High blood pressure (cardiovascular)	Atenolol	438	2640	10,000	0.04	0.3	PNEC Minguez et al. 2016[2]
Cholesterol-lowering (cardiovascular)	Atorvastatin	14.2	128	14,000	0.001	0.01	PNEC Vestel et al. 2015
Antibiotic	Azithromycin	544	787	21	25	37	PNEC Minguez et al. 2016[2]
Cocaine metabolite	Benzoylecgonine	14.2	336	NA	NA	NA	
Parkinson's disease treatment (CNS)	Benztropine	ND	0.661	NA	NA	NA	
Coricosteroid	Betamethasone	ND	3.42	NA	NA	NA	
Stimulant	Caffeine	ND	13000	15,000	NA	0.9	EC Fabbri and Franzellitti 2016[2]
Anti-convulsant (CNS)	Carbamazepine	209	276	25	8	11	PNEC Tran et al. 2018
Gastric Issues	Cimetidine	1.26	139	176,000	0.000007	0.0008	PNEC Vestel et al. 2015
Antibiotic	Ciprofloxacin	119	286	5.0	24	57	PNEC Grung et al. 2007
Antibiotic	Clarithromycin	156	417	0.02	10,000	27,000	PNEC Minguez et al. 2016[2]
Antibiotic	Clinafloxacin	37.4	48.7	NA	NA	NA	
Recreational drug	Cocaine	1.7	59.2	NA	NA	NA	
Painkiller	Codeine	148	262	100	1	3	PNEC Tran et al. 2018
Nicotine metabolite	Cotinine	36.2	555	1,000	0.04	0.6	PNEC Gosset et al. 2017
High blood pressure (cardiovascular)	Dehydronifedipine	11.8	23	2,899,000	0.000004	0.000008	PNEC Deo 2014
High blood pressure (cardiovascular)	Desmethyldiltiazem	45.7	73.2	NA	NA	NA	
Anti-anxiety (CNS)	Diazepam	1.7	3.54	4,200	0.0004	0.0008	PNEC Stuer-Lauridsen et al. 2000
Insect repellent (DEET)	Diethyl-3-methyl-benzamide, N,N-	156	1880	500,000	0.0003	0.004	NOEC Weeks et al. 2010[2]
High blood pressure (cardiovascular)	Diltiazem	132	217	8,200	0.02	0.03	PNEC Kim et al. 2007
Antihistamine (CNS)	Diphenhydramine	145	955	100	1.5	10	PNEC WET Center
High blood pressure (cardiovascular)	Enalapril	0.608	13.5	1,200,000	0.000001	0.00001	PNEC Deo 2014
Antibiotic (veterinary)	Enrofloxacin	ND	6.95	NA	NA	NA	
Antibiotic	Erythromycin-H2O	45.3	79.3	206	0.2	0.4	PNEC Besse et al. 2010
CNS (antidepressant)	Fluoxetine	26.8	91.2	4.3	6	21	PNEC Minguez et al. 2016[2]
Corticosteroid	Fluticasone propionate	7.09	12.7	NA	NA	NA	
Diuretic	Furosemide	737	1360	1,560	0.5	0.9	PNEC Besse et al. 2010
Cholesterol-lowering (cardiovascular)	Gemfibrozil	15.6	2050	78	0.20	26.28	PNEC Tran et al. 2018
Anti-diabetic	Glipizide	13.9	66	NA	NA	NA	
Anti-diabetic	Glyburide	7.13	14.4	NA	NA	NA	
Diuretic	Hydrochlorothiazide	570	965	200,000	0.003	0.005	PNEC Vestel et al. 2015
Painkiller	Hydrocodone	61.1	207	2,500,000	0.00002	0.0001	PNEC Deo 2014
Anti-depressant (CNS)	Hydroxy-amitriptyline, 10-	15	41.4	NA	NA	NA	
Painkiller	Hydroxy-ibuprofen, 2-	ND	5920	NA	NA	NA	
Painkiller	Ibuprofen	ND	1330	10	NA	133	PNEC Bouissou-Schurtz et al. 2014
Antibiotic	Lincomycin	ND	7.4	8,200	NA	0.0009	PNEC Tran et al. 2018
Anti-anxiety (CNS)	Meprobamate	195	959	NA	NA	NA	
Anti-diabetic	Metformin	2,780	96,900	1,000	3	97	EC Crago et al. 2016
Coricosteroid	Methylprednisolone	9.12	31.3	NA	NA	NA	
High blood pressure (cardiovascular)	Metoprolol	499	751	100	5	8	PNEC Tran et al. 2018
Antibiotic	Miconazole	3.2	4.02	17	0.2	0.2	PNEC Minguez et al. 2016[2]

Class	Pharmaceutical	Effluent Median	Effluent Max	Environmental Threshold (ng/L)	Ratio (Median/Threshold)	Ratio (Max/Threshold)	Reference
Painkiller	Naproxen	31.1	2,340	4,440	0.01	0.5	PNEC Minguez et al. 2016[2]
Anti-depressant (CNS)	Norfluoxetine	4.5	11.8	17	0.3	0.7	
High blood pressure (cardiovascular)	Norverapamil	4.45	11.9	NA	NA	NA	
Antibiotic	Ofloxacin	256	363	100	3	4	PNEC Besse et al. 2010
Antibiotic	Oxolinic Acid	ND	5.46	NA	NA	NA	
Painkiller	Oxycodone	46.2	80.6	3.3	14	24	PNEC MacGillvray 2013[1]
Anti-depressant (CNS)	Paroxetine	ND	6.11	12	NA	0.5	PNEC Minguez et al. 2016[2]
Painkiller	Propoxyphene	0.4	15.8	NA	NA	NA	
High blood pressure (cardiovascular)	Propranolol	46.3	106	20	2	5	PNEC Vestel et al. 2015
Antibiotic	Roxithromycin	3.7	25.2	10,000	0.0004	0.003	NOEC WikiPharma[2]
Anti-depressant (CNS)	Sertraline	22.3	51.6	6.7	3	8	PNEC Minguez et al. 2016[2]
Antibiotic	Sulfadiazine	7.6	13	2,190,000	0.000003	0.000006	EC50 WikiPharma
Antibiotic	Sulfadimethoxine	ND	22.3	NA	NA	NA	
Antibiotic	Sulfamethoxazole	**501**	731	118	4	6	PNEC Grung et al. 2007
Antibiotic	Sulfanilamide	69.3	128.3	NA	NA	NA	
Antibiotic	Sulfathiazole	ND	5.36	NA	NA	NA	
Antibiotic (fungicide)	Thiabendazole	46.2	72	840	0.06	0.09	PNEC Oh et al. 2006
Hormone	Trenbolone acetate	ND	2.19	NA	NA	NA	
Diuretic	Triamterene	119	211	560,000	0.0002	0.0004	PNEC, MacGillvray, 2013[1]
Antimicrobial	Triclocarban	11.1	47.6	58	0.2	0.8	PNEC Tran et al. 2018
Antimicrobial	Triclosan	ND	245	50	NA	5	PNEC Tran et al. 2018
Antibiotic	Trimethoprim	178	568	319	0.56	2	PNEC Minguez et al. 2016[2]
Antibiotic (veterinary)	Tylosin	ND	56.2	64,000	NA	0.00	LOEC WikiPharma
High blood pressure (cardiovascular)	Valsartan	453	4020	10,000	0.05	0.4	PNEC Minguez et al. 2016[2]
High blood pressure (cardiovascular)	Verapamil	13.8	45.4	401	0.03	0.1	PNEC Minguez et al. 2016[2]
Anticoagulant	Warfarin	ND	4.69	NA	NA	NA	

ND = non-detect

NR = not reported by lab or censored after QA

NA = not applicable

CNS = Central nervous system

PNEC = probably no effects concentration

LOEC = lowest observable effects concentration

NOEC = no observable effects concentration

EC = effects concentration; EC50 concentration necessary to affect 50% of the population

[1]Based on modeled endpoint in EPA's ECOSAR (Ecological Structure Activity Relationships Predictive Model), not experimental data

[2]Derived for marine environments. Most ecotoxicity thresholds are based on freshwater species data and for freshwater environments, which may not be sufficiently conservative for marine and estuarine species

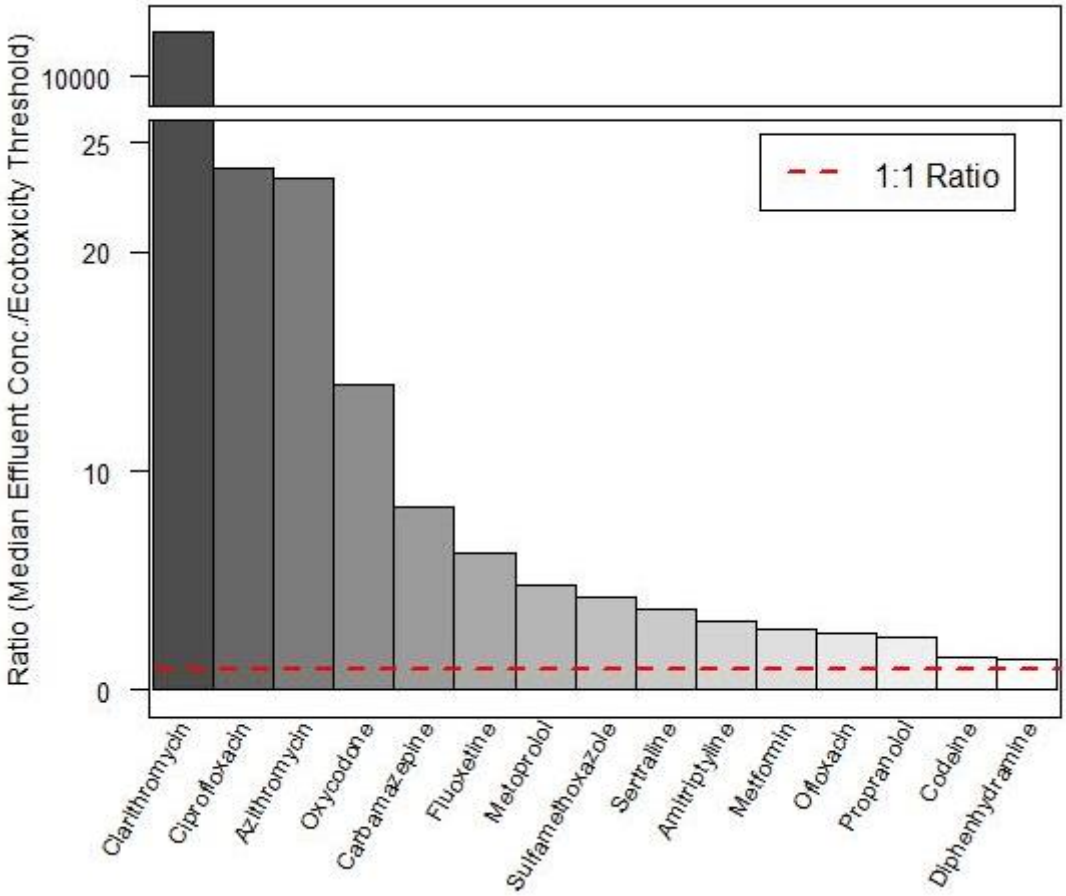

Figure 2: Fifteen pharmaceuticals were detected in effluent at median concentrations greater than ecotoxicity thresholds.

Antibiotics and antimicrobials

Antibiotics are used to treat infections caused by bacteria and other organisms. Potential impacts of antibiotics in surface water include direct ecotoxicity, as well as the selection and evolution of antibiotic resistant genes (ARG) and antibiotic resistant bacteria (ARB). The rise of ARG and ARB threatens the efficacy of antibiotics, and is a growing national and global public health concern. Several antibiotics were detected in final effluent at concentrations higher than ecotoxicity thresholds, including clarithromycin (maximum, median ratios = 10,000, 27,000, respectively), ciprofloxacin (57, 24), azithromycin (37, 25), sulfamethoxazole (6, 4), ofloxacin (4, 3), and trimethoprim (2, 0.6).

Antibiotics in the environment are not only an ecotoxicity concern, but also a growing public health concern due to the rise and potential spread of antibiotic resistant bacteria and antibiotic resistance genes. The Centers for Disease Control and Prevention has identified antibiotic resistance as one of the most serious public health problems in the US, and has established initiatives designed to improve how antibiotics are prescribed and used through education of practitioners and patients. Fostering such initiatives to improve antibiotic stewardship may be an effective means of source control.

Ecotoxicity concerns for antibiotics are dominated by clarithromycin. The reported PNECs for clarithromycin ranged between a marine PNEC of 0.015 ng/L (Minguez et al., 2016) and a freshwater PNEC value of 40 ng/L (Bengtsson-Palme and Larsson, 2016). This highlights that PNECs derived for freshwater environments may not be sufficiently conservative for marine environments. Available ecotoxicity data for pharmaceuticals are limited, particularly for marine or estuarine organisms (Minguez et al., 2016). Ecotoxicity thresholds limited to freshwater species, when noted in the study, are noted in Table 3.

Median concentrations of clarithromycin, azithromycin, ciprofloxacin, ofloxacin also exceeded the PNECs for resistance selection, which ranged between 20 - 150 ng/L (Tran et al., 2018). The sum of weighted median detected antibiotics in final effluent samples is 1,900 ng/L, and there are likely other antibiotics present in wastewater effluent that were not included in the analyte list. Exposure to a mixture of antibiotics may lower the minimum effects concentrations (Tran et al., 2018). Studies from other regions, such as the southeastern US and Norway (Bradley et al., 2016; Grung et al., 2007), have also prioritized antibiotics due to surface water concentrations exceeding ecotoxicity thresholds.

Triclosan and triclocarban are antimicrobials used in household products, such as dish and hand soaps, shampoos, dermal creams, toothpastes, and shower gels. In this dataset, the maximum triclosan concentration was 245 ng/L, while the median was below the detection limit (120-140 ng/L, Table A-2). The PNEC for triclosan is 50 ng/L (Tran et al., 2018). Triclocarban concentrations were below the available ecotoxicity threshold of 58 ng/L.

Of note, the State Water Board has established a monitoring trigger level (MTL) for triclosan in effluent-dominated inland waterways of 250 ng/L (Tadesse, 2016). Monitoring trigger levels (MTLs) are calculated from available toxicity information using conservative safety factors. Exceedance of a monitoring trigger level does not necessarily indicate a risk exists, but instead indicates a need for monitoring (Anderson et al., 2012).

Painkillers

Painkillers, especially nonsteroidal anti-inflammatory drugs (NSAIDs) like acetaminophen, ibuprofen, and naproxen, are widely used to relieve pain or suppress inflammation. Additionally, NSAIDs are being used to prevent development and progression of cardiovascular diseases, and colorectal and several types of cancers through reduced inflammation (Davis et al., 2017; Ulrich et al., 2006).

Maximum effluent concentrations of ibuprofen (NSAID) and codeine (opiate) exceeded PNEC values (maximum ratios 130 and 2.6, respectively), although the median concentration of ibuprofen was below the detection limit. The maximum concentration of ibuprofen was also above the State Water Board's recommended MTL of 100 ng/L for effluent-dominated inland waterways (Tadesse, 2016).

Anti-diabetic drugs

Among anti-diabetic drugs, metformin is widely used for the prevention and treatment of type-II diabetes. Metformin is used to regulate glucose levels by activating signaling pathways involved in the regulation of metabolism in cells and important in insulin signaling (Crago et al., 2016).

Metformin is also a potential treatment for polycystic ovarian syndrome. In 2013, it was the 7th most prescribed drug in the U.S., and is predicted as the pharmaceutical with the highest emissions to the environment on a mass basis (Scheurer et al., 2012). Metformin is poorly metabolized by humans (nearly 100% excreted), and environmentally recalcitrant.

Metformin was by far the highest concentration pharmaceutical in wastewater effluent, with weighted median and maximum concentrations of 2,080 ng/L and 96,900 ng/L, both of which exceed concentrations at which changes in estrogen-associated gene expression in juvenile fathead minnows have been observed (Crago et al., 2016). Juvenile minnows were found to be particularly susceptible to the estrogenic effect of metformin at low µg/L levels.

Other anti-diabetic drugs were below published thresholds.

Central nervous system agents

Pharmaceuticals that correct chemical imbalances of neurotransmitters in the brain are widely prescribed to treat depression, anxiety, epilepsy, and seizures. Antidepressants are one of the most commonly prescribed drugs in the US; the CDC reported that during 2011-2014, 12.7% of persons aged 12 and over took antidepressants medication in the past month, and one-fourth of persons who took antidepressant medication had done so for the past 10 years (CDC, 2017). These drugs can have physiological effects on fish, mollusks, crustaceans, algae, and protozoans, and can affect fish behavior and survival at the low µg/L level (Weinberger and Klaper, 2014). Six different antidepressants were detected in final effluent, with maximum concentrations of fluoxetine, sertraline, and amitriptyline exceeding ecotoxicity thresholds by factors of 22, 8, and 7.

Diphenhydramine is most often used for allergies, but is also used to treat symptoms of insomnia, tremors in Parkinson's disease, and nausea. Maximum and median diphenhydramine effluent concentrations exceeded the PNEC (maximum, median ratios = 9.6, 1.4).

Carbamazepine is used as an anticonvulsant to treat and prevent seizures. The drug works by reducing the spread of seizure activity in the brain and restoring the normal balance of nerve activity. Median and maximum effluent concentrations exceeded the PNEC (25 ng/L) by a factor of 8 and 11, respectively.

Cardiovascular drugs

Cardiovascular disease is the leading cause of mortality in the US, and elevated blood cholesterol is a major risk factor. Cholesterol-lowering medication is prescribed to prevent cardiovascular disease. Nationally, more than a quarter of adults over the age of 40 use cholesterol lowering medication (Gu et al., 2014), and these drugs are among the most commonly detected pharmaceutical in wastewater effluent (Tran et al., 2018). In particular, maximum effluent concentration of gemfibrozil exceeded the PNEC by a factor of 27, while the median effluent concentration was below the PNEC.

A variety of drugs are prescribed to treat high blood pressure by changing the rhythm of the heart or pressure in the blood vessels through various mechanisms. Some of these drugs are also prescribed for migraines. Maximum metoprolol effluent concentrations exceed the PNEC by a factor of 8 (median ratio: 5), and propranolol exceeded the PNEC by a factor of 5 (median ratio 2). The beta-blockers propranolol, atenolol, valsartan, enalapril were also detected in effluent, but did not individually exceed their PNECs.

3.3.2 Prioritizing Pharmaceuticals for Future Work: Measured and Modeled Bay Concentrations

Effluent pharmaceutical levels that are greater than ecotoxicity thresholds do not necessarily indicate a risk for aquatic life, in large part because effluent is significantly diluted within the Bay. For a limited number of pharmaceuticals, past Bay surface water data (Harrold et al. 2009; Klosterhaus et al., 2013; Nödler et al. 2014) can be compared to thresholds to gauge whether additional monitoring may be warranted. Where no Bay surface water measurements are available, modeling can be used to estimate ambient water concentrations based on measured effluent concentrations. Both past surface water data and modeled estimates were used to prioritize 17 pharmaceuticals for further evaluation. Table 4 provides a summary of measured and estimated Bay concentrations for these key pharmaceutical compounds. This section describes how these 17 pharmaceuticals were selected.

Of the 19 pharmaceuticals detected in effluent at levels greater than ecotoxicity thresholds, previous Bay data indicate sporadic detections above thresholds for four of these pharmaceuticals (Table 4). Clarithromycin (antibiotic) has been the subject of past RMP monitoring, and was detected in Bay water at a maximum concentration of 17.6 ng/L (Klosterhaus et al., 2013), above the marine PNEC of 0.02 ng/L. Likewise, previous Bay data indicate maximum sulfamethoxazole levels (1,060 ng/L; Harrold et al. 2009) greater than the PNEC of 118 ng/L; maximum carbamazepine levels (44 ng/L; Klosterhaus et al., 2013) greater than the PNEC of 25 ng/L; and maximum ibuprofen levels (38 ng/L; Klosterhaus et al., 2013) greater than the PNEC of 10 ng/L. An independent study also reported a maximum concentration of erythromycin (217 ng/L; Nödler et al. 2014) greater than the PNEC of 206 ng/L. Surface water concentrations measured in this independent study were higher than the maximum measured effluent concentration in the present study. The continued presence of these compounds in effluent according to the data presented here, and occasional exceedances of ecotoxicity thresholds in prior Bay monitoring studies, suggest that these five compounds are appropriate monitoring targets in the future.

Particularly for pharmaceuticals where no surface water data are available, the Bay hydrodynamic dilution spreadsheet model can be used to estimate potential diluted effluent pharmaceutical concentrations in Bay water. This was done using weighted median effluent concentrations for each pharmaceutical to represent all Bay wastewater discharges. The model does not include degradation processes, sorption to sediment, and exchange in the atmosphere, which can further reduce concentrations of contaminants discharged into the Bay. Therefore, these estimates are considered at the high end of the range of possible concentrations in the Bay. This screening exercise was performed to identify pharmaceuticals in effluent that may warrant further examination, as dilution alone may not be sufficient to reduce ambient water concentrations below ecotoxicity thresholds.

In general, the ranges of modeled ambient concentrations were comparable to historic measured concentrations, where available (Table 4). For sulfamethoxazole, the maximum measured concentration was significantly higher than the modeled range, but there was good correspondence between the measured and modeled concentrations for the lower end of the range. The comparison of measured results and model estimates illustrates the power of using multiple approaches to identify priorities for future evaluation.

The modeling results indicate an additional 12 pharmaceuticals have the potential for Bay ambient water concentrations to be similar to or greater than ecotoxicity thresholds in one or more subembayments (Table 4), suggesting monitoring in Bay matrices is warranted. Five of these twelve compounds have been targeted for monitoring in the Bay, and have not been detected above ecotoxicity thresholds previously; these five pharmaceuticals include the antidepressants amitriptyline, sertraline, and fluoxetine, the antihistamine diphenhydramine, and the blood pressure medication metoprolol. While previous monitoring has indicated lower levels to be present in the Bay, modeling results using current effluent concentrations from this study suggest that in the worst case scenario, ambient surface water concentrations may be in the same range as ecotoxicity thresholds. For example, fluoxetine (Prozac), an antidepressant, has been below detection limits (16 ng/L and 1.5 ng/L) in prior studies of Bay surface water (Klosterhaus et al., 2013; Nödler et al., 2014) . Modeling results suggest concentrations are likely to remain well below ecotoxicity thresholds in much of the Bay; however, concentrations estimated for the Lower South Bay (1.7 ng/L) are in the same range as the ecotoxicity threshold (4.3 ng/L), suggesting further attention may be warranted.

The remaining seven pharmaceuticals with estimated ambient Bay water concentrations similar to or greater than ecotoxicity thresholds based on the modeling exercise have not been targeted for monitoring in the Bay previously. These include three antibiotics, ciprofloxacin, azithromycin, and ofloxacin; two painkillers, codeine and oxycodone; the anti-diabetic metformin; and propranolol for treatment of high blood pressure. Modeled ambient Bay concentrations of azithromycin, for example, suggest water concentrations in the Lower South Bay could be 1.4 times higher than the ecotoxicity threshold, while estimated concentrations were below the threshold in other subembayments. Modeled ambient Bay concentrations of ofloxacin are predicted to be one-fifth of the PNEC in the Lower South Bay; while this is below the PNEC, it is within an order of magnitude and warrants further evaluation based on this screening exercise. Modeled estimates greater than or equal to 10% of the PNEC were considered appropriate priorities for further examination. Metformin is also prioritized for further evaluation, based on high concentrations in effluent, expected increases in prescription, and the rapidly evolving science indicating risks to fish. As noted previously, metformin is ubiquitous in wastewater-influenced surface waters. For example, in a regional study of wadeable streams in the southeastern US, metformin was detected at 97% of the sampled sites at concentrations up to the µg/L range, which could not be fully accounted for from wastewater discharges (Bradley et al., 2016). In Lake Michigan, the maximum concentration of metformin detected 1.6 km away from an outfall was 840 ng/L (Blair et al., 2013).

A number of recent toxicological assessments have indicated that metformin is endocrine-active, producing estrogenic effects in fish and impacting reproduction at environmentally relevant levels (e.g., Niemuth and Klaper, 2015). An assessment of juvenile fathead minnows exposed to metformin using a number of sensitive estrogenicity endpoints revealed a concentration necessary to affect 50% of the population (EC_{50}) of 1,000 ng/L (Crago et al., 2016), which is greater than the model predictions for ambient Bay waters (180 ng/L). While a recent RMP pilot study using a cell-based assay found no significant estrogenicity in Lower South Bay water and sediment (Denslow et al., 2018), it is unknown whether this bioassay is sensitive to the effects of metformin (A.C. Mehinto, personal communication). Metformin has only recently been identified as a pharmaceutical with significant potential environmental concerns, and as such the ecotoxicological examination of its impacts is just beginning. Given the rapidly evolving

understanding of potential risks, and the high levels discharged to the Bay, continued examination of this pharmaceutical is warranted.

In summary, 17 pharmaceuticals have been identified as priorities for future work: amitriptyline, azithromycin, carbamazepine, ciprofloxacin, clarithromycin, codeine, diphenhydramine, erythromycin, fluoxetine, ibuprofen, metformin, metoprolol, ofloxacin, oxycodone, propranolol, sertraline, and sulfamethoxazole (Table 4). Detailed assessment of the expected fate of these pharmaceuticals in environmental matrices is anticipated as part of development of a future special study proposal for the RMP.

4. Conclusions

The goal of this study was to review data on pharmaceutical compounds in wastewater to guide the RMP's CEC monitoring strategy for this contaminant class, and to recommend specific chemicals for additional examination including targeted monitoring in the Bay. The dataset for this analysis was generously contributed by seven wastewater treatment plants in the Bay Area. Several of these agencies have played a major role in promoting pharmaceutical take-back programs, now active in counties around the Bay, as a means of preventing pharmaceutical pollution from going down the drain.

The results indicate that Bay Area influent and effluent pharmaceutical concentrations are generally within the range of values measured in other studies in the US. Based on the concentrations measured in effluent, as well as previous studies of pharmaceuticals in ambient Bay waters, 17 pharmaceuticals are prioritized for further evaluation. These 17 compounds are:

- antibiotics – azithromycin, ciprofloxacin, clarithromycin, erythromycin, ofloxacin, and sulfamethoxazole;
- antidepressants – amitriptyline, fluoxetine, and sertraline;
- anti-convulsant – carbamazepine;
- painkillers – codeine, ibuprofen, and oxycodone;
- antihistamine – diphenhydramine;
- anti-diabetic – metformin; and
- treatments for high blood pressure – metoprolol and propranolol.

Surface waters in the Lower South Bay are likely to have the highest concentrations of pharmaceuticals due to low dilution from infrequent flushing in this subembayment.

Future studies to monitor these high priority compounds in the Bay should consider including other commonly used or environmentally detected drugs in the same class to track changes in usage patterns. Additionally, known and commonly detected metabolites, degradation products, and transformation products of the drug should be considered in the analyte list.

Table 4: Modeled and measured ambient water pharmaceutical concentrations relative to predicted no effect concentrations. All concentrations are in ng/L.

Pharmaceutical	Influent Conc Med (Min - Max)	Effluent Conc Med (Min - Max)	Removal Efficiency[1]	Ecotoxicity Threshold	Modeled Ambient Water Conc.[2] (Min - Max)	Measured Ambient Water Conc.[3,4,5] (Min - Max)
Amitriptyline (antidepressant)	890 (690 - 1,540)	13 (5.9 - 27)	L,M,H	4.1	0.1 - 0.8	<0.3 - 1
Azithromycin (antibiotic)	189 (129 - 389)	544 (37 – 787)	L	25	2 - 35	NA
Carbamazepine (anti-convulsant)	378 (239 - 1,290)	209 (157 – 276)	M	25	0.9 – 13	5.2 – 44.2
Ciprofloxacin (antibiotic)	427 (130 - 648)	119 (<50 – 286)	L,M,H	5	0.5 – 8	NA
Clarithromycin (antibiotic)	175 (95 - 349)	155 (28 - 417)	L	0.02	0.6 - 10	<1.5 – 17.6
Codeine (painkiller)	486 (81 - 1,120)	148 (<8 - 262)	L,M,H	100	0.6 - 10	NA
Diphenhydramine (antihistamine)	67 (30 - 109)	145 (82.4 - 955)	L,M	100	0.6 - 9	<0.8 - 1.9
Erythromycin-H2O (antibiotic)	28 (ND - 64)	45.5 (25.3 - 79.3)	L,M	206	0.2 - 3	1 -217
Fluoxetine (antidepressant)	15,200 (9,665 - 21,350)	26.8 (14.5 – 91)	H	4.3	0.1 – 1.7	<1.5
Ibuprofen (painkiller)	146,000 (72,800 - 157,000)	<34 (<34 - 1,330)	L,H	10	0.1 - 1	<14 - 37.9
Metformin (anti-diabetic)	530 (228 - 877)	2,780 (320 - 96,900)	L	1,000	12 - 180	NA
Metoprolol (high blood pressure)	225 (27.8 - 538)	499 (350 - 751)	L,M	100	2 -32	<4 - 26.2
Ofloxacin (antibiotic)	40.3 (34.2 - 175)	256 (70 - 363)	L,M	100	1 -16	NA
Oxycodone (painkiller)	42.7 (ND - 113)	46.2 (27.4 - 80.6)	L	3.3	0.2 - 3	NA
Propranolol (high blood pressure)	33 (16 - 77)	46.3 (31.9 - 106)	L,M	20	0.2 - 3	NA
Sertraline (antidepressant)	875 (365 - 3,570)	22.3 (9.6 - 51.6)	M,H	6.7	0.1 - 1.4	<0.4
Sulfamethoxazole (antibiotic)	875 (365 - 3,570)	501 (192 – 731)	M,H	118	2 - 32	2.4 – 1,060

NA = data not available, compounds have not been targeted for monitoring in Bay waters.

[1]L = low removal efficiency (<50%), M = moderate removal efficiency (50-80%), H = high removal efficiency (>80%)

[2]Non-detect effluent concentrations modeled using half the MDL value

[3]Klosterhaus et al., 2013; [4]Nodler et al. 2014; [5]Harrold et al. 2009.

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5. References

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Appendix - Field and Laboratory Methods

Table A-1 Field Samples Collected, Sample Type, and Preservation Method

Plant	Field Samples	Sample Type	Preservation Method
WWTP A	1 Effluent	Grab	Frozen
WWTP B	3 Influent + 1 duplicate, 3 Effluent, 3 Recycled Water	Grab	Frozen, Ascorbic acid added to Recycled Water
WWTP C	1 Influent, 1 Effluent	24-hour Composite	Frozen
WWTP D	1 Influent, 1 Influent Blank, 1 Effluent, 1 Secondary Effluent before Disinfectcion, 1 Recycled Water	24-hour Composite	Frozen, Ascorbic acid added to Recycled Water
WWTP E	3 Influent, 3 Effluent + 1 Duplicate, 2 Effluent Blank, 3 Secondary Effluent before Filtration + 1 Duplicate, 3 Tertiary Effluent before Disinfection, 3 Reverse Osmosis Reject + 1 Duplicate	24-hour Composite	Frozen, Ascorbic acid added to Reverse Osmosis Reject
WWTP F	1 Influent, 1 Effluent	24-hour Composite	Frozen, Ascorbic acid added to Effluent
WWTP G	2 Influent, 2 Effluent + 1 Duplicate, 2 Primary Effluent, 3 Secondary Effluent before Disinfection + 1 Duplicate, 2 Field Blank	24-hour Composite	Frozen

Table A-2 Laboratory MDLs

Analyte	Final Effluent MDL (Min - Max)
Acetaminophen	(29.4 - 34.2)
Albuterol	(0.6 - 5.9)
Alprazolam	(0.3 - 1.9)
Amitriptyline	(0.3 - 1.9)
Amlodipine	(1.5 - 9.6)
Amphetamine	(2.9 - 273)
Atenolol	(1.2 - 3)
Atorvastatin	(2.9 - 4)
Azithromycin	(3 - 21.9)
Benzoylecgonine	(0.5 - 5.9)
Benztropine	(0.5 - 3.2)
Betamethasone	(1.5 - 10.8)
Bisphenol A	(979 - 1140)
Caffeine	(29.4 - 34.2)
Carbadox	(2.9 - 4.2)
Carbamazepine	(2.9 - 3.4)
Cefotaxime	(4 - 27.2)
Cimetidine	(1.2 - 2)
Ciprofloxacin	(12.3 - 50)
Clarithromycin	(2.9 - 3.4)
Clinafloxacin	(20.9 - 48.7)
Clonidine	(2.9 - 4)
Cloxacillin	(5.9 - 6.8)
Cocaine	(0.2 - 1.1)
Codeine	(5.8 - 8)
Cotinine	(2.9 - 4)
Dehydronifedipine	(1.2 - 6.7)
Desmethyldiltiazem	(0.1 - 1)
Diazepam	(0.4 - 1.9)
Diethyl-3-methyl-benzamide, N,N-	(0.8 - 5.1)
Digoxigenin	(62.3 - 332)
Digoxin	(11.8 - 13.7)
Diltiazem	(0.6 - 0.8)
Dimethylxanthine, 1,7-	(118 - 137)
Diphenhydramine	(1.2 - 1.4)
Enalapril	(0.6 - 0.8)
Enrofloxacin	(5.9 - 7.8)
Erythromycin-H2O	(4.5 - 5.2)
Flumequine	(2.9 - 3.4)
Fluocinonide	(5.9 - 38.2)
Fluoxetine	(2.9 - 31.7)
Fluticasone propionate	(2.6 - 12.7)
Furosemide	(78.4 - 132)

Analyte	Final Effluent MDL (Min - Max)
Gemfibrozil	(2.9 - 3.4)
Glipizide	(11.8 - 13.7)
Glyburide	(5.9 - 6.8)
Hydrochlorothiazide	(39.2 - 51.4)
Hydrocodone	(3 - 54.8)
Hydrocortisone	(59 - 382)
Hydroxy-amitriptyline, 10-	(0.3 - 1)
Hydroxy-ibuprofen, 2-	(157 - 182)
Ibuprofen	(29.4 - 34.2)
Lincomycin	(5.9 - 6.8)
Lomefloxacin	(8.3 - 19.3)
Meprobamate	(3.9 - 25.5)
Metformin	(5.8 - 79.1)
Methylprednisolone	(3.9 - 31.3)
Metoprolol	(7.2 - 40.5)
Miconazole	(2.9 - 3.4)
Naproxen	(5.9 - 34.5)
Norfloxacin	(29.4 - 79.3)
Norfluoxetine	(1.5 - 9.6)
Norgestimate	(6 - 11.1)
Norverapamil	(0.1 - 1)
Ofloxacin	(3 - 5)
Ormetoprim	(1.2 - 1.4)
Oxacillin	(5.9 - 6.8)
Oxolinic Acid	(1.3 - 12)
Oxycodone	(1.2 - 1.7)
Paroxetine	(3.9 - 25.5)
Penicillin G	(5.9 - 6.8)
Penicillin V	(5.9 - 6.8)
Prednisolone	(5.9 - 53.9)
Prednisone	(19.7 - 304)
Promethazine	(0.4 - 2.6)
Propoxyphene	(0.3 - 2.6)
Propranolol	(2 - 12.7)
Ranitidine	(1.2 - 6.6)
Roxithromycin	(0.6 - 2.2)
Sarafloxacin	(29.4 - 34.2)
Sertraline	(0.5 - 2.6)
Simvastatin	(19.7 - 127)
Sulfachloropyridazine	(2.9 - 3.4)
Sulfadiazine	(2.9 - 5.3)
Sulfadimethoxine	(0.6 - 16.4)
Sulfamerazine	(1.2 - 5.6)
Sulfamethazine	(1.2 - 41.5)

Analyte	Final Effluent MDL (Min - Max)
Sulfamethizole	(1.2 - 1.6)
Sulfamethoxazole	(1.2 - 14)
Sulfanilamide	(29.4 - 31.9)
Sulfathiazole	(2.9 - 3.8)
Theophylline	(74 - 382)
Thiabendazole	(2.9 - 3.4)
Trenbolone	(3.9 - 25.5)
Trenbolone acetate	(0.3 - 1.9)
Triamterene	(0.6 - 6.4)
Triclocarban	(5.9 - 6.8)
Triclosan	(118 - 137)
Trimethoprim	(2.9 - 5.8)
Tylosin	(11.8 - 13.7)
Valsartan	(4.5 - 25.5)
Verapamil	(0.1 - 1)
Virginiamycin M1	(5.9 - 7.1)
Warfarin	(2.9 - 3.4)

Table A-3 QA/QC Results

Analyte	Max Detection in Lab Blank (ng/L)	Max Detection in Field Blank (ng/L)	# Effluent Data Points Censored (out of 14)	# Effluent Non-Detect Data Points (out of 14)
Acetaminophen			0	12
Albuterol		0.7	0	0
Alprazolam			0	0
Amitriptyline	1.5		0	0
Amlodipine			0	6
Amphetamine	2.2		0	1
Atenolol		4.2	0	0
Atorvastatin		3.4	0	2
Azithromycin			0	0
Benzoylecgonine	18.1		3	0
Benztropine		0.6	0	12
Betamethasone			0	14
Bisphenol A			0	14
Caffeine			0	6
Carbadox			3	11
Carbamazepine			0	0
Cefotaxime			14	0
Cimetidine		3.3	0	6
Ciprofloxacin			0	1
Clarithromycin			1	0
Clinafloxacin			0	14
Clonidine			0	14
Cloxacillin			14	0
Cocaine	0.7		2	3
Codeine		7.9	0	3
Cotinine			0	0
Dehydronifedipine			0	0
Desmethyldiltiazem	2.8		0	0
Diazepam			0	3
Diethyl-3-methyl-benzamide, N,N-	48.1		3	0

Analyte	Max Detection in Lab Blank (ng/L)	Max Detection in Field Blank (ng/L)	# Effluent Data Points Censored (out of 14)	# Effluent Non-Detect Data Points (out of 14)
Digoxigenin			0	14
Digoxin			0	14
Diltiazem			0	0
Dimethylxanthine, 1,7-			14	0
Diphenhydramine			0	0
Enalapril			0	11
Enrofloxacin		3.9	0	12
Erythromycin-H2O			0	0
Flumequine			0	14
Fluocinonide			0	14
Fluoxetine			0	0
Fluticasone propionate			0	10
Furosemide			0	0
Gemfibrozil			0	0
Glipizide			0	6
Glyburide			0	6
Hydrochlorothiazide			0	0
Hydrocodone		3.0	0	1
Hydrocortisone			0	14
Hydroxy-amitriptyline, 10-	1.7		0	2
Hydroxy-ibuprofen, 2-			0	10
Ibuprofen			0	10
Lincomycin			0	13
Lomefloxacin	3.2		0	14
Meprobamate	33.4		0	0
Metformin	7.1		0	0
Methylprednisolone			0	14
Metoprolol	34.0		0	0
Miconazole			0	7
Naproxen		4.7	0	0
Norfloxacin			0	14

Analyte	Max Detection in Lab Blank (ng/L)	Max Detection in Field Blank (ng/L)	# Effluent Data Points Censored (out of 14)	# Effluent Non-Detect Data Points (out of 14)
Norfluoxetine			0	8
Norgestimate			0	14
Norverapamil	0.2		0	0
Ofloxacin			0	0
Ormetoprim			0	14
Oxacillin			14	0
Oxolinic Acid			0	13
Oxycodone		1.6	0	0
Paroxetine			0	11
Penicillin G			14	0
Penicillin V			3	11
Prednisolone			0	14
Prednisone			0	14
Promethazine			0	14
Propoxyphene			0	8
Propranolol	3.4		0	0
Ranitidine		13.5	14	0
Roxithromycin			1	1
Sarafloxacin		16.1	0	14
Sertraline	1.4		0	0
Simvastatin			0	14
Sulfachloropyridazine			1	13
Sulfadiazine			1	8
Sulfadimethoxine			1	10
Sulfamerazine			1	13
Sulfamethazine			1	13
Sulfamethizole			1	13
Sulfamethoxazole			1	0
Sulfanilamide			4	5
Sulfathiazole			1	11
Theophylline	371.0		14	0

Analyte	Max Detection in Lab Blank (ng/L)	Max Detection in Field Blank (ng/L)	# Effluent Data Points Censored (out of 14)	# Effluent Non-Detect Data Points (out of 14)
Thiabendazole			0	0
Trenbolone			0	14
Trenbolone acetate			0	13
Triamterene		3.5	0	0
Triclocarban			0	0
Triclosan			0	8
Trimethoprim			0	0
Tylosin			1	8
Valsartan	49.9		2	0
Verapamil	0.8		0	0
Virginiamycin M1			0	14
Warfarin			0	12

1. RMP QA/QC Procedures: Evaluation

a. Dataset completeness evaluation

Dissolved pharmaceuticals (104) were reported for 41 effluent samples (for several matrices including influent, secondary final effluent, tertiary final effluent, primary partially treated effluent, secondary partially treated effluent, tertiary partially treated effluent, recycled water, and reverse osmosis reject) analyzed in 13 lab batches. Field replicates, lab replicates, field blanks, method blanks and laboratory control samples (LCS's) were also analyzed. All data was reported not blank corrected.

Thirteen method blanks, 1 laboratory replicate, 15 laboratory control samples (LCSs), and 6 field replicates were reported for the 41 samples, which satisfies the requirements in the 2017 RMP QAPP of 1 per 20 samples, except for the number of lab replicates analyzed (1 for 41 instead of the preferred 2).

A majority of the results (~70%) were flagged with the QA code of VH for a holding time violation, as they were analyzed more than the 21 days after collection. All of these results were included in the analysis.

b. Overall acceptability evaluations

i. MDLs sensitivity

59.6% (62 of 104) pharmaceuticals for the matrix "secondary final effluent" had non-detects (NDs) ranging from 66.7% to 100%; Acetaminophen, Benztropine, Betamethasone, Bisphenol A, Carbadox, Cefotaxime, Clinafloxacin, Clonidine, Digoxigenin, Digoxin, Enrofloxacin, Flumequine, Fluocinonide, Fluticasone propionate, Hydrocortisone, Lincomycin, Lomefloxacin, Methylprednisolone, Norfloxacin, Norgestimate, Ormetoprim, Oxolinic Acid, Paroxetine, Penicillin V, Prednisolone, Prednisone, Promethazine, Sarafloxacin, Simvastatin, Sulfachloropyridazine, Sulfadiazine, Sulfamerazine, Sulfamethazine, Sulfamethizole, Sulfanilamide, Sulfathiazole, Trenbolone, Trenbolone acetate, Virginiamycin M1, and Warfarin had extensive NDs (>50% NDs).

64.4% (67 of 104) pharmaceuticals for the matrix "tertiary final effluent" had non-detects (NDs) ranging from 12.5% to 100%; Acetaminophen, Amlodipine, Benztropine, Betamethasone, Bisphenol A, Carbadox, Clinafloxacin, Clonidine, Digoxigenin, Digoxin, Enalapril, Enrofloxacin, Flumequine, Fluocinonide, Fluticasone propionate, Hydrocortisone, 2-Hydroxy-ibuprofen, Ibuprofen, Lincomycin, Lomefloxacin, Methylprednisolone, Miconazole, Norfloxacin, Norfluoxetine, Norgestimate, Ormetoprim, Oxolinic Acid, Paroxetine, Penicillin V, Prednisolone, Prednisone, Promethazine, Propoxyphene, Sarafloxacin, Simvastatin, Sulfachloropyridazine, Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfamethizole, Sulfathiazole, Theophylline, Trenbolone, Trenbolone acetate, Triclosan, Tylosin, Virginiamycin M1, and Warfarin had extensive NDs (>50% NDs).

57.7% (60 of 104) pharmaceuticals for the matrix "influent " had non-detects (NDs) ranging from 7.69% to 100%; Betamethasone, Bisphenol A, Carbadox, Clinafloxacin, Clonidine,

Digoxigenin, Digoxin, Enrofloxacin, Flumequine, Fluocinonide, Glyburide, Lincomycin, Lomefloxacin, Methylprednisolone, Norfloxacin, Norgestimate, Ormetoprim, Oxolinic Acid, Paroxetine, Penicillin V, Prednisolone, Prednisone, Propoxyphene, Sarafloxacin, Simvastatin, Sulfachloropyridazine, Sulfadiazine, Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfamethizole, Sulfathiazole, Trenbolone, Tylosin, Virginiamycin M1, and Warfarin had extensive NDs (>50% NDs).

ii. Procedural and blank contamination evaluation

Samples from the same laboratory analytical batch with sample concentrations within three times the method blank contamination levels were censored. Seventeen compounds were detected in at least one method blank; these were Amitriptyline, Amphetamine, Benzoylecgonine, Cocaine, Desmethyldiltiazem, N,N-Diethyl-3-methyl-benzamide, 10-Hydroxy-amitriptyline, Lomefloxacin, Meprobamate, Metformin, Metoprolol, Norverapamil, Propranolol, Sertraline, Theophylline, Valsartan, and Verapamil.

Censored secondary final effluent included Benzoylecgonine (17%), N,N-Diethyl-3-methyl-benzamide (17%), and Theophylline (17%). Percentages represent percentage of data points censored. Censored tertiary final effluent included Benzoylecgonine (25%), Cocaine (25%), N,N-Diethyl-3-methyl-benzamide (25%), Theophylline (~38%), and Valsartan (25%). Censored influent included Lomefloxacin (~8%) and Sertraline (15%).

Fifteen compounds were detected in field blanks. Concentrations in blanks were generally less than 5% of the average field sample concentrations. Compounds in blanks were Albuterol, Atenolol, Atorvastatin, Benztropine, Cimetidine, Codeine, N,N-Diethyl-3-methyl-benzamide, Enrofloxacin, Hydrocodone, Naproxen, Oxycodone, Ranitidine, Sarafloxacin, Sulfamethoxazole, and Triamterene were measured in the field blanks. Benztropine was detected in one field blank just above the MDL at 0.6 ng/L, all field samples were below the MDL (0.5 – 3 ng/L) except for two effluent samples that were also reported at concentrations just above the MDL at 0.6 and 0.7 ng/L. Enrofloxacin was detected in one field blank just above the MDL at 3.93 ng/L, all effluent field samples were below MDL (3-7 ng/L), except for two effluent samples also measured just above the MDL at 7 ng/L. Sarafloxacin was not-detected in the field samples, but was measured in one field blank at a concentration of 16.1 ng/L. These results were included in the analysis.

iii. Accuracy evaluation

Accuracy was calculated based on recovery of lab controls samples as follows:

% error = [Difference (between Measurement and Control) / Control] x 100%

Data was censored if the % error was > 70%; censored data was not included in the analysis. The average % error ranged from 1.3% to 165.3% with the majority of pharmaceuticals (85%, 88 out of 104) having average % errors less than the 35% target measurement quality objectives. Atorvastatin, Carbadox, Ciprofloxacin, Diltiazem, Enrofloxacin, Fluocinonide, Lincomycin, Lomefloxacin, Norfloxacin, Ofloxacin, Sarafloxacin, and Sulfanilamide had average % errors > 35%, but < 70%, these data were qualified and still included in analysis. Cefotaxime, 1,7-

Dimethylxanthine, Ranitidine, and Theophylline results were censored because % errors were >70%. Censored data was not included in the analysis.

iv. Precision evaluation

Precision was evaluated for the matrices influent, effluent (secondary partially treated effluent, secondary final effluent, tertiary partially treated effluent, and tertiary final effluent) and reverse osmosis reject using lab and field replicates.

Relative Standard Deviation (RSD) was calculated as:

RSD = [Standard Deviation (all replicate samples) / Average (all replicate samples)] x 100%

The precision in general was good (RSD was less than the 35% measurement quality objective target), apart for three exceptions. Sulfanilamide results for matrix reverse osmosis reject were qualified because RSD <70% but >35% (RSD 41.09%). Amphetamine results for the matrix reverse osmosis reject, and Prednisone results for the matrix influent were censored for poor precision (RSD was 83.79% and 141.42%, respectively). Censored data was not included in the analysis.

2. AXYS Method MLA-075