Special Study Proposal: Characterization of Pharmaceutical Contamination in South and Lower South Bay Water

Summary: Pharmaceutical contamination is widely detected in the Bay, and the most recent Bay study indicates key pharmaceutical contaminants may approach levels of concern for wildlife. This study will monitor South Bay and Lower South Bay water (and effluent if there is sufficient project funding) for pharmaceutical contamination, providing data essential to a current evaluation of the potential risks of approximately 150 pharmaceutical contaminants to inform the RMP's Tiered CEC Risk and Management Framework.

Estimated Cost: $65,900 - $159,600
Oversight Group: ECWG
Proposed by: Diana Lin and Rebecca Sutton (SFEI)
Time Sensitive: Yes (leverage monitoring priorities from previous effluent evaluation)

PROPOSED DELIVERABLES AND EXAMPLE TIMELINE

Deliverable	Example Due Date
Task 1. Develop scope of work and sampling design	January 2020
Task 2. Develop sampling plan with collaborators (MPSL-MLML and wastewater treatment facilities)	May 2020
Task 3. Field sampling	August 2020
Task 4. Lab analysis	December 2020
Task 5. QA/QC and data management	February 2021
Task 6. Presentation at ECWG	April 2021
Task 7. Draft report	June 2021
Task 8. Final report	August 2021

Background

Pharmaceuticals are detected frequently in U.S. waterways, creating concern for their potential to impact 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, Simmons et al., 2017). Antibiotic medications, designed specifically to kill organisms, may disrupt bacterial communities and essential ecosystem services provided by these microorganisms (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 can enter the environment through waste streams from human uses in households, hospitals, and nursing homes; manufacturing losses; or animal uses in veterinary clinics and industrial animal farming operations. Pharmaceuticals from human consumer use

can enter the wastewater pathway through ingestion and subsequent excretion of unmetabolized medication, or disposing of unused medication down the drain. Wastewater effluent is expected to be the primary pathway for pharmaceutical contamination to enter the Bay. The Bay Area population is projected to increase and age in the coming decades, which will likely lead to increased use of pharmaceuticals and loadings via wastewater to the Bay. Therefore, periodic and vigilant monitoring of pharmaceuticals in the Bay is warranted.

In 2018, California passed the first legislation requiring a state-wide take-back program for pharmaceuticals and sharps used in households. California Senate Bill SB 212 (Jackson) was motivated by concerns about human health (e.g., antibiotic resistance in infectious bacteria, drug abuse, and accidental poisoning), rising drug expenditures, and environmental contamination (Wagoner, 2018). Given this growing policy focus on pharmaceuticals, it would be appropriate at this time for the RMP to gather new data to evaluate the level of concern that should be associated with the presence of these contaminants in the Bay.

The RMP has assessed pharmaceutical pollution in the Bay in two previous special studies in 2006 (Harrold et al., 2009) and 2009-2010 (Klosterhaus et al., 2013a). In another special study, the RMP evaluated results of pharmaceutical analysis in wastewater effluent from participating Bay wastewater treatment facilities (Lin et al., 2018). This most recent RMP study identified 17 pharmaceuticals in wastewater effluent that merit further monitoring in Bay waters. These pharmaceuticals 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 high blood pressure medications metoprolol and propanolol.

Previous work indicated dilution of effluent may not be sufficient to reduce effluent-derived surface water concentrations below ecotoxicity thresholds, particularly in the Lower South Bay. Further monitoring for pharmaceuticals in the Bay was recommended. Of the 17 pharmaceuticals identified in wastewater in Lin et al. (2018), nine have not been targeted for analysis in Bay matrices or were below detection limits in previous studies; the remaining eight pharmaceuticals have been detected in open waters by previous studies (Klosterhaus et al., 2013, Nödler et al., 2014).

Study Objectives and Applicable RMP Management Questions

This study will provide data essential to determining the level of concern associated with pharmaceutical contamination in the Bay. The most recent evaluation of pharmaceuticals in wastewater effluent identified 17 pharmaceuticals that warrant further monitoring, which include antibiotics, antidepressants, painkillers, an antihistamine and anti-convulsant and antidiabetic, and high blood pressure medication. Should new monitoring show Bay levels of these pharmaceuticals frequently exceed toxicity thresholds, reclassification as moderate concern contaminants in the RMP tiered framework may be appropriate.
Laboratory analysis targeting only the 17 pharmaceuticals is not possible because the pharmaceuticals come from separate lists that require different extraction procedures and different runs on the LC-MS/MS instrument (SGS AXYS analytical method MLA-075,

Table 2). MLA-075 (Lists 1, 3, 4, and 5) was used most recently to screen 104 pharmaceuticals in wastewater effluent (Lin et al., 2018; Table 2), and the method can also be used to analyze surface water and sediment. Therefore, additional pharmaceuticals will be analyzed as part of the same analytical method for the 17 prioritized pharmaceuticals.

Additionally, List 6 from MLA-075 and MLA-104 List SA (SGS AXYS) include an additional 38 drugs of interest (23 [Table 2] and 15 [Table 3], respectively) that have not been targeted by the RMP for analysis in the Bay previously. MLA-075 List 6 includes pharmaceuticals that have been observed to cause impacts to biota in laboratory studies at low exposure levels, such as oxazepam (e.g., Brodin et al., 2013). MLA-104 includes diclofenac, a nonsteroidal anti-inflammatory drug (NSAID) that has been detected in effluent-dominated Los Angeles and San Gabriel Rivers above a risk-based state threshold for monitoring (Tadesse, 2016). The RMP has not analyzed for diclofenac in the Bay, although another group did not detect diclofenac in margin waters in the Bay in 2010 (n = 20, Nödler et al., 2014).

This study will evaluate concentrations of pharmaceuticals in South Bay and Lower South Bay. Wastewater-related contaminants, such as pharmaceuticals, are expected to be highest in Lower South Bay followed by South Bay because of high wastewater inputs and low dilution and flushing. Pharmaceutical levels in Lower South Bay will be evaluated as a worst case scenario for the Bay area, and levels in South Bay will also be evaluated to assess the geographic extent in which pharmaceutical may be of concern. Concentrations of pharmaceuticals in surface water can be compared to published ecotoxicity thresholds to evaluate risks to aquatic life.

This proposal is for the evaluation of pharmaceuticals in Bay water. Additionally, if there is sufficient project budget, a limited set of effluent samples will also be evaluated. Comparison of pharmaceutical concentrations in surface water with varying degrees of wastewater influence can provide preliminary information as to pharmaceutical pathways and fate in the Bay. If data from this project suggest that specific compounds are especially persistent in the environment, special attention, perhaps in the form of additional, targeted monitoring and management actions may be required in the future.

Table 2. Pharmaceutical analytes in MLA-075 Lists 1-6 (SGS AXYS). Superscripts indicate analytes for which only estimates of concentration are available.

List 1 - Acid Extraction in Positive Ionization
Acetaminophen
Azithromycin
Caffeine
Carbadox
Carbamazapine
Cefotaxime
Ciprofloxacin
Clarithromycin
Clinafloxacin
Cloxacillin [1]
Dehydronifedipine
Digoxigenin
Digoxin
Diltiazem
1,7-Dimethylxanthine
Diphenhydramine
Enrofloxacin
Erythromycin-H20
Flumequine
Fluoxetine
Lincomycin
Lomefloxacin
Miconazole
Norfloxacin
Norgestimate
Ofloxacin
Ormetoprim
Oxacillin [1]
Oxolinic acid
Penicillin G [1]
Penicillin V
Roxithromycin
Sarafloxacin
Sulfachloropyridazine
Sulfadiazine
Sulfadimethoxine
Sulfamerazine
Sulfamethazine
Sulfamethizole
Sulfamethoxazole
Sulfanilamide
Sulfathiazole
Thiabendazole
Trimethoprim
Tylosin
Virginiamycin

List 2 - Tetracyclines in Positive Ionization
Anhydrochlortetracycline
Anhydrotetracycline
Chlortetracycline
Demeclocycline
Doxycycline
4-Epianhydrochlortetracycline
4-Epianhydrotetracycline
4-Epichlortetracycline
4-Epioxytetracycline
4-Epitetracycline
Isochlortetracycline [2]
Minocycline
Oxytetracycline
Tetracycline

List 3 - Acid Extraction in Negative Ionization
Bisphenol A
Furosemide
Gemfibrozil
Glipizide
Glyburide
Hydroclorothiazide
2-hydroxy-ibuprofen
Ibuprofen
Naproxen
Triclocarban
Triclosan
Warfarin

Table 2 *continued*.

List 4 - Basic Extraction in Positive Ionization
Albuterol
Amphetamine
Atenolol
Atorvastatin
Cimetidine
Clonidine
Codeine
Cotinine
Enalapril
Hydrocodone
Metformin
Oxycodone
Ranitidine
Triamterene

List 5 - Acid Extraction in Positive Ionization
Alprazolam
Amitriptyline
Amlodipine
Benzoylecgonine
Benztropine
Betamethasone
Cocaine
DEET
Desmethyldiltiazem
Diazepam
Fluocinonide
Fluticasone propionate
Hydrocortisone
10-hydroxy-amitriptyline
Meprobamate
Methylprednisolone
Metoprolol
Norfluoxetine
Norverapamil
Paroxetine
Prednisolone
Prednisone
Promethazine
Propoxyphene
Propranolol
Sertraline
Simvastatin
Theophylline
Trenbolone
Trenbolone acetate
Valsartan
Verapamil

List 6 - Acid Extraction in Positive Ionization
Amsacrine
Azathioprine
Busulfan
Citalopram
Clotrimazole
Colchicine
Cyclophosphamide
Daunorubicin
Diatrizoic acid
Doxorubicin
Drospirenone
Etoposide
Iopamidol
Medroxyprogesterone acetate
Melphalan
Metronidazole
Moxifloxacin [3]
Oxazepam
Rosuvastatin
Tamoxifen
Teniposide
Venlafaxine
Zidovudine

Table 3. Pharmaceutical analytes in MLA-104 SA (SGS AXYS Analytical).

Clopidogrel
Diclofenac
Eprosartan
Fenofibrate
Irbesartan
Lamotrigine
m-Chlorophenylpiperazin
Melengestrol acetate
Mycophenolate mofetil
Norquetiapine
Quetiapine
Ramipril
Tilmicosin
Topiramate
Trazadone

Management questions to be addressed by monitoring pharmaceuticals in Bay water and wastewater effluent are shown in Table 3.

Table 4: Study objectives and information relevant to RMP management questions

Management Question	Study Objective	Example Information Application
1) Which CECs have the potential to adversely impact beneficial uses in San Francisco Bay?	Monitor up to 156 pharmaceuticals in Bay water and wastewater effluent. Compare measured concentrations to toxicity thresholds to determine levels of concern associated with each according to the Tiered CEC Risk Framework.	Do target pharmaceuticals have the potential to cause impacts to Bay aquatic life? Do data indicate a need for management actions?
2) What are the sources, pathways and loadings leading to the presence of individual CECs or groups of CECs in the Bay?	Compare effluent pathway estimated loads to concentrations in the water.	Do pharmaceutical loads from effluent explain loads observed in Bay water?

3) What are the physical, chemical, and biological processes that may affect the transport and fate of individual CECs or groups of CECs in the Bay?	Obtain information on pharmaceutical contamination in ambient Bay water and wastewater effluent.	Are relative distributions of pharmaceutical contaminants in effluents versus Bay water consistent with our expectations for various contaminant processes?
4) Have the concentrations of individual CECs or groups of CECs increased or decreased?	Review new results alongside available data from previous RMP studies for indications of trends in pharmaceutical contamination over time.	Are pharmaceuticals for which we have previous measurements found at increasing or decreasing levels in Bay media?
5) Are the concentrations of individual CECs or groups of CECs predicted to increase or decrease in the future?		
6) What are the effects of management actions?		

Approach

This study will focus on analyzing pharmaceuticals in water samples from South Bay and Lower South Bay. If there is sufficient project funding, a limited set of effluent samples will be collected to evaluate potential loadings in wastewater effluent and compare to effluent measurements from previous years.

South Bay and Lower South Bay Water Sampling

Water samples will be collected in South Bay and Lower South Bay in the dry season by the Marine Pollution Studies Laboratory at Moss Landing Marine Labs (MPSL-MLML). Grab samples of ambient water will be collected from at least eight Bay sites, in addition to one field duplicate and one field blank (minimum of 10 total samples). Depending on the project budget, a second set of samples may be collected during a second sampling event in order to capture potential variations in concentrations on different days. Each sample will consist of up to 4 x 500 mL of water (2 x 500 mL required for analysis; an additional 2 x 500 mL may be collected as backup) collected in pre-cleaned HDPE containers provided by the analytical laboratory (SGS AXYS). MPSL-MLML will collect water samples, freeze them, and ship samples to SGS AXYS overnight.

Sampling sites will be selected randomly to capture an accurate representation of surface water concentrations in South Bay and Lower South Bay; additional sites may be targeted to evaluate wastewater influence. Sampling times will be scheduled when practical, particularly for margin sites that need to be sampled during high tide. Tide schedule is not expected to significantly influence sampled concentrations because of long water residence times in Lower South Bay. Our conceptual model is that pharmaceutical concentrations in the Bay do not fluctuate significantly within a day due to tidal mixing and significant wastewater discharge rates.

Effluent Sampling

Effluent samples provide essential information on the major pathway for pharmaceutical contaminants to enter the Bay. The state guidance on CEC monitoring generally directs agencies to include sampling WWTP effluent when screening for emerging contaminants (Dodder et al., 2015).

Depending on the project budget, effluent samples may be collected from wastewater treatment facilities in the South Bay or Lower South Bay. Twenty four-hour composite samples are preferred to better represent wastewater discharge and loading into the Bay. Sample volumes for effluent samples are the same as surface water samples (4 x 500 mL). Wastewater treatment facilities will be consulted on the best method for sample collection. Samples will be frozen and shipped overnight to SGS AXYS.

Analytical Methods

Samples will be analyzed by SGS AXYS (Sidney, BC, Canada) for pharmaceuticals. SGS AXYS has several analytical options, including SGS AXYS MLA-075 Lists 1, 3-6 and SGS AXYS MLA 104 List SA (Tables 2 and 3) using liquid chromatography tandem mass spectrometry (LC-MS/MS). SGS AXYS was selected to provide analytical services for this study because they have unique qualifications for analyzing pharmaceuticals in environmental media. They analyzed pharmaceutical compounds for the 2018 RMP Special study on pharmaceuticals in wastewater using the same methods.

Previous studies in the Bay have utilized Lists 1, 3, 4, and 5 only.

Budget

The following budget represents estimated costs for this proposed special study of water and effluent (Table 5). Efforts and costs can be scaled up or down by changing the types of analyses (e.g., MLA-104) and the number and type of samples.

Table 5. Proposed Budget.

	Estimated Cost
SFEI Labor	$32,000 - $64,000
Sample Collection (Moss Landing subcontract, 8-25 sites)	$12,300 - $30,600
Analytical Budget (SGS AXYS subcontract, n = 10-30 samples)	$21,600 - $65,000
Grand Total	$65,900 - $159,600

Budget Justification

SFEI Labor
Labor hours are estimated for SFEI staff to manage the project, develop sampling design, analyze data, support sample collection, conduct literature review, and write a report. Also

included in SFEI labor are data management costs; the level of data services provided, including level of QA/QC review and data upload to CEDEN, will depend on the budget.

Sample Collection
Sample collection costs includes a subcontract with MPSL-MLML for the collection of surface water samples.

Laboratory Costs (SGS AXYS)
The analytical cost will be proportional to the number of samples to be analyzed. The analytical costs per sample for pharmaceuticals will depend on the target analyte list. The cost for MLA-075 List 1,3,4,5,6 and MLA-104 List SA are expected to be $2,158 per sample.

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