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Method validation and reconnaissance of pharmaceuticals, personal care products, and alkylphenols in surface waters, sediments, and mussels in an urban estuary

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ABSTRACT

Novel methods utilizing liquid chromatography–tandem mass spectrometry and gas chromatography–mass spectrometry were validated for low-level detection of 104 pharmaceuticals and personal care products ingredients (PPCPs) and four alkylphenols (APs) in environmental samples. The methods were applied to surface water, sediment, and mussel tissue samples collected from San Francisco Bay, CA, USA, an urban estuary that receives direct discharge from over forty municipal and industrial wastewater outfalls. Among the target PPCPs, 35% were detected in at least one sample, with 31, 10, and 17 compounds detected in water, sediment, and mussels, respectively. Maximum concentrations were 92 ng/L in water (valsartan), 33 ng/g dry weight (dw) in sediments (triclocarban), and 14 ng/g wet weight (ww) in mussels (N,N-diethyl-m-toluamide). Nonylphenol was detected in water (<2–73 ng/L), sediments (22–86 ng/g dw), and mussels (<0.04–95 ng/g ww), and nonylphenol mono- and diethoxylates were detected in sediments (<1–40 ng/g dw) and mussels (<5–192 ng/g ww). The concentrations of PPCPs and APs detected in the San Francisco Bay samples were generally at least an order of magnitude below concentrations expected to elicit toxic effects in aquatic organisms. This study represents the first reconnaissance of PPCPs in mussels living in an urban estuary and provides the first field-derived bioaccumulation factors (BAFs) for select compounds in aquatic organisms.

1. Introduction

The continuous introduction of pharmaceuticals and personal care product ingredients (PPCPs) to surface waters worldwide via the discharge of treated and untreated wastewater has lead to a number of efforts to assess their occurrence and potential impacts on nontarget organisms in aquatic environments (Berninger and Brooks, 2010; Bruce et al., 2010; Daughton and Ternes, 1999; Fent et al., 2006; Khetan and Collins, 2007; Kolpin et al., 2002). For pharmaceuticals, the majority of occurrence studies have focused on effluents and surface waters (e.g., Glassmeyer et al., 2005; Hummel et al., 2006; Kim and Carlson, 2007; Kolpin et al., 2002; Loffler et al., 2005; Ternes, 1998; Waiser et al., 2011), including drinking water sources (Benotti et al., 2009; Focazio et al., 2008), with a much smaller number of studies conducted on sediments (Burkhardt et al., 2005; Jelic et al., 2009; Kim and Carlson, 2007; Loffler et al., 2005; Martin et al., 2010; Stein et al., 2008). Studies of occurrence in aquatic life are few in number and have primarily focused on accumulation of select pharmaceuticals in wild-caught fish (reviewed in Ramirez et al., 2009), with a recent study also observing accumulation in caged mussels (Bringolf et al., 2010). Most of these efforts have been conducted in freshwater rivers and streams heavily impacted by wastewater effluent, where concentrations are anticipated to represent worst-case scenario conditions with regard to aquatic life exposure. However, because urban estuarine and marine environments typically receive inputs of complex mixtures of chemical contaminants from a variety of sources, including numerous municipal and industrial wastewater outfalls, characterization of PPCP concentrations in these environments is also important. Data on the occurrence in marine or estuarine systems for pharmaceuticals in particular are currently limited to a small number of surface water studies (Benotti and Brownawell, 2007; Langford and Thomas, 2011; Thomas and Hilton, 2004; Togola and Budzinski, 2008; Weigel et al., 2002; Wille et al., 2010; Yang et al., 2011), two of which also analyzed surface sediments (Langford and Thomas, 2011; Yang et al., 2011). To our knowledge, occurrence of pharmaceuticals in wildlife living in estuarine or marine environments has not yet been reported. Until recently, a lack of analytical methods for reliable, low level quantitation of PPCPs has limited the generation of occurrence data for PPCPs in systems with a high degree of wastewater dilution, particularly in sediments and tissues.

In contrast, it is well established that alkylphenols (APs) are common contaminants of surface waters and aquatic sediments worldwide, and can accumulate in wildlife tissues (David et al., 2009; Soares et al., 2008). APs are nonionic surfactants in widespread use in many industrial applications. Despite their frequent detection in environmental matrices, analytical methods for APs have historically

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been limited by high laboratory blank levels and high detection limits caused by matrix interference in complex matrices including sediments and tissues.

In this study we report the validation of analytical methods to significantly improve selectivity and sensitivity in the measurement of PPCPs in ambient estuarine waters, sediments, and tissues, and APs in tissues. For PPCPs, United States Environmental Protection Agency (USEPA) Method 1694 (US EPA, 2007) was modified to include additional compounds and extended to the analysis of tissue matrices. Multiple labeled internal standards and liquid chromatography–tandem mass spectrometry (LC/MS/MS) analysis with multiple reaction monitoring (MRM) were used to produce recovery corrected concentrations for all compounds. For APs, recovery correction using labeled APs, derivatization by acetylation, and gas chromatography–mass spectrometry (GC/MS) analysis with multiple ion detection (GC/MS MID) were employed for water and sediment analysis, while recovery correction using labeled APs combined with steam extraction and subsequent analysis by LC MS/MS/MRM were employed for tissue matrices. The AP method allows for determination of low-levels in tissue (2–50 ng/g) while eliminating the typically encountered tissue lipid interferences. We have applied these methods to characterize the occurrence of PPCPs and APs in surface water, sediments, and mussels collected from a representative urban estuary, San Francisco Bay, CA, USA. Further, application of these low-level detection methods provided an opportunity to calculate the first field-derived bioaccumulation factors (BAFs) for select compounds in marine invertebrates. To our knowledge, this study provides results from the first reconnaissance of a broad suite of PPCPs in marine mussels and advances our understanding of the bioaccumulation potential of these compounds and APs in the marine environment.

2. Materials and methods

2.1. Sample collection

Co-located surface waters, sediments, and benthic mussels (Ribbed horsemussel, *Geukensia demissa*) were collected from five nearshore sites in San Francisco Bay, CA, USA in December of 2009 and January 2010 (Supporting information (SI) Table 1 and SI Fig. 1). Sample sites were spatially distributed throughout the major urbanized segments of the Bay and targeted areas historically influenced by a variety of potential contaminant sources (e.g. oil refineries, stormwater runoff, municipal and industrial wastewater). Whole water samples (unfiltered) were collected in high-density polyethylene (HDPE) bottles (3×1 L for PPCPs) or amber glass bottles (2×1 L for APs) and stored at 4 °C until analysis. Sediments were collected in HDPE and amber glass jars for PPCP and AP analyses, respectively. Mussels were collected from the sediment surface and placed in either re-sealable plastic bags or amber glass bottles for PPCP and AP analyses, respectively. Sediment and mussel samples were frozen until analysis. Mussel gut contents were not purged prior to freezing. Samples were extracted within one week of collection.

2.2. Target compounds

The 108 compounds analyzed in this study are listed in SI Table 2. All of the compounds were analyzed in surface waters and mussel tissues. A reduced list of 74 target analytes (those not indicated by an asterisk in SI Table 2) is reported for the sediment samples due to interference between the sediment matrix and some of the labeled standards used for quantification (research to resolve the issues for these compounds is ongoing). PPCPs selected for analysis were based on EPA method 1694 (US EPA, 2007) with 45 additional compounds targeted in Lists 3 and 4, and an additional run for List 5. This expanded EPA 1694 analyte list represents those PPCP compounds identified by the USEPA and other AXYS clients (AXYS Analytical Services, Sidney, BC, Canada) as priorities for assessment based on annual consumption, expected toxicity, and persistence. List 2 (14 tetracycline compounds) in the EPA 1694 method was not analyzed in the present study. The method was originally developed and validated to provide occurrence information for a broad spectrum of PPCPs in all relevant aqueous and solid matrices. Modification of EPA 1694 extraction processes and subsequent validation has allowed the application of the method to tissue matrices. The AP target compounds were 4-nonlyphenol (NP), 4-nonylphenol monoethoxylates (NP1EO), 4-nonylphenol diethoxylates (NP2EO), and octylphenol (OP), and were selected based on existing methods developed by AXYS.

2.3. Analytical methods

The analytical methods used in the present study are briefly summarized below. Method details, including quality assurance and quality control and method performance information, are provided in the Supporting information (SI).

2.3.1. PPCPs in water and sediment

The sediment samples (1 g dry weight) were first extracted with either an aqueous phosphate buffer (pH 2.0) for analysis of Lists 1, 3, and 5 compounds or with a pH 10 solution of NH_4OH for List 4 compounds. Each sample was further extracted with acetonitrile and the solvent evaporated to produce an aqueous solution. Sediment extracts and water samples were filtered (1.6 μm), adjusted to pH 2 by addition of HCl (for analysis of List 1, 3, and 5 compounds) or to pH 10 by addition of NH_4OH (for analysis of List 4 compounds). Na_4EDTA was added to each acidic extract prior to extraction on an Oasis HLB solid phase extraction (SPE) cartridge. The extracts were analyzed by LC/MS/MS operated in the ESI positive mode for List 1, 4 and 5 compounds and in the ESI negative mode for List 3 compounds.

2.3.2. PPCPs in tissues

Tissue samples (2.5 g wet weight for the acidic extraction and 1 g wet weight for the basic extraction) were extracted using the same procedure as for the sediment samples except that the extraction was with acetonitrile followed by the pH buffered aqueous solution. The acetonitrile and aqueous extracts from each extraction were combined and processed in the same manner as for the sediments.

2.3.3. APs in water and sediment

Sediment samples (5 g dry weight) were digested in methanolic KOH, extracted with hexane, and acetylated by treatment with acetic anhydride and pyridine. Water samples (1 L, unfiltered) were adjusted to pH 11–12, treated with acetic anhydride, and extracted with hexane at pH 6. Water and sediment extracts were cleaned up by silica column chromatography and analyzed by GC/MS operated in the multiple ion detection (MID) mode.

2.3.4. APs in tissue

Tissue samples (2 g wet weight) were mixed with water and then extracted by steam extraction into isooctane. The isooctane extract cleanup was performed using SPE on aminopropyl cartridges. Tissue extracts were analyzed using LC/MS/MS in the ESI negative mode for NP and OP and in ESI positive mode for NP1EO and NP2EO. For all matrices, NP, NP1EO, and NP2EO are reported as total concentrations, representing the sum of all the detected isomers in a specific target group.

2.4. Bioaccumulation factors (BAFs)

Field-derived BAFs were calculated for the target compounds detected in both mussel tissue and surface waters at a minimum of three sample sites. Biota-sediment accumulation factors (BSAFs) were not calculated because only one compound (triamterene) met this criterion (SI Table 8). Field-derived BAFs were calculated as the

ratio of the chemical concentration in the mussel tissue (wet weight basis) and the chemical concentration in the surface water at each same sample site, with units of L kg^{-1}. Because surface waters were filtered (1.6 μm) prior to chemical extraction, surface water concentrations are considered to include more than the freely dissolved phase chemical.

Field-derived BAFs were compared to bioconcentration factors (BCFs) estimated using the regression equation developed by Veith and Kosian (1983):

$$\log\ BCF = 0.79 * \log\ P - 0.40.$$

This regression was developed for the prediction of neutral organic chemical uptake in fish using empirical data and works well for compounds with log P ranging from 1 to 7. This method has been reported to be a good predictor for the uptake of ionizable compounds from water when the distribution coefficient, *D*, is used in place of P, the *n*-octanol–water partition coefficient (Fu et al., 2009). The distribution coefficient, *D*, is considered an 'apparent P' because it accounts for both the neutral and ionized forms of the compound in water and is therefore pH dependent. In the present study, the surface water pH was not collected at the time of sample collection; however, the mean pH (± one standard deviation) in surface water samples collected between 1993 and 2011 from the same Bay segments where samples were collected in the present study was 7.9 ± 0.2 (http://www.sfei.org/rmp/wqt). Estimates for log *D* at a pH of 8.0 were therefore used to derive predicted BCFs. Log P values were obtained using Virtual Computational Chemistry Laboratory software, 2005 (http://www.vcclab.org). Log *D* values were calculated following the methods developed by Scherrer and Howard (1977).

2.5. Regression analysis

SigmaPlot 10.0 was used to perform the regression analysis on mussel lipid content vs. compound concentration in mussel tissue. An α of 0.05 was used for test significance.

3. Results and discussion

3.1. Occurrence in San Francisco Bay

Table 1 provides a summary of the pharmaceuticals and personal care products (PPCPs) and APs detected in the San Francisco Bay samples. The site-specific concentrations for each of the compounds detected are provided in SI Table 8. Percent total organic carbon in sediments and percent moisture and lipid in mussels are provided in SI Table 1.

3.1.1. Surface waters

Of the 108 target compounds, 32 (30%) were detected in at least one surface water sample and 12 of these were detected at all five sites (valsartan, sulfamethoxazole, carbamazepine, caffeine, gemfibrozil, atenolol, meprobamate, N,N-diethyl-m-toluamide (DEET), erythromycin-H_2O, triamterene, benzoylecgonine, and diltiazem). The compounds detected in the highest concentrations (valsartan, nonylphenol, sulfamethoxazole, carbamazepine, caffeine, and gemfibrozil) were among those most frequently detected. The detected compounds represent a variety of chemical types and therapeutic uses, and most have been frequently observed in other surface water studies (Benotti and Brownawell, 2007; Benotti et al., 2009; Fent et al., 2006; Focazio et al., 2008; Glassmeyer et al., 2005; Kolpin et al., 2002). Two notable exceptions are valsartan and triamterene, drugs commonly used to treat high blood pressure in the United States (www.rxlist.com, accessed January 2011). Valsartan was the compound detected in the highest concentration in any water sample (92 ng/L), and both valsartan and triamterene were detected in all water samples in this study, however, only a few studies have previously investigated their occurrence in the environment (Batt et al., 2008; Kasprzyk-Hordern et al., 2008). Several other compounds that have been suggested as tracers of wastewater contamination due to inefficient metabolism in humans, low removal efficiency during wastewater treatment, and persistence in the environment (Benotti and Brownawell, 2009; Kasprzyk-Hordern et al., 2009) were also detected in the Bay water samples, these include carbamazepine, caffeine, trimethoprim, and sulfamethoxazole.

Concentrations were less than 100 ng/L for all the compounds detected in Bay surface waters. These concentrations are lower than those typically reported for sites in freshwater systems, which are often located near wastewater outfalls (Daughton and Ternes, 1999; David et al., 2009; Focazio et al., 2008; Kasprzyk-Hordern et al., 2008; Kolpin et al., 2002), and are in closer agreement to concentrations reported for other marine and estuarine environments, where wastewater discharges are also common but dilution occurs to a greater extent (Benotti and Brownawell, 2007; Langford and Thomas, 2011; Madureira et al., 2010; Thomas and Hilton, 2004; Togola and Budzinski, 2008; Weigel et al., 2002; Wille et al., 2010; Yang et al., 2011). More than 40 municipal and industrial wastewater outfalls discharge treated effluent to San Francisco Bay surface waters but substantial freshwater inflow in the northern portion of the Bay (SI Fig. 1) and tidal exchange with the Pacific Ocean results in a high degree of dilution. In this study, PPCP concentrations were generally highest in the southern portion of the Bay (SI Table 8), where surface waters receive a large volume of treated wastewater, have the highest hydraulic residence time, and experience the least amount of dilution compared to other Bay segments.

3.1.2. Sediments

Thirteen (18%) of the 74 target analytes were detected in one or more Bay sediment samples. Compounds detected in the highest concentrations were nonylphenol (maximum 86 ng/g dw), nonylphenol monoethoxylates (40 ng/g dw), triclocarban (maximum 33 ng/g dw), and caffeine (maximum 30 ng/g dw). In contrast to the other compounds detected in Bay sediments, triclocarban was not detected in any surface water samples in this study, supporting previous observations that this compound sorbs strongly to sediments (Cordova-Kreylos and Scow, 2007; Miller et al., 2008). Only three compounds were detected at all five sites (triamterene, nonylphenol, and nonylphenol monoethoxylate) and unlike the water data, the most frequently detected compounds in sediments were not the compounds detected in the highest concentrations. Detection in sediments was sporadic and did not show the same trend of higher frequency of detection and higher concentrations for most compounds in the southern portion of the Bay seen in the water samples.

While nonylphenol and nonylphenol ethoxylates are detected frequently in sediments around the world (David et al., 2009), very few studies have investigated the occurrence of the other compounds detected in this study (Martin et al., 2010; Miller et al., 2008; Tang et al., 2009; Vazquez-Roig et al., 2010; Yang et al., 2010, 2011). To our knowledge, the occurrence of DEET, amphetamine, cocaine, and triamterene in sediments has not been reported previously in the peer-reviewed literature.

3.1.3. Mussels

Twenty (18%) of the 108 target compounds were detected in one or more Bay mussel samples. The compounds detected in the highest concentrations were nonylphenol diethoxylate (192 ng/g ww), nonylphenol (95 ng/g ww), nonylphenol monoethoxylate (41 ng/g ww), DEET (14 ng/g ww), digoxigenin (10 ng/g ww), carbamazepine (5 ng/g ww), amphetamine (4 ng/g ww), triclocarban (2 ng/g ww), and sertraline (1 ng/g ww). Only four compounds were detected at all five sites (DEET, carbamazepine, sertraline, and dehydronifedipine). Several compounds that were frequently detected in Bay surface waters were

Table 1
Summary results for the PPCPs and APs detected in the San Francisco Bay water, sediment, and mussel samples. Co-located samples were analyzed from five sites. A list of all 108 target compounds analyzed in this study is provided in the Supporting information (SI Table 2).

	Water (ng/L)				Sediment (ng/g dw)				Mussels (ng/g ww)			
PPCPs	% detect	Min	Max	Med	% detect	Min	Max	Med	% detect	Min	Max	Med
Albuterol	20	<RL	1.0	<RL	0	<RL	–	–	0	<RL	–	–
Amitriptyline	40	<RL	0.6	<RL	0	<RL	–	–	40	<RL	0.2	<RL
Amphetamine	40	<RL	9.7	<RL	40	<RL	3.3	<RL	60	<RL	4.2	1.1
Atenolol	100	3.8	37.0	15.7	0	<RL	–	–	20	<RL	0.3	<RL
Benzoylecgonine	100	2.8	7.2	5.2	0	<RL	–	–	0	<RL	–	–
Caffeine	100	15	40.8	28.5	60	<RL	29.7	18.7	0	<RL	–	–
Carbamazepine	100	5.2	44.2	15.2	NQ	–	–	–	100	1.3	5.3	2.4
Clarithromycin	40	<RL	17.6	<RL	0	<RL	–	–	0	<RL	–	–
Cocaine	80	<RL	2.4	0.6	20	<RL	0.2	<RL	40	<RL	0.3	<RL
Cotinine	80	<RL	24.9	10.3	0	<RL	–	–	0	<RL	–	–
Dehydronifedipine	80	<RL	1.3	0.7	NQ	–	–	–	100	0.2	0.7	0.3
Desmethyldiltiazem	40	<RL	1.7	<RL	0	<RL	–	–	0	<RL	–	–
Diazepam	20	<RL	0.5	<RL	0	<RL	–	–	0	<RL	–	–
DEET	100	4.9	21.0	10.7	40	<RL	3.4	<RL	100	3.7	13.7	3.8
Digoxigenin	0	<RL	–	–	NQ	–	–	–	60	<RL	9.7	6.6
Diltiazem	100	0.4	3.5	0.5	NQ	–	–	–	40	<RL	0.1	<RL
Diphenhydramine	80	<RL	1.9	1.2	NQ	–	–	–	60	<RL	0.3	0.1
Enalapril	0	<RL	–	–	0	<RL	–	–	40	<RL	0.1	<RL
Erythromycin–H_2O	100	1.0	12.1	2.4	20	<RL	3.4	<RL	80	<RL	0.1	0.1
Gemfibrozil	100	12	38.2	27.0	0	<RL	–	–	0	<RL	–	–
Hydrocodone	20	<RL	7.2	<RL	0	<RL	–	–	0	<RL	–	–
10-Hydroxy-amitriptyline	40	<RL	0.3	<RL	0	<RL	–	–	0	<RL	–	–
Ibuprofen	20	<RL	37.9	<RL	0	<RL	–	–	0	<RL	–	–
Meprobamate	100	6.2	36.1	21.5	0	<RL	–	–	0	<RL	–	–
Metoprolol	60	<RL	26.2	1.7	0	<RL	–	–	0	<RL	–	–
Naproxen	20	<RL	8.2	<RL	0	<RL	–	–	0	<RL	–	–
Propoxyphene	40	<RL	0.7	<RL	0	<RL	–	–	0	<RL	–	–
Ranitidine	0	<RL	–	–	0	<RL	–	–	60	<RL	0.3	0.2
Sertraline	0	<RL	–	–	0	<RL	–	–	100	0.1	1.4	0.3
Sulfamethizole	20	<RL	15.6	<RL	0	<RL	–	–	20	<RL	0.2	<RL
Sulfamethoxazole	100	2.4	66.7	6.3	20	<RL	0.7	<RL	0	<RL	–	–
Thiabendazole	20	<RL	2.5	<RL	40	<RL	9.1	<RL	0	<RL	–	–
Triamterene	100	1.1	9.6	2.3	100	0.3	10.8	1.1	60	<RL	0.6	0.1
Triclocarban	0	<RL	–	–	60	<RL	32.7	5.9	40	<RL	1.5	<RL
Trimethoprim	40	<RL	4.1	<RL	20	<RL	18.2	<RL	0	<RL	–	–
Valsartan	100	18	92.1	45.2	NQ	–	–	–	0	<RL	–	–
APs												
4-NP	60	<RL	72.9	34.7	100	21.5	86.3	34.7	40	[a]	94.5	[a]
4-NP1EO	0	<RL	–	–	100	4.1	39.8	13.5	20	[a]	41.3	[a]
4-NP2EO	0	<RL	–	–	80	<RL	18.7	8.6	20	[a]	192	[a]

dw = dry weight; ww = wet weight; Min = minimum concentration, '<RL' = concentrations less than the reporting limit (see SI Table 4 for reporting limits). Max = maximum concentration detected; Med = median concentration, including non-detects; NQ = not quantified (i.e., these compounds were not included in the analysis of sediment samples due to interference between the sediment matrix and some of the labeled standards used for quantification during method development); NP = nonylphenol; NP1EO, NP2EO = nonlyphenol mono- and diethoxylates.

[a] Result censored because it was less than three times the average concentration of the mass detected in the blank samples.

not detected in mussels (atenolol, caffeine, gemfibrozil, sulfamethoxazole, meprobamate, valsartan), suggesting low bioaccumulation potential or a metabolic capability for these compounds in mussels. It is not clear whether the accumulation of dehydronifedipine, a nifedipine metabolite, was the result of direct uptake from surface waters or metabolism of the parent compound (nifedipine was not analyzed in this study).

Compared to aquatic organisms living in effluent-dominated systems, concentrations of nonylphenol and nonylphenol mono- and diexthoxylates in Bay mussels were generally much lower and more comparable to wildlife in other marine environments (David et al., 2009; Soares et al., 2008). Among the PPCPs detected in Bay mussels, only diphenhydramine, diltiazem, carbamazepine, sertraline and triclocarban have been previously detected in aquatic organism tissues (Brooks et al., 2005; Coogan and La Point, 2008; Ramirez et al., 2007, 2009; Shultz et al., 2010). Interestingly, while concentrations of sertraline and triclocarban in Bay mussels were much lower than concentrations in fish and snails living in effluent-dominated rivers in the US, concentrations of diphenhydramine, carbamazepine, and diltiazem in Bay mussels were similar to concentrations in those fish and snails. To our knowledge, the occurrence of DEET, digoxigenin, amphetamine, dehydronifedipine, triamterene, ranitidine, atenolol, cocaine, amitryptiline, sulphamethizole, erythromycin–H_2O, and enalapril in wildlife collected from the field has not been reported previously.

3.2. Factors influencing compound detection in Bay samples

The fact that we could not detect 68 of the target compounds (63%) in any of the San Francisco Bay samples is noteworthy, particularly since many of the compounds are high volume use pharmaceuticals and method reporting limits were generally in the low ng/L or ng/g range (SI Table 4). Other target compounds, including fluoxetine and triclosan, were not detected in the present study but have been detected in other systems receiving wastewater effluent (Bringolf et al., 2010; Brooks et al., 2005; Kolpin et al., 2002; Shultz et al., 2010). Lack of detection for many compounds in the Bay samples is the result of a number of factors, with extensive dilution likely a major contributing factor. As noted previously, Bay surface waters receive wastewater effluent from more than 40 municipal outfalls, but the Bay is a relatively well-flushed system compared to effluent-dominated environments. The use of advanced secondary wastewater treatment with filtration, which has been found to be more efficient at PPCP removal compared to other treatment processes (Lubliner et al., 2010),

is prevalent in the southern portion of the Bay and likely also played a role in the low detection frequency (Dunlavey et al., 2010). Other key processes affecting detection, but not unique to San Francisco Bay, include human or wildlife metabolism of the ingested compound, as well as other natural processes transforming pollutants to compounds not targeted in this study. These transformation processes include microbial degradation and photodegradation during wastewater treatment or following entry into surface waters (Benotti and Brownawell, 2009; Khetan and Collins, 2007). Higher reporting limits than typically found for single or limited target analysis of some target compounds may have also impacted detection frequency (SI Table 4). For example, triclosan was not detected in surface water or sediment samples in the present study (reporting limits 60 ng/L and 62 ng/g dry weight, respectively), likely because typical surface water concentrations in estuaries (<1 to 15 ng/L, Fair et al., 2009; Singh et al., 2010) and concentrations in San Francisco Bay sediments detected in a previous study (<5–40 ng/g, unpublished data) were lower.

Similar to observed pharmaceutical occurrence in drinking water sources (Benotti et al., 2009), pharmaceutical prescription volume was not a good predictor for occurrence in San Francisco Bay samples. Among the 87 parent, human pharmaceutical compounds analyzed in this study, 39 were among the top 200 most prescribed drugs in the US in 2008 (www.rxlist.com, accessed January 2011), but only 18 of these were detected in Bay samples. Valsartan and sulfamethoxazole, the compounds detected in the highest concentrations in water at all sites, were on the top 200 list for 2008 (valsartan in drugs ranked no. 22 and 36, sulfamethoxazole in drugs ranked no. 138 and 141). In contrast, the most prescribed pharmaceutical compound in the US in 2008, atorvastatin, was analyzed in this study but not detected in any sample, likely due to extensive metabolism (Khetan and Collins, 2007). Conversely, carbamazepine, the compound occurring in the third highest concentration in the present study, was not on the top 200 list. This indicates that other factors such as dosage, pharmacokinetics, transformation or removal during wastewater treatment, and environmental fate are critical influences on the occurrence of these compounds in San Francisco Bay.

3.3. BAFs

BAFs are commonly used metrics in risk assessments to predict the bioaccumulation, and resultant potential toxicity, of chemical contaminants in aquatic organisms. In the present study BAFs were calculated using field measurements for the six compounds that accumulated in both mussels and surface water at a minimum of three sample sites (the pharmaceuticals carbamazepine, triamterene, diphenhydramine, dehydronifedipine, and erythromycin-H_2O, and the insecticide, DEET) (Table 2). BAFs for these compounds were <1500, which suggests low bioaccumulation potential and is consistent with their relatively low octanol–water partition coefficients (logK_{ow}<3). Chemicals with BAFs or BCFs ≥1000, 2000, or 5000 are considered bioaccumulative by various regulatory authorities (Arnot and Gobas, 2006). DEET and dehydronifedipine exhibited the highest mean BAFs (779 and 511, respectively), while triamterene and erythromycin–H_2O exhibited the lowest BAFs (65 and 40, respectively). BAFs for each compound varied from more than one up to seven-fold among sites, which may have been influenced by a number of factors. In particular, the extent to which the chemical concentration in the discrete, surface water grab sample collected at each site represented the actual, long-term exposure to the mussels is unknown and may have varied among sites (i.e., the grab sample concentration may be similar, low, or high relative to the long-term average concentration at the site, e.g., depending on when in the tidal cycle a given grab sample was collected). Secondly, tissue and water concentrations were often near reporting limits resulting in some uncertainty in quantitation as shown in replicate RPDs (SI Table 6). Despite these uncertainties, to our knowledge, these are the first field-derived BAFs for these compounds reported for mussels or any other aquatic organism.

The field-derived BAFs were compared to the 'apparent' octanol–water distribution coefficient, *D*, which accounts for both neutral and ionized compound fraction at a given pH and has been identified as a good predictor of the bioaccumulation potential of ionizable compounds (Fu et al., 2009). To our knowledge, the relationship between field-derived BAFs and *D* has not been examined previously. Log BAF generally increased with log *D*, suggesting that lipid partitioning is an important process in the bioaccumulation of these compounds (which include both neutral and ionizable compounds) (Table 2, Fig. 1). This finding supports the conclusion from a recent study that pharmaceutical uptake into invertebrates can be estimated using pH-corrected liposome–water partition coefficients (Meredith-Williams et al., 2012). However, concentrations of the pharmaceutical compounds examined in mussel samples in this study were not correlated with lipid content (SI Fig. 2). In contrast, concentrations of DEET, the only compound examined that is not a pharmaceutical, were positively correlated with mussel lipid content ($R^2 = 0.87$, $p = 0.02$). Similar relationships between fish tissue concentration and lipid content were previously observed by Ramirez et al. (2009) for the uptake of ionizable pharmaceutical compounds and the musk fragrance compounds galaxolide and tonalide. Like DEET, galaxolide and tonalide are not pharmaceutical compounds and are similar to those used to develop traditional lipid partitioning assumptions. The results from this study appear to support the suggestion by others (Bertelsen et al., 1998; Ramirez et al., 2009) that, in addition to lipid partitioning, partitioning to non-water, non-lipid cellular components may influence the uptake of ionizable compounds such as pharmaceuticals in tissue. It has also been suggested that ionizable organic compounds may undergo active transport in tissues (Daughton and Brooks, 2011).

The field-derived BAFs were also compared to model-predicted BCFs to provide insight into possible factors influencing the uptake

Table 2
Physico-chemical properties and field-derived bioaccumulation factors (BAFs; L/kg) for the six compounds detected in both water and mussel samples at a minimum of three San Francisco Bay sample sites.

Compound	Acid/base	pKa[a]	Log P[b]	Log *D*[c]	Field-derived BAF		
					Min	Max	Mean (± SD)
DEET	Neutral	–	2.42	–	206	1448	779 (±558)
Dehydronifedipine	Neutral	–	2.72	–	290	764	511 (±196)
Carbamazepine	Neutral	–	2.45	–	90	322	208 (±102)
Diphenhydramine	Base	8.98	3.27	2.25	118	218	164 (±50)
Triamterene	Base	6.20	0.98	1.21	57	71	65 (±7)
Erythromycin–H_2O[d]	Base	8.88	3.06	2.13	11	54	40 (±20)

Min = minimum; Max = maximum; SD = one standard deviation of the mean.
[a] Predicted for pH 8.0 using ACD/PhysChem Suite SciFinder Scholar 2007.
[b] Log P values were obtained using Virtual Computational Chemistry Laboratory software, 2005 (http://www.vcclab.org).
[c] Log *D* values were calculated following the methods developed by Scherrer and Howard (1977).
[d] Values are for the parent compound, erythromycin; values for erythromycin–H_2O were not available.

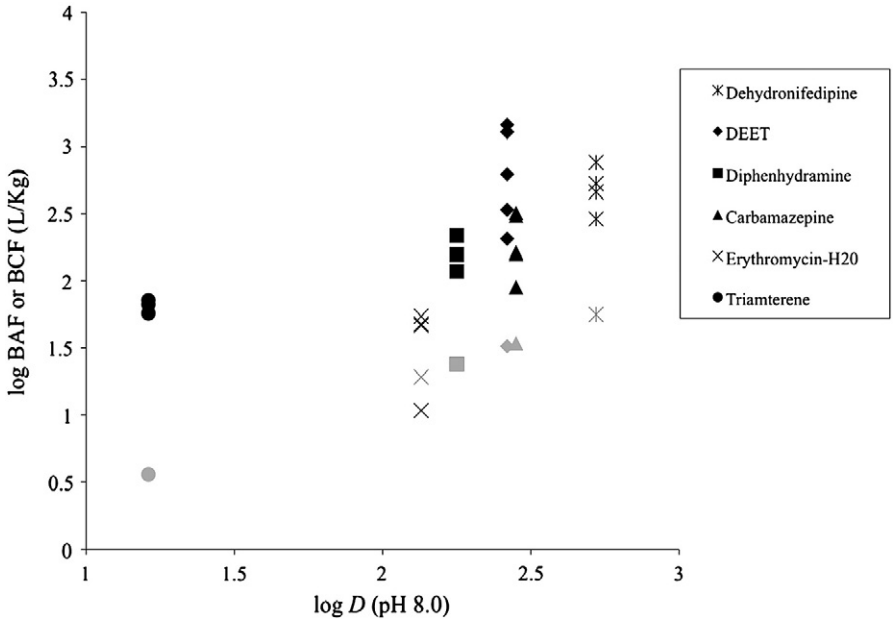

Fig. 1. The relationship between compound field-derived bioaccumulation factor (BAF) or model-predicted bioconcentration factor (BCF) and its distribution coefficient, *D*. Only compounds detected in mussels and surface waters at a minimum of three sites were included. Dark color symbols represent field-derived BAFs and light color symbols represent the model-predicted BCFs.

of these compounds into Bay mussel tissue (Fig. 1). Field-derived BAFs for the mussels were consistently higher than model-predicted BCFs. This observation is in agreement with previous studies with other compounds (Arnot and Gobas, 2006) and may be due to a number of factors. BCF models, which have been developed using fish under controlled conditions in the laboratory, are designed to account for uptake of only the dissolved phase chemical. Model-predicted BCFs are therefore expected to underestimate field-derived BAFs because they do not account for chemical uptake via other routes of chemical exposure to aquatic organisms in the environment (e.g., dietary uptake, trophic transfer, sediment–water disequilibria) (Arnot and Gobas, 2006). As benthic filter feeders, the Bay mussels analyzed in the present study were likely exposed to contaminated particles in the water column, such as algae and suspended sediment, in addition to dissolved phase chemical. Consequently, the BAFs may include chemical contaminants on these particles that have not yet been incorporated in tissue as a portion of cumulative exposure and result in BAF values that are higher than model-predicted BCFs. BAFs for carbamazepine in the Bay mussels were as much as two orders of magnitude higher than the BCF values calculated for fish (<1–4.2) (summarized in Daughton and Brooks, 2011) and invertebrates (<1–8.9) (Meredith-Williams et al., 2012) in other studies. To our knowledge, empirical BCFs for the other compounds examined in the present study were not available for comparison.

Partitioning to a non-lipid compartment in mussel tissue and equilibrium assumptions may have also contributed to the observed differences in field-derived BAFs vs. model-predicted BCFs. As discussed previously, partitioning or binding to a non-lipid compartment (e.g., protein binding or active transport processes rather than passive diffusion) may have been occurring in mussels and would not have been accounted for in the BCF model, which was developed for lipophilic sorption of neutral compounds. It is also possible that the mussels were not at equilibrium with surface waters at the time of sample collection. Samples were collected during the beginning of the rainy season, which may have diluted water concentrations and resulted in surface water concentrations that were systematically lower than those experienced by the mussels in the longer term. These lower surface water concentrations would result in BAFs that were higher than the model-predicted BCFs, which are assumed to represent equilibrium conditions. The extent of the concentration variation for these chemicals in Bay surface waters is unknown, though fluctuations are likely to coincide with fluctuations in wastewater effluent concentrations, which are also largely unknown for the Bay, and variations in flow from tidal mixing, wastewater effluent, and urban runoff from rivers and other small tributaries.

3.4. Implications

The concentrations of PPCPs and APs detected in the San Francisco Bay samples were generally low and at least an order of magnitude below concentrations expected to elicit toxic effects in aquatic organisms (Brausch and Rand, 2010; Fent et al., 2006; Khetan and Collins, 2007; Kolpin et al., 2002). However, the majority of data currently available are based on acute effect studies, and the potential for sublethal effects remains a concern. Chronic toxicity data available for the compounds detected in the present study suggest the potential for impacts on barnacle settlement due to exposure to nonylphenol in Bay surface waters (Billinghurst et al., 1998). Pharmaceuticals are inherently biologically active compounds, thus accumulation in mussels may indicate the potential for effects, and for some compounds, effects may occur even without accumulation. In general, however, few toxicity studies have evaluated effects due to long-term exposures to environmentally relevant concentrations, particularly via sediments. These toxicity studies, along with an improved understanding of the potential for impacts due to exposure to the vast number and types of chemicals typically present in urban aquatic environments (i.e., effects of chemical mixtures), are needed to thoroughly assess the risk of PPCPs and other compounds to estuarine aquatic life. In addition to these research needs, recent publications have highlighted the need for further research to better understand the relationships between exposure and effects based on pharmacological mode of action, and the need for studies employing adverse outcome pathway approaches that leverage mammalian pharmacology information (Boxall et al., 2012; Brausch et al., 2012; Valenti et al., 2012). While available toxicity data suggest a low potential for effects at the nearshore Bay sites investigated in the present study, water and sediment near wastewater or stormwater outfalls in the Bay may contain higher concentrations that may increase the likelihood of impacts.

3.5. Conclusions

The analytical methods validated to support the present study allow for the low-level analysis of 104 PPCPs and select APs in estuarine surface waters, sediments, and tissue samples using relatively small sample volumes (a total of 3 L water, 7 g sediment, and 5.5 g wet tissue). The methods are capable of detecting low parts per trillion concentrations in water samples and low parts per billion concentrations in sediment and tissue samples. Application of these methods indicated that APs and several PPCPs are present in San Francisco Bay surface waters and sediments and accumulate in Bay mussels. The concentrations detected in surface waters were generally low relative to effluent-dominated receiving waters but may be representative of the concentration ranges anticipated to be present in highly urbanized estuaries that receive wastewater effluent and urban runoff but are subject to tidal mixing and dilution by non-urban freshwater sources. The detection of PPCPs and APs in Bay mussels and in the ambient environment highlights the importance of continued monitoring in coastal environments, particularly given the paucity of data on long-term exposure and potential toxicity impacts. Lastly, together with results from other studies, the Bay mussel BAF data suggest that lipid partitioning processes do not sufficiently explain the bioaccumulation observed, and that future models of ionizable organic compound uptake in the environment likely need to consider other mechanisms of uptake.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2013.01.009.

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