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Pharmaceuticals and Personal Care Products in Surface Water - Occurrence, Fate and Transport, and Effect on Aquatic Organisms

Prepared for the State Water Resources Control Board

By

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DEFINITIONS

adsorption – the gathering of a gas, liquid, or dissolved substance on a surface in a condensed layer

aerobic – requires free oxygen

anaerobic – occurs without oxygen

analyte – chemical compound that is the subject of analysis

BOD_5 or biochemical oxygen demand - the rate of oxygen consumption by microorganisms during a 5-day test period at 20 ºC in the dark. The test is used to evaluate organic carbon in treated wastewater

conjugate - a more stable molecular form where electrons are distributed more evenly

fecundity - number of eggs spawned per female

food-microorganism ratio - the ratio of biodegradable matter within wastewater divided by the microorganisms by weight in the treatment system

hydraulic residence time - the average time a soluble compound remains in a water body or bioreactor during wastewater treatment

hydrolysis - a process where a molecule is cleaved into two parts through reaction with a water molecule

hydrophobicity - the tendency of a compound to repel water molecules, relates to water solubility

lipophilicity – ability of a compound to dissolve in lipids and other non-polar solvents

metabolites - products of hydrolysis or enzyme-catalyzed reactions in the body

mixed liquor suspended solids - the concentration of solids suspended in a mixture of wastewater and activated sludge in an aeration basin

pharmacodynamics – chemical reactions, receptor binding, and associated effects induced in the body by a pharmaceutical

pharmacokinetics – chemical transformation of a pharmaceutical resulting from processes while in the body

photolysis - chemical degradation by exposure to light

solids retention time - the average time that activated sludge solids or solids formed during biodegradation remain in a wastewater treatment system.

vitellogenin – egg yolk precursor protein found only in female fish

volatilization - the vaporizing of a liquid

INTRODUCTION

Pharmaceuticals and personal care products (PPCPs) are recognized surface water pollutants, in widespread use worldwide, and can be found at trace levels in surface waters around the globe (Kolpin, Furlong et al. 2002; Bendz, Paxeus et al. 2005; Kim, Cho et al. 2007). The presence of PPCPs in surface waters was documented as early as 1969 (Swann 1969). Possible impacts of these pollutants on fish species were first recognized in the late 1990s and this recognition was followed by an increased attention to this issue by the scientific community (Petrovic 2007). In the past decade, the many aspects of the presence of PPCPs in surface waters have been studied and an expansive literature has emerged. To illustrate the volume of publications on the topic, the US EPA National Exposure Research Laboratory maintains a database of resources that includes over 7,000 entries (USEPA 2009a). These publications address issues including but not limited to, origins, sources, occurrence, monitoring, fate and transport, treatment, analytical methods, regulation, stewardship, management, exposure, and impacts to human health and aquatic and terrestrial ecosystems. Despite recent research, there is little understanding of the impact of PPCPs on aquatic freshwater organisms and ecosystems (Fent, Weston et al. 2006; Kummerer 2009). The lack of understanding stems from:

- the number of chemical compounds involved,
- the number and variety of potentially affected species,
- a lack of understanding of the modes of action of PPCPs in target and non-target organisms (Fent et al. 2006),
- limited information of the combined effects of these compounds in the environment,
- analytical challenges presented by environmental concentrations in the range of micrograms to nanograms per liter (µg/L and ng/L, respectively),
- a paucity of information on the fate and transport of these chemicals.

Many of the challenges associated with detecting trace levels of PPCP compounds have been overcome by employing analytical methods such as high performance liquid chromatography/tandem mass spectroscopy (Halling-Sorensen, Nielsen et al. 1998). Advancements in analytical techniques have resulted in the detection of over 50 PPCPs in surface waters and wastewater treatment plant (WWTP) effluent in recent years (Carballa, Omil et al. 2004).

The following report is organized into six sections that discuss background information, sources, occurrence, fate and transport, removal during wastewater treatment, and effect on aquatic organisms and ecosystems. The current state of knowledge about PPCPs in the Bay-Delta system is also addressed as are research needs for the Bay-Delta ecosystem.

BACKGROUND

The organic pollutants classified as PPCPs include thousands of chemical compounds. The United States Environmental Protection Agency (USEPA) defines PPCPs as products that include prescription and over-the-counter therapeutic drugs, veterinary drugs, fragrances, cosmetics, sunscreen products, diagnostic agents (e.g., contrast agents used in magnetic resonance imaging and indicators in pregnancy tests), and nutraceuticals (e.g., vitamins and dietary supplements) (USEPA 2009b). Biologically active metabolites and environmental degradation products of specific PPCPs are also included in the category. Naturally synthesized and excreted hormones and steroids are often grouped with PPCPs because of environmental concentrations comparable to their synthetic analogs and similar chemical behavior and effects on aquatic organisms (Routledge, Sheahan et al. 1998). Other organic contaminants are frequently studied along with PPCPs and originate from products such as flame retardants, surfactants, plasticizers, and pesticides although these compounds are not classified as PPCPs. The following is the scope of compounds included volume 50 of Wilson and Wilson's Comprehensive Analytical Chemistry Series (Petrovic 2007), which is devoted to the topic of PPCPs in the water cycle. The definition of PPCPs provided below is used in this report.

> *"the universe of chemicals encompassed in the scope of PPCPs will be defined to include all chemicals used for humans, domestic animals, or agricultural crops that: (i) treat disease, (ii) alter or improve physiological, cosmetic, or emotional function, appearance, or status, (iii) prevent disease (prophylaxis) or maintain health, (iv) help in the diagnosis or monitoring of health or disease, or (v) serve to formulate the active ingredient into a commercial product (e.g., excipients and delivery vehicles). The scope includes all preparations intended for topical, pulmonary, or parenteral (injection) administration or ingestion, as well as suppositories and enemas. The obvious galaxies of chemicals in this universe are the diverse arrays of human and veterinary prescription and OTC medications. But others include diagnostic agents (e.g., X-ray contrast media, radiopharmaceuticals), vaccines, and 'nutraceuticals' (bioactive dietary supplements such as huperzine A and "functional foods) and food supplements (including vitamins)… Illicit drugs, in particular, comprise an unknown but possibly significant fraction of total drug usage, and consequently contribute to individual environmental residues and to the overall environmental loading of PPCPs".*

SOURCES

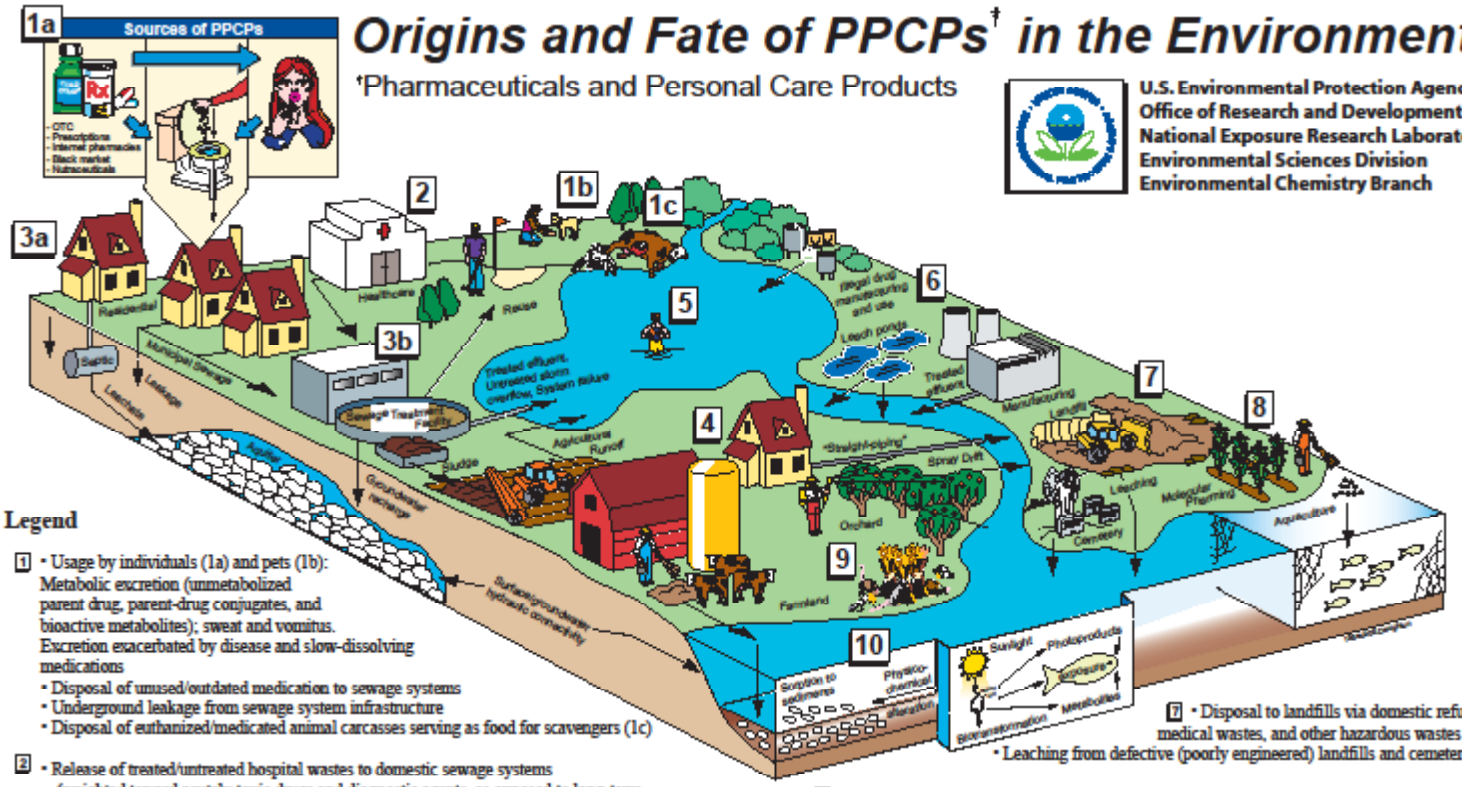
Sources of PPCPs in surface waters include wastewater treatment plant (WWTP) effluent, treated industrial effluent and leach ponds, leaks in municipal sewage conveyance infrastructure, septic systems, untreated sewage, landscape irrigation with treated wastewater, runoff from land where manure or sludge has been applied, runoff from farmland or other areas with medicated animals, aquaculture, spray drift from direct land application (e.g., antibiotics applied to crops), swimming in surface water bodies, leaching from poorly designed landfills or cemeteries, and dumping associated with illegal drug manufacturing (Petrovic 2007). Some PPCPs have multiple purposes such as warfarin, which is prescribed as an anticoagulant in humans and used as rat poison (Figure 1).

Wastewater treatment plant effluent is the most significant source for human PPCPs and animal husbandry operations, including Concentrated Animal Feeding Operations (CAFOs) and factory farming, are the most important in terms of veterinary PPCP (Daughton and Ternes 1999; Brain, Hanson et al. 2008). After ingestion by humans or animals, parent compounds and metabolites are excreted through urine and feces and released into wastewater streams and septic systems or onto land associated with animal husbandry operations (Daughton and Ternes 1999). Runoff from animal husbandry operations carries PPCPs into receiving water bodies. In addition to excretion, PPCPs are disposed of into home plumbing systems. The relative contributions of excretion and disposal are unknown though it is expected that disposal is minor (Heberer 2002). Use within the general population rather than use within hospitals represents the primary origin of PPCPs in municipal wastewater (Kümmerer 2008, Schuster et al. 2008). In the United States, general population use accounts for 75% of the municipal wastewater PPCP load and in the United Kingdom, the figure is reported at 70% (Kummerer 2009). Similar to swimming in open waters, bathing washes any topical PPCPs or compounds excreted in perspiration into wastewater streams. Existing wastewater treatment systems were not designed to remove the compounds found in PPCPs and a cost-effective treatment option is not currently available (Ternes 1999; Bolonga 2008). However, wastewater treatment processes reduce the concentrations of some PPCPs to varying degrees.

Origins and Fate of PPCPs† in the Environment

†Pharmaceuticals and Personal Care Products

U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory
Environmental Sciences Division
Environmental Chemistry Branch



Legend

1 • Usage by individuals (1a) and pets (1b): Metabolic excretion (unmetabolized parent drug, parent-drug conjugates, and bioactive metabolites); sweat and vomitus. Excretion exacerbated by disease and slow-dissolving medications
- Disposal of unused/outdated medication to sewage systems
- Underground leakage from sewage system infrastructure
- Disposal of euthanized/medicated animal carcasses serving as food for scavengers (1c)

2 • Release of treated/untreated hospital wastes to domestic sewage systems (weighted toward acutely toxic drugs and diagnostic agents, as opposed to long-term medications); also disposal by pharmacies, physicians, humanitarian drug surplus

3 • Release to private septic/leach fields (3a)
- Treated effluent from domestic sewage treatment plants discharged to surface waters, re-injected into aquifers (recharge), recycled/reused (irrigation or domestic uses) (3b)
- Overflow of untreated sewage from storm events and system failures directly to surface waters (3b)

4 • Transfer of sewage solids ("biosolids") to land (e.g., soil amendment/fertilization)
- "Straight-piping" from homes (untreated sewage discharged directly to surface waters)
- Release from agriculture: spray drift from tree crops (e.g., antibiotics)
- Dung from medicated domestic animals (e.g., feed) - CAFOs (confined animal feeding operations)

5 • Direct release to open waters via washing/bathing/swimming

6 • Discharge of regulated/controlled industrial manufacturing waste streams
- Disposal/release from clandestine drug labs and illicit drug usage

7 • Disposal to landfills via domestic refuse, medical wastes, and other hazardous wastes
- Leaching from defective (poorly engineered) landfills and cemeteries

8 • Release to open waters from aquaculture (medicated feed and resulting excreta)
- Future potential for release from molecular pharming (production of therapeutics in crops)

9 • Release of drugs that serve double duty as pest control agents: examples: 4-aminopyridine, experimental multiple sclerosis drug → used as avicide; warfarin, anticoagulant → rat poison; azacholesterol, antilipidemics → avian/rodent reproductive inhibitors; certain antibiotics → used for orchard pathogens; acetaminophen, analgesic → brown tree snake control; caffeine, stimulant → *coqui* frog control

10 Ultimate environmental transport/fate:
- most PPCPs eventually transported from terrestrial domain to aqueous domain
- phototransformation (both direct and indirect reactions via UV light)
- physicochemical alteration, degradation, and ultimate mineralization
- volatilization (mainly certain anesthetics, fragrances)
- some uptake by plants
- respirable particulates containing sorbed drugs (e.g., medicated-feed dusts)

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March 2006
(original February 2001)

http://epa.gov/nerlesd1/chemistry/pharma/images/drawing.pdf
from: http://epa.gov/nerlesd1/chemistry/pharma/

OCCURRENCE

Many studies have evaluated the occurrence of specific PPCPs in surface waters, particularly in the United States, Europe, and Asia (Kolpin, Furlong et al. 2002; Bendz, Paxeus et al. 2005; Kim, Cho et al. 2007). **Table 1** lists the compounds that were detected most often in three specific studies. Because drinking water, water quality, aquatic-life criteria, and/or health advisory standards have not been established for most of the analytes, concentration information is difficult to interpret (Kolpin, Furlong et al. 2002). As shown in Table 1, concentrations of detected PPCPs ranged from ng/L or parts per trillion (ppt) to µg/L or parts per billion (ppb). Basic information on each study such as spatial and temporal scales is also provided.

Commonly detected PPCP types include antidepressants, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), tranquilizers, lipid regulators, anti-epileptics, β-blockers, contraceptives, and X-ray contrast agents (Petrovic 2007). Forms of PPCP compounds found in surface waters include the ingested or injected form, metabolites, conjugates of both the ingested form and metabolites, and environmental degradation products (Daughton and Ternes 1999). Most investigations into the occurrence of PPCPs in surface waters have focused on the presence of PPCPs in the ingested form and bioactive metabolites (Petrovic 2007). Though consumption of PPCPs varies geographically in the areas where monitoring studies have been conducted, the concentrations found in various surface waters are comparable. Volumes of PPCPs found in surface waters are comparable to pesticide loads (Brain, Hanson et al. 2008).

The United States Geological Survey (USGS) conducted a series of national reconnaissance projects to measure concentrations of organic wastewater contaminants (OWCs), including PPCPs, in some of the surface water and groundwater bodies considered most susceptible to these contaminants (Kolpin, Furlong et al. 2002; Barnes, Kolpin et al. 2008; Focazio, Kolpin et al. 2008). The first, summarized in Table 1, was conducted in 1999 and 2000 and included analysis of 95 OWCs in 139 streams across 30 states. Two subsequent studies were published in April 2008. The first included testing of 25 groundwater and 49 surface water sources of drinking water for 100 different OWCs. The second study reported on the analysis for 65 different OWCs in groundwater resources that were not necessarily used as sources of drinking water. The results of the USGS analyses indicate that antibiotics, cholesterol, caffeine, caffeine metabolite 1,7-dimethylxanthine, steroid hormones, cotinine, and triclosan were frequently detected in surface water samples taken during the 2002 and 2008 studies.

Other monitoring studies summarized in Table 1 include a study of locations upstream and downstream of three WWTPs along the Tennessee River and a similar study of the Höle River in Sweden (Bendz, Paxeus et al. 2005; Conley, Symes et al. 2008). Concentrations and detection frequencies are generally consistent among the three studies. In some instances, detection frequencies were greater in the Tennessee River

study. For example, a commonly detected antibiotic, sulfamethoxazole was found in 19 percent of the USGS samples at a maximum concentration of 0.52 µg/L while it was found in the Tennessee River 85.9 percent at a maximum of 0.33 µg/L. (Kolpin, Furlong et al. 2002; Conley, Symes et al. 2008)The results of these studies are representative of other monitoring studies found in the literature.

Table 1
PPCPs Frequently Detected in Surface Waters
Kolpin et. al., 2002

Spatial range included 139 streams within 30 states in the U.S.

Each stream sampled once in 1999-2000; vertical profile composite samples at 4-6 depths

Samples tested for 95 organic wastewater contaminants (OWCs), including PPCPs; 82 of 95 compounds detected in one or more sample; median of 7 and maximum of 38 compounds per sample

One or more compounds found in 80 percent of sampled sites

Compounds listed below were detected in >9 % of samples; if one method resulted in detection in >9 % of samples, figures for all methods are provided

	Concentration (µg/L)			**Concentration (µg/L)**	
Antibiotics - % of samples)	**Maximum**	**Median**	**Nonprescription Drugs Continued**	**Maximum**	**Median**
erythromycin-H2O (metabolite) – 21.5%	1.7	0.1	cotinine (nicotine metabolite)[4] – 31.5%	0.57	0.05
lincomycin – 19.2%	0.73	0.06	1,7-dimethylxanthine (caffeine metabolite) – 28.6%	3.1[3]	0.11[3]
sulfamethoxazole[1] – 12.5%	1.9	0.15	ibuprofen (NSAID) – 9.5%	1.0	0.20
sulfamethoxazole[2] – 19.0%	0.52	0.066	**Other PPCPs**		
trimethoprim[1] – 12.5%	0.71	0.15	acetophenone (fragrance) – 9.4%	0.41	0.15
trimethoprim[2] – 27.4%	0.30	0.013	triclosan (antimicrobial disinfectant) – 57.6%	2.3	0.14
tylosin – 13.5%	0.28	0.04	cis-androsterone (urinary steroid) – 14.3%	0.214	0.017
Prescription Drugs			cholesterol (plant/animal steroid)[4] – 55.3%	10[3]	1[3]
cimetidine (antacid) – 9.5%	0.58[3]	0.074[3]	cholesterol (plant/animal steroid)[5] – 84.3%	60[6]	0.83
codeine (analgesic)[2] – 6.5%	0.019	0.012	coprostanol (fecal steroid)[4] – 35.3%	9.8	0.70

Table 1
PPCPs Frequently Detected in Surface Waters

codeine (analgesic)[4] – 10.6%	1.0[3]	0.2[3]	coprostanol (fecal steroid)[5] – 85.7%	150[6]	0.088
dehydronifedipine (antianginal) – 14.3%	0.03	0.012	17α-ethinylestradiol (ovulation inhibitor) – 15.7%	0.831	0.073
diltiazem (antihypertensive) – 13.1%	0.049	0.021	17β-estradiol (reproductive hormone)[4] – 10.6%	0.2	0.16
Nonprescription Drugs			17β-estradiol (reproductive hormone)[5] – 10.0%	0.093	0.009
acetaminophen (antipyretic) – 23.8%	10	0.11	estriol – (reproductive hormone) – 21.4%	0.051	0.019
caffeine (stimulant)[2] – 61.9%	6.0	0.081	mestranol (ovulation inhibitor) – 10.0%	0.407	0.074
caffeine (stimulant)[4] – 70.6%	5.7	0.1	19-norethisterone (ovulation inhibitor) – 12.8%	0.872	0.048
cotinine (nicotine metabolite)[2] – 38.1%	0.90	0.024			

[1] Analysis by single quadrupole LC/MS-ESI (+) using SIM
[2] Analysis by HPLC
[3] Concentration estimated due to <60% recovery
[4] Analysis by capillary-column GC/MS
[5] Analysis by GC/MS
[6] Concentration estimated, value greater than highest point on calibration curve

Conley et. al., 2008

Spatial range included 15 sites along the Tennessee River in the vicinity of 3 WWTPs

Each site sampled twice (1 composite, 1 surface) during 4 seasons in 2006 and 2007 for a total of 120 samples

Samples tested for 14 pharmaceuticals

Compound	Detection Frequency	Concentration Range (ng/L)	Median Concentration (ng/L)
caffeine (stimulant)	92.2%	18.1 – 175.7	28.8 ± 14.0
sulfamethoxazole (antibiotic)	85.9%	3.0 – 33.0	7.9 ± 4.6
carbamazepine (antiepileptic)	79.7%	2.9 – 23.1	5.0 ± 2.3

Table 1
PPCPs Frequently Detected in Surface Waters

trimethoprim (antibiotic)	32.0%	2.3 – 63.3	5.6 ± 5.4
acetaminophen (NSAID)	13.3%	2.1 – 12.3	2.9 ± 1.7
diltiazem (antihypertensive)	10.2%	1.3 – 9.7	1.9 ± 1.6
ciprofloxacin (antibiotic)	10.2%	4.7 – 54.2	6.9 ± 10.6
levofloxacin (antibiotic)	6.3%	6.2 – 59.3	11.9 ± 5.3
atorvastatin (lipid regulator)	4.7%	3.0 – 101.3	6.8 ± 17.0
sertraline (SSRI)	3.1%	2.4 – 12.4	3.5 ± 3.6
lovastatin (lipid regulator)	2.3%	10.6 – 102.9	18.3 ± 46.1
fluoxetine (SSRI)	1.6%	3.9 – 10.1	7.0 ± 3.1
norfluoxetine (fluoxetine metabolite)	0.6%	2.88	one detection

Bendz et al., 2005

Spatial range included influent and effluent of the Källby Sewage Treatment Plant (STP), effluent of 3 dams downstream of the STP, one site upstream of the STP, and 3 sites downstream of the sampled dam farthest downstream of the STP.

All samples were collected on October 21, 2002.

Samples tested for 31 PPCPs including lipid regulators, NSAIDs, ibuprofen metabolites, anti-epileptic β-blockers, antibiotics, a synthetic musk, a biocide (triclosan), and caffeine. For comparison purposes, a flame retardant, antifoam additive, antioxidant, and surfactants were included as analytes.

Compounds listed below include all detected PPCPs

Compound	**Concentration at STP Effluent (µg/L)**	**Concentration Farthest Downstream (µg/L)**
gemfibrozil (lipid regulator)	0.18	0.001
ibuprofen (NSAID)	0.15	0.11

Table 1
PPCPs Frequently Detected in Surface Waters

ketoprofen (NSAID)	0.33	0.01
naproxen (NSAID)	0.25	0.11
diclofenac (NSAID)	0.12	not found
carbamazepine (anti-epileptic β-blocker)	1.18	0.1
atenolol (anti-epileptic β-blocker)	0.16	0.06
propranolol (anti-epileptic β-blocker)	0.03	0.01
trimethoprim (antibiotic)	0.04	0.01
sulfamethoxazole (antibiotic)	0.05	0.01
hydroxi-ibuprofen (ibuprofen metabolite)	0.05	0.05
carboxy- ibuprofen (ibuprofen metabolite)	0.43	0.29
triclosan (biocide, active ingredient in antibacterial PCPs)	0.16	not found
galaxolide (polycyclic musk)	1.08	0.13
Caffeine	0.22	0.01

TREATMENT

Existing wastewater treatment plants were not designed to remove PPCPs and a single effective treatment technology does not currently exist (Ternes 1999; Bolonga 2008). Conventional wastewater treatment processes reduce the concentrations of some PPCPs to varying degrees. Many studies have evaluated partial removal in conventional systems and the efficacy of advanced treatment techniques.

Three processes that result in partial removal include biodegradation (aerobic and anaerobic), adsorption onto suspended solids, and chemical degradation (e.g., hydrolysis or photolysis) are the primary removal mechanisms of PPCPs from wastewater. Characteristics of specific compounds that determine the effective mode of removal from wastewater include biodegradability, solubility in water (sorption potential and hydrophobicity), and susceptibility to chemical degradation and volatilization. Parameters that regulate biological removal include biochemical oxygen demand (BOD_5), suspended solids (SS) load, hydraulic residence time (HRT), solids retention time (SRT), food-microorganism ratio (F/M ratio), mixed liquor-suspended solids (MLSS), pH, and temperature. These parameters are controlled by WWTP operators to meet treatment standards. The tendency to adsorb to sludge can be predicted using three measures. The octanol-water partition coefficient, K_{ow}, is a measure of the hydrophobicity of organic compounds. Some controversy over the reliability of established K_{ow} values has been described in the literature. Fewer empirically determined K_{ow} values due to frequent reuse of values contained in other publications together with a range of original values that differ by up to four orders of magnitude have generated questions about the studies (Eganhouse 2002). While the general mechanisms are known, there is a paucity of detailed information on removal processes pertinent to PPCPs in wastewater and, therefore, empirically determining K_{ow} values for commonly detected compounds is particularly worthwhile. Another measure of sorption tendency is the solid-water distribution coefficient, K_d, which indicates the relative adsorbed and aqueous quantities of a compound in equilibrium. Most PPCPs have low K_d values, indicating low adsorption affinity (Petrovic 2007). Finally, the organic partition coefficient, K_{oc}, measures the tendency for organic compounds to by adsorbed by soil or sediment and is generally independent of soil properties.

In the United States, up to three levels of wastewater treatment are used to prepare raw sewage for release into a receiving water body. Primary treatment facilitates sedimentation of sludge to the base of a large tank and allows floating materials such as grease to collect on the surface. After settled sludge and floating material have been removed, secondary treatment uses aerobic biodegradation by bacteria and protozoa to break down organic matter within sewage. Federal regulations require all publicly treatment works (POTWs) to meet secondary treatment standards. If a WWTP is equipped for tertiary treatment, one or more processes to remove nutrients and residual suspended matter are engaged prior to rerelease into the environment.

Disinfection is the final step prior to effluent discharge. Approximately 56 percent of WWTPs in the United States treat wastewater to secondary levels prior to release into receiving water bodies (USEPA 2000). Just over 30 percent of WWTPs utilize tertiary treatment (USEPA 2000). The population that is served by each type of facility is nearly equal (USEPA 2004).

Each stage of conventional wastewater treatment generally corresponds to partial removal of specific PPCPs based on chemical characteristics. Removal efficacy at each stage varies within compound classes. Certain PPCPs are generally resistant to removal. In particular, carbamazepine is very resistant to wastewater treatment processes (Ternes 1998; Clara, Kreuzinger et al. 2005; Zhou, Zhang et al. 2009). Additionally, iopromide and hydrochlorothiazide have passed through primary and secondary treatment without adsorption to sludge (Petrovic 2007; Radjenovic, Petrovic et al. 2009). Primary treatment removes compounds that have a tendency to adsorb to sludge. Partial removal during primary treatment has been observed for NSAIDs, including ibuprofen, diclofenac, ketoprofen, the fluoroquinolone antibiotic ofloxacin, the macrolide antibiotic azithromycin, the antihistamine loratidine, the β-blocker propanolol, the musks galaxolide and tonalide, and the reproductive hormone 17β-estradiol (Carballa, Omil et al. 2004; Radjenovic, Petrovic et al. 2009). Diclofenac and some fluoroquinolone antibiotics tend to partition in primary sludge more so than other drugs in their classes (Petrovic 2007). Biological degradation during secondary treatment is responsible for the majority of removal during wastewater treatment (Onesios, Yu et al. 2009). Published secondary treatment removal efficiencies for PPCPs vary, which can be attributed to experiment design and how removal is defined in each study (Onesios, Yu et al. 2009). Removal generally increases with SRT, which is influenced by temperature and the maximum growth rate of microbial species (Clara, Kreuzinger et al. 2005; Petrovic 2007). HRT is also important in determining the degree of removal (Petrovic 2007). The SRT for complete removal has been experimentally determined for some PPCPs and varies with compound. For example, complete removal of ibuprofen, bezafibrate, 17β-estradiol, estrone, estriole, and 17α-ethinylestradiol has been demonstrated with an SRT of 10 days (Clara, Kreuzinger et al. 2005). Some PPCPs such as the antimicrobial agents triclosan and triclocarban have been shown to increase resistance in the bacteria used in secondary treatment (Chalew and Halden 2009). Fewer studies have evaluated tertiary treatment technologies. Coagulation and flocculation is a common form of tertiary treatment and provides very limited removal of PPCPs (Ternes, Meisenheimer et al. 2002; Petrovic, Diaz et al. 2003; Westerhoff, Yoon et al. 2005). Adsorption to powdered or granular activated carbon is effective at removing clofibric acid, ibuprofen, gemfibrozil, fenoprofen, naproxen, ketoprofen, diclofenac, indomethacin, propyphenazone, and otherwise recalcitrant carbamazepine (Simazaki, Fujiwara et al. 2008; Yu, Peldszus et al. 2008). However, competitive adsorption to activated carbon reduces removal, particularly for clofibric acid and ibuprofen (Yu, Peldszus et al. 2008). Disinfection by chlorination has been found to partially remove steroid hormones and NSAIDs at chlorine concentrations below those

used in wastewater treatment (Petrovic 2007). Evidence of unknown chlorination byproducts after disinfection has been found and have the potential to be contaminants in themselves (Simazaki, Fujiwara et al. 2008). All stages of conventional wastewater treatment reduce PPCP concentrations to some degree. While reported removal efficacies vary, biodegradation via secondary treatment is the primary removal mechanism during conventional wastewater treatment. Activated carbon is an effective tertiary treatment technology at removing some PPCPs, including those that are generally resistant to removal.

Several advanced treatment technologies have been evaluated and show varied efficacies of removal of PPCPs from wastewater. Membrane bioreactors (MBRs), reverse osmosis, ultrafiltration, nanofiltration, and advanced oxidation processes (AOPs) are the most common technologies tested. Ozone, hydrogen peroxide and ultraviolet light are used in advanced oxidation. In a study comparing activated sludge treatment to MBRs, residues of mefenamic acid, indomethacin, diclofenac, propyphenazone, pravastatin, and gemfibrozil that remained after activated sludge treatment were removed by MBRs (Radjenovic, Petrovic et al. 2009). However, removal of β-blockers, ranitidine, famotidine, and erythromycin in MBRs was hindered when compared to activated sludge treatment (Radjenovic, Petrovic et al. 2009). Reverse osmosis is very effective and removed more than 95 percent of 17β-estradiol and 17α-ethinylestradiol in one study (Huang and Sedlak 2001) and complete removal of sulphonamides, diaminopyrimidine and fluoroquinolone antibiotics in another (Dolar, Kosutic et al. 2009). Ultrafiltration involves membrane pores that allow PPCPs to pass through, but can remove highly hydrophobic pharmaceuticals by adsorption (Yoon, Westerhoff et al. 2007). Nanofiltration removes PPCPs to varying degrees by filtration and adsorption (Yoon, Westerhoff et al. 2006). Ozone successfully removes PPCPs that have an ozone rate constant within a specific range (Snyder, Westerhoff et al. 2003). Ozone effectiveness dramatically increases when coupled with hydrogen peroxide or ultraviolet light (Kosaka, Yamada et al. 2000; Snyder, Westerhoff et al. 2003). Ultraviolet light alone, which is also used in disinfection as an alternative to chlorine, initiates PPCP degradation via photolysis. However, this method is relatively cost prohibitive because it requires doses several orders of magnitude greater than those used in disinfection (Snyder, Westerhoff et al. 2003). Reverse osmosis and AOPs along with activated carbon, which was discussed above in the context of tertiary treatment, are the most effective advanced treatment technologies.

As PPCPs include a variety of compound types, different treatment methods are effective against specific types or groups of compounds. As new PPCPs are developed and enter the market, new challenges for wastewater treatment could emerge even with the development of a treatment solution for compounds currently found in wastewater effluent and surface waters. No legal requirements are in place in any country that require removal of PPCPs from wastewater effluent (Petrovic 2007). Despite increasing attention and research efforts on the issue of PPCPs in surface waters

and the potential repercussions for ecosystem and human health, the cost associated with developing an effective treatment technology followed by the necessary retrofit of existing wastewater treatment infrastructure is prohibitive and very likely to impede the development and implementation of effective treatment technologies absent government mandates.

FATE AND TRANSPORT

Forms of PPCPs found in surface waters include the ingested or injected form, metabolites, conjugates of both the ingested form and metabolites, and environmental degradation products (Daughton and Ternes 1999). Metabolites are products of hydrolysis or enzyme-catalyzed reactions in the body. Conjugates are more stable versions of the ingested form because electrons are distributed more evenly, which is often accomplished by bonding to a small organic fragment. If a PPCP compound in the consumed form is present in the environment, it is either resistant to chemical or biochemical transformation or it has returned to original form via degradation of conjugates during wastewater treatment (Petrovic 2007). While PPCPs do degrade in the environment, they are continually replaced by wastewater effluent (Daughton and Ternes 1999). This behavior has been termed "pseudo-persistence" and explains the prevalence of PPCPs in the aquatic environment (Daughton 2002).

Both direct and indirect photolysis transform PPCPs in surface waters. Photolysis is a chemical reaction induced by light exposure. Direct photolysis applies when a compound absorbs light and a chemical transformation results. Indirect photolysis occurs when light initiates a reaction in other molecules, most often dissolved organic matter (DOM) or nitrate in surface waters, that go on to react with a PPCP. Depending on the photostability of a compound, which is determined by structure, PPCPs undergo direct and/or indirect photolysis at different rates. Photolysis produces a number of reaction products via several competing and simultaneous pathways (Poiger, Buser et al. 2001; Andreozzi, Raffaele et al. 2003; DellaGreca, Fiorentino et al. 2003). Several environmental photochemistry studies have been conducted to observe direct photolysis in PPCPs and approximately 40 compounds have been evaluated (Petrovic 2007). Examples of compounds subject to photodegradation where indirect photolysis is dominant over direct photolysis include ibuprofen, ketoprofen, and cimetidine (Petrovic 2007). Compounds found to degrade primarily by direct photolysis include triclosan, diclofenac, iopromide, and sulfonamide antibiotics (Tixier, Singer et al. 2003; Latch, Packer et al. 2005; Pérez 2006; Petrovic 2007). It is important to note that PPCPs with the same therapeutic effect may absorb light differently and, therefore, may have different photoreactivity characteristics (Petrovic 2007). Photolysis rates vary greatly and direct photolysis half-lives range from one day to hundreds of days. An analysis of eight PPCPs including acetaminophen, atorvastatin, caffeine, carbamazepine, levofloxacin, sertraline, sulfamethoxazole, and trimethoprim showed half-lives ranging from approximately 1.5 days for caffeine and acetaminophen and up to 92 days for carbamazepine (Lam, Young et al. 2004). Another study evaluating the photodegradation of six pharmaceuticals found that half-lives of around 100 days for carbamazepine and clofibric acid and 2.4, 5.0, 10.6, and 16.8 days for sulphamethoxazole, diclofenac, ofloxacin, and proponolol, respectively (Andreozzi, Raffaele et al. 2003).

Adsorption to sediment is a significant process in the fate and transport of PPCPs in surface waters. As discussed above, sorbtion is controlled by properties described by the related properties, organic partition coefficient K_{oc}, the octanol-water partition coefficient K_{ow}, and the solid-water distribution coefficient K_d. It is important to note that the degree to which a given compound will partition into sludge and soil are not equivalent due to differences in mineral and lipid content (Kummerer 2009). Studies demonstrate that other factors influence sorption of PPCPs to soils and these factors are particularly important for antibiotics. For example, sorbtion of ciprofloxacin was found to be directly related to clay content and inversely related to pH (Cordova 2007). Ibuprofen, benzafibrate, fluoxetine, and fluvoxaminehave been shown to have a relatively high sorbtion tendency (Heberer 2002; Tixier, Singer et al. 2003; Johnson 2005). Clofibric acid, carbamazepine, primidone, caffeine, and cotinine primarily remain in the water column with very little adsorption to the substrate (Heberer 2002). In a USGS study of the occurrence of PPCPs in 47 U.S. groundwater sources within 18 states, sulfamethoxazole, lincomycin, dehydronifedipine, diltiazem, fluoxetine, 1,7-dimethylxanthine, acetaminophen, caffeine, cotinine, ibuprofen, 1,4-dichlorobenzene, cholesterol, coprostanol, and stigmastanol were detected (Barnes, Kolpin et al. 2008) suggesting very little binding to particles. While information on the relative contribution of adsorption of PPCPs to the substrate is limited, the presence in groundwater supplies implies that it could be an important process for those specific compounds.

Biodegradation, hydrolysis, and volatilization are not significant transformation processes for PPCPs in the environment. As PPCPs in surface waters have avoided biodegradation during transport through the human body and wastewater treatment process, this process is not a significant removal mechanism in the aquatic environment, particularly where light penetration occurs (Lam, Young et al. 2004; Petrovic 2007). However, caffeine and cotinine, which can be used as indicators of human waste pollution because of their persistence in surface waters, have been found to biodegrade in the substrate (Bradley 2007). As stated above, caffeine and cotinine primarily remain in the water column, but do partition into sediment and subsequently biodegrade. Additionally, in one study, naproxen degraded efficiently in anoxic sediments (Kunkel 2008). A chemical is resistant to acid- or enzyme-promoted hydrolysis reactions if it is able to pass through the digestive system unchanged (Petrovic 2007). Hydrolysis has been demonstrated as not significant for the degradation of PPCPs found in surface waters (Andreozzi, Raffaele et al. 2003; Lam, Young et al. 2004). Finally, volatilization is not a significant process in the fate and transport of PPCPs in surface waters as these compounds generally have low volatility by design (Fent, Weston et al. 2006).

EFFECT ON AQUATIC ORGANISMS AND ECOSYSTEMS

Recent studies have only begun to elucidate the effect that PPCPs in surface waters have on aquatic organisms and ecosystems. Though many studies have evaluated acute toxicity, it is generally not a concern because PPCPs are rarely found in sufficient concentrations in the environment to elicit an acute response (Halling-Sorensen, Nielsen et al. 1998). Exposure in the aquatic environment is constant throughout the life cycle of many generations (Daughton and Ternes 1999; Fent, Weston et al. 2006). Due to the "pseudo-persistent" nature and low concentrations of this type of contaminant, understanding the chronic effects is the key to understanding the impact that PPCPs may have on aquatic organisms. Part of understanding the impact on aquatic organisms is knowing how environmental conditions such as pH influence toxicity. By design, PPCPs are biologically active compounds and while they are designed for target organism physiology, many physiological pathways and receptor targets are evolutionarily conserved (Beulig and Fowler 2008; Brain, Hanson et al. 2008). A toxicological response to a bioactive compound in an aquatic organism can result when the organism uses the same receptor or pathway as in humans with enzymes that are almost structurally identical (Brain, Hanson et al. 2008). Some PPCPs act as endocrine disrupting chemicals or compounds (EDCs) in the environment and interfere with natural hormone function in organisms by mimicking, blocking, or disrupting hormones. Three major types of EDCs include estrogenic, androgenic, and thyroidal compounds (Snyder, Westerhoff et al. 2003). A comprehensive list of EDCs or PPCPs that qualify as EDCs has not been compiled (Kim, Cho et al. 2007). Characteristics such as lipophilicity to allow transport through membranes and persistence to avoid inactivity before the therapeutic effect is achieved can facilitate bioaccumulation and biochemical response in non-target organisms (Halling-Sorensen, Nielsen et al. 1998). Additionally, pharmacodynamics apart from the intended therapeutic effect may harm aquatic organisms (Fent, Weston et al. 2006). While studies of chronic effects have been conducted, the impact of PPCPs to aquatic freshwater organisms and ecosystems is not well understood (Fent, Weston et al. 2006; Kummerer 2009). Further, many published chronic effects studies involve PPCPs at concentrations much higher than are found in the environment (Halling-Sorensen 2000; Wollenberger, Halling-Sorensen et al. 2000; Isidori, Nardelli et al. 2006; Dussault, Balakrishnan et al. 2008). Studies using concentrations that greatly exceed those found in the environment often demonstrated that PPCPs are toxic to aquatic organisms. However, because PPCPs in such high concentrations are not likely to be encountered, the results of those studies are less useful in assessing the impact of PPCPs to aquatic organisms. The following discussion summarizes the known chronic effects of PPCPs on aquatic organisms and ecosystems at environmentally relevant concentrations, including the physiological pathways and receptors targeted where that information is available. The discussion is divided into general categories of PPCPs and includes a section on studies involving mixtures of PPCPs.

PPCPs Nontoxic at Environmental Concentrations

Studies have found certain PPCPs nontoxic to aquatic organisms at concentrations found in the environment. Pharmaceuticals that are categorized as non-steroidal anti-inflammatory, analgesic, antiepileptic, fibrates, β-blockers, vasodilators, and antihyperglycemic do not elicit a toxicological response at concentrations below 500 µg/L in aquatic plants (Brain, Hanson et al. 2008). A 35-day experiment exposed the macrophytes *Myriophyllum sibiricum* and *Lemna gibba* to a mixture of atorvastatin, acetaminophen, caffeine, sulfamethoxazole, carbamazepine, levofloxacin, sertraline, and trimethoprim at four concentrations (Brain, Johnson et al. 2004). The lowest concentration was environmentally relevant and did not result in a toxic effect to either macrophyte (Brain, Johnson et al. 2004). The freshwater crustacean *Hyalella azteca* was exposed to a mixture of acetaminophen, diclofenac, gemfibrozil, ibuprofen, naproxen, salicylic acid, and triclosan for eight weeks (Borgmann, Bennie et al. 2007). The only statistically significant effect to *H. azteca* was an increase in males from 50 percent to 58 percent when averaging the percentage of males from the six populations used in the study (Borgmann, Bennie et al. 2007). The study concluded that the mixture does not pose a risk for *H. azteca* populations (Borgmann, Bennie et al. 2007). Chronic toxicity thresholds for fish exposed to triclosan range from 34 to 290 µg/L and 5 µg/L for triclocarban (Chalew and Halden 2009). Fish have not been shown to be directly impacted by triclosan or triclocarban at environmentally relevant concentrations, but could be indirectly affected due to decreased algal food quality or reduced crustacean populations (Chalew and Halden 2009). Results of several studies evaluating the toxicity of human and veterinary antibiotics indicate that antibiotics do not pose a risk to fish (Kummerer 2009). However, published studies either evaluated acute toxicity or used concentrations that were much greater than those found in the environment.

Antibiotics

Antibiotics are both naturally occurring and synthetic and function as antibacterial, antifungal, or antiparasitical agents. Antimicrobials, which are also antiviral, and chemotherapeuticals are similar to antibiotics and treat disease by attacking microorganisms and cancer cells, respectively. Antibiotics are complex compounds and often have more than one function within a given molecule. There are many classes of antibiotics, which differ in molecular structure or pharmacologic mechanism. Important classes of antibiotics include β-lactams, tetracyclines, aminoglycosides, macrolides, glycopeptides, sulfonamides, and quinolones (Kummerer 2009). Bacteria that are resistant to antibiotics are found in surface and groundwater as well as in organisms, including biota in remote areas such as the Arctic Sea (Kummerer 2009). Bacterial resistance has been seen primarily a human and veterinary health issue and is not well

studied. However, as variability in resistance naturally occurs, the possibility for altering bacterial communities in aquatic systems is present.

Chronic toxicity studies involving antibiotics at environmentally relevant concentrations are extremely limited, but studies involving higher concentrations have demonstrated adverse effects to cyanobacteria, microalgae, and zooplankton. Several studies of antibiotic toxicity above environmentally relevant concentrations among bacteria, algae, and macrophytes find that cyanobacteria (blue-green algae) and microalgae are consistently 2-3 orders of magnitude more sensitive to antibiotics than other types of algae (Lutzhoft, Halling-Sorensen et al. 1999; Halling-Sorensen 2000; Brain, Hanson et al. 2008). Higher aquatic plants are generally sensitive to the same categories of compounds as algal species, but to a lesser degree by one or more orders of magnitude and only at concentrations far exceeding those occurring in the environment (Brain, Hanson et al. 2008). Cyanobacteria are very sensitive to β-lactam and fluoroquinolone antibiotics, especially ciprofloxacin (Brain, Hanson et al. 2008). Ciprofloxacin is a widely-used antibiotic and has been applied in several exposure experiments. The maximum and median concentrations of ciprofloxacin detected in the USGS national reconnaissance study were 0.03 and 0.02 µg/L, respectively (Kolpin, Furlong et al. 2002). One study evaluated chronic toxicity of ciprofloxacin to freshwater algae populations at the environmentally relevant concentration 0.012 µg/L as well as higher concentrations (Wilson, Smith et al. 2003). Tests on algal communities were run twice at each concentration and the first indicated no response to ciprofloxacin at 0.012 µg/L. Samples associated with the later screening were lost for the 0.012 µg/L treatment and analyses could not be performed (Wilson, Smith et al. 2003). In these experiments, ciprofloxacin did decrease biomass and diversity among algal species at 0.12 µg/L (Wilson, Smith et al. 2003). Additionally, exposure to ciprofloxacin caused a significant increase in the population of the common diatom *Synedra* at concentrations of 0.015 µg/L (Wilson, Smith et al. 2003), indicating that as part of decreasing diversity, exposure may promote the growth of certain species. Decreases in algal biomass and diversity have also been observed in experiments involving a range of concentrations above 0.12 µg/L (Brain, Hanson et al. 2008). Regarding other organisms, in an experiment exposing two detritivores, the amphipod (*Gammarus spp.*) and caddisfly (*Lepidostoma liba*), to 0.1 µg/L of ciprofloxacin for 30 days, no effects were observed (Maul, Schuler et al. 2006). While 0.1 µg/L exceeds environmentally relevant concentrations, the study concluded that the impact of ciprofloxacin at environmentally relevant concentrations is low for the two species tested and that other species should be evaluated (Maul, Schuler et al. 2006).

In contrast to the observed effects of ciprofloxacin, concentrations of 0.03 and 0.1 µg/L of the human and veterinary antiparasitic ivermectin did not affect photosynthetic pigment, species richness, or species distribution in algae populations (Sanderson, Laird et al. 2007). However, after exposure to concentrations of 0.03 µg/L, cladoceran populations dramatically declined and species distribution shifted from being

dominated by species associated with sediment to littoral and pelagic species (Sanderson, Laird et al. 2007). The same study observed the rapid sorption of ivermectin to soils. Overall richness of zooplankton species and the *Ephemeroptera* populations also decreased due to ivermectin exposure (Sanderson, Laird et al. 2007). In another study, ivermectin as low as 0.001 ng/L impaired survival, reproduction, and growth of the cladoceran *Daphnia magna* (Garric, Vollat et al. 2007). Limited research indicates that commonly used antibiotics may have adverse effects on algae and zooplankton. Given the importance of algae and zooplankton in aquatic ecosystems and the widespread occurrence of antibiotics in surface waters, further research is crucial.

Several receptors and pathways in aquatic plants have been identified as being susceptible to interference by antibiotics. Plant chloroplast and bacteria DNA function in an analogous manner such that antibiotics in the quinolone and cyclothialidine classes can impair the replication of chloroplast DNA in aquatic plants (Brain, Hanson et al. 2008). Transcription and translation of DNA are affected when aquatic plants are exposed to other antibiotic classes including tetracyclines, macrolides, lincosamides, β-aminoglycosides, and pleuromutilins (Brain, Hanson et al. 2008). Sulfonamide antibiotics inhibit folate biosynthesis (Brain, Hanson et al. 2008). These methods of action were recognized in experiments using concentrations higher than those found in surface waters, but are applicable to lower concentrations.

Triclosan and Triclocarban

Triclosan and triclocarban are broad-spectrum antimicrobial agents used in many products such as antimicrobial soaps, toothpaste, and deodorant and are toxic to algae, freshwater crustaceans, and cause endocrine disruption in tadpoles. Both compounds function by inhibiting fatty acid synthesis in bacteria (Heath, Rubin et al. 1999). Plants synthesize fatty acids via the same pathway as bacteria (Harwood 1996). Plants are nearly the sole natural source of polyunsaturated fatty acids (PUFAs), which contribute to the function of cell membranes and are crucial to animals as hormone precursors (Brett and Muller-Navarra 1997). A subset of PUFAs are the highly unsaturated fatty acids (HUFAs), which are key components in determining the quality of algae as a food source (Brett and Muller-Navarra 1997). Triclosan may degrade the quality of algae as a food source to zooplankton. Triclosan has been found to inhibit fatty acid biosynthesis and reduce biomass and diversity in algae at environmentally relevant concentrations (Wilson, Smith et al. 2003; Brain, Hanson et al. 2008). Algal food quality has been identified as a very important characteristic in the health and function of the aquatic food web. Zooplankton growth and resilience to fish predation is directly related to the quality of the algae that it consumes (Danielsdottir, Brett et al. 2007). Additionally, when algal quality is high and a robust zooplankton community results, production at higher trophic levels is improved through efficient energy transfer (Danielsdottir, Brett et al. 2007). Therefore, a reduction of algal species that are able to synthesize fatty

acids and provide HUFAs to zooplankton due to exposure to triclosan could result in adverse impacts to organisms throughout the food web, including fish species. Microalgae are most sensitive to triclosan and blue-green and green algae vary in sensitivity up to two orders of magnitude (Franza 2008). Chronic toxicity to algal communities has been demonstrated with environmentally relevant concentrations of triclosan from 0.015 to 2.8 μg/L and triclocarban from 10 to 30 μg/L (Wilson, Smith et al. 2003; Chalew and Halden 2009). Environmental concentrations of triclosan and triclocarban range from below detection limits to 2.3 and 0.25 μg/L, respectively (Chalew and Halden 2009). Therefore, triclocarban is toxic to algae at levels much higher than are typically found in surface waters. Freshwater crustaceans are adversely affected when concentrations range from 6 to 182 μg/L for triclosan and from 0.06 to 4.7 μg/L for triclocarban (Chalew and Halden 2009). Similar to algae, crustaceans are important members of the aquatic food web and exposure to triclocarban could result in impacts throughout an aquatic ecosystem. Endocrine disruption by triclosan via interference with thyroid hormones, which controls metamorphosis of tadpoles into froglets, was observed in premetamorphic North American bullfrog (*Rana catesbeiana*) tadpoles at concentrations as low as 0.15 μg/L (Veldhoen, Skirrow et al. 2006). The American toad (*Bufo americanus*) tadpoles and northern leopard frog (*Rana pipiens*) exhibited earlier and higher mortality and African clawed frog (*Xenopus laevis)* tadpoles exhibited decreased activity with exposure to triclosan at 2.3 μg/L (Fraker and Smith 2004; Smith and Burgett 2005). The studies described above indicate that triclosan and triclocarban are toxic to algae, freshwater crustaceans, and frog species via at least two identified mechanisms at environmentally relevant concentrations. More information is available for triclosan because it has been studied more frequently than triclocarban. However, both compounds have demonstrated chronic toxicity to aquatic organisms and would be expected to significantly degrade ecosystem quality as a result.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are widely used to treat depression and other mental health conditions. The active compounds in this class of prescription drugs include fluoxetine (Prozac), citalopram (Celexa), paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox), and escitalopram (Lexapro). This class of drug induces an extracellular supply of serotonin, a mood-regulating neurotransmitter and neurohormone (Kreke 2008). Serotonin is highly conserved and found in vertebrates and invertebrates (Beulig and Fowler 2008; Kreke 2008). Occurrence data on SSRIs in surface waters is sparse and fluoxetine is the compound found most often. The maximum and median concentrations of fluoxetine found during the USGS national reconnaissance study were both 0.012 μg/L though these are estimated concentrations due to a recovery rate on less than 60 percent in the laboratory (Kolpin, Furlong et al. 2002). Fluoxetine was found in 1.2 percent of the streams sampled by the USGS (Kolpin, Furlong et al. 2002). Another study of Canadian surface waters reported median

fluoxetine concentrations up to 0.099 µg/L in WWTP effluent and 0.013 and 0.046 µg/L in two of four sampled rivers with no detection in the remaining two rivers (Metcalfe, Miao et al. 2003).

Limited research indicates that SSRIs may result in decreased activity in fish and crustaceans. After exposure to 10 and 100 ng/L of fluoxetine, the freshwater crustacean *Gammarus pulex* exhibited significantly reduced activity while behavior at concentrations of 1 µg/L to 1 mg/L was equivalent to the control population (De Lange 2006). One study found concentrations of fluvoxamine as low as 0.032 µg/L to induce spawning in zebra mussels (Fong 1998). Demonstrated effects in fish include lethargic behavior in western mosquitofish (*Gambusia affinis*) at concentrations as low as 0.05 µg/L (Henry 2008). Goldfish exposed to fluoxetine were also less active when compared to the control group in the study though concentrations were not environmentally relevant (Beulig and Fowler 2008). Decreased activity resulting from SSRI exposure could have ecological impacts though no studies have investigated the possibility.

Studies indicate that SSRIs and their metabolites may bioaccumulate in fish. Fluoxetine, norfluoxetine, sertraline, and desmethylsertraline were found in brain, liver, and lateral muscle tissues of bluegill (*Lepomis macrochirus*), channel catfish (*Ictalurus punctatus*), and black crappie (*Pomoxis nigromaculatus*) from an effluent dominated stream in Texas (Brooks, Chambliss et al. 2005). Fish tissues from a regional reference stream used in the study that does not receive wastewater effluent did not contain fluoxetine (Brooks, Chambliss et al. 2005). Brain tissue had the highest concentrations followed by liver and muscle. The metabolites norfluoxetine and desmethylsertraline were found in higher concentrations than their parent compounds in all tissues of each species, which is consistent with the behavior of SSRIs in human and rat tissues (Brooks, Chambliss et al. 2005). Average concentrations in the brain were: fluoxetine, 1.58 ± 0.74 ng/g; norfluoxetine, 8.86 ± 5.9 ng/g; sertraline, 4.27 ± 1.4 ng/g; desmethylsertraline, 15.6 ± 14.3 ng/g. In the liver, average concentrations were: fluoxetine, 1.34 ± 0.65 ng/g; norfluoxetine, 10.27 ± 5.73 ng/g; sertraline, 3.59 ± 1.67 ng/g; desmethylsertraline, 12.94 ± 10.45 ng/g). Muscle tissues contained: fluoxetine, 0.11 ± 0.03 ng/g; norfluoxetine, 5 1.07 ± 0.41 ng/ g; sertraline, 0.34 ± 0.09 ng/g; desmethylsertraline, 0.69 ± 0.59 ng/g (Brooks, Chambliss et al. 2005). The ecological implications of SSRIs in fish tissues are unknown.

Synthetic and Natural Hormones

There have been several reviews of EDCs in surface waters and only a brief review will be included here. The ovulation inhibitor found in oral contraceptives 17α-ethinylestradiol at concentrations detected in surface waters cause a variety of adverse effects in aquatic organisms. Sex steroid receptors have been identified in aquatic invertebrates including gastropods, bivavlves, and cephalopods and similar receptors

have been found in deuterosomes and crustacean (Kohler 2007). Exposure of the aquatic invertebrates *Hydra vulgaris*, *Gammarus pulex*, *Chironomus riparius*, *Hyalella azteca*, and *Lymnaea stagnalis* to 17α-ethinylestradiol resulted in adverse effects to the midge *C. riparius* and the snail *L. stagnalis* (Segner, Caroll et al. 2003). Concentrations from 10 ng/L to 10 µg/L caused mouthpart deformities, primarily in the mentum (a thin projection below the mouth), in *C. riparius*. Another study produced the same effect in the mentum of *C. riparius* in this concentration range and identified interference with the ecdysteroid (moulting hormone) receptor as a potential cause (Watts, Pascoe et al. 2003). Effects on *L. stagnalis* included deformations in developing snails at 100 to 1,000 ng/L, altered protein pattern and reduced growth in hatchlings at 50 to 500 ng/L, delayed hatching in second generation eggs at 500 ng/L, and detachment of second generation eggs from the substrate at 50 to 100 ng/L (Segner, Caroll et al. 2003). Exposure of the freshwater crustacean *Hyalella azteca* to 17α-ethinylestradiol at 0.1 and 0.32 µg/L resulted in significantly smaller gnathopods (claws on second thoracic segment used to grasp females during copulation) in second generation males and the ratio of females to males after two generations of exposure increased though not enough to be statistically significant (Vandenbergh, Adriaens et al. 2003). Additionally, signs of hermaphroditism and disruption of both germ cell maturation and spermatogenesis occurred after four weeks of exposure in males at all tested concentrations, which ranged from 0.1 to 10 µg/L (Vandenbergh, Adriaens et al. 2003). Interaction with the androgenic gland or androgenic gland hormone, which stimulates male sexual differentiation in crustaceans is a possible cause of the effects (Vandenbergh, Adriaens et al. 2003). The maximum and median concentrations of 17α-ethinylestradiol found in surface waters during the USGS nationwide reconnaissance study were 0.831 and 0.073 µg/L, respectively (Kolpin, Furlong et al. 2002). Therefore, the lower concentrations used in the studies discussed above are environmentally relevant. A study evaluating growth, survival, fecundity, fertilization rate, gonad differentiation, and time of first spawn of zebrafish (*Danio rerio*) after exposure to concentrations of 17α-ethinylestradiol ranging from 0.05 to10 ng/L found several adverse effects. Effects included vitellogenin induction, modified gonad differentiation, delay of first spawning, and decreased fertilization success (Segner, Caroll et al. 2003). Vitellogenin is a protein normally synthesized by females during oocyte maturation. The lowest-observed-effect concentration was 1.67 ng/L and at 10 ng/L reproduction including spawning and mating ceased (Segner, Caroll et al. 2003). In a life cycle exposure experiment, fathead minnows (*Pimephales promelas*) were exposed to 17α-ethinylestradiol at concentrations of 0.32, 0.96, 3.5, 9.6, and 23 ng/L (Parrott and Blunt 2005). The earliest response was increased ovipositor (egg-dispensing tube) length in females and occurred 60 days after hatching at 3.5 ng/L (Parrott and Blunt 2005). Other effects included decreased egg fertilization and an increased ratio of females to males at 0.32 ng/L and demasculinization of males at 0.96 ng/L (Parrott and Blunt 2005). A study in the Experimental Lakes Area in Ontario, Canada evaluated the response of fathead minnows (*Pimephales promelases)* to introduced concentrations of 17α-ethinylestradiol (Kidd 2006). Results of the seven-year experiment included production of vitellogenin,

impacts to gonadal development, and altered oogenesis in females followed by a near extinction of the species at 5 to 6 ng/L (Kidd 2006). This study was of particular importance because it addresses the potential ecosystem-scale impacts of 17α-ethinylestradiol in surface waters.

Steroid hormones including 17β-estradiol, estrone, 17α-estradiol, estriol, progesterone, and testosterone are naturally synthesized in the human body and induce several adverse responses in aquatic organisms. As with other classes of PPCPs, most toxicity studies have evaluated effects associated with concentrations that are not environmentally relevant. Observed effects in fish in those studies include reduced egg production, reduced egg fertility, decreased egg hatchability, reduced live young, skewed sex ratio, reduced male and female Gonadosomatic Index, decreased sexual behavior in males, intersex gonads, decrease in male sexual characteristics, males with no milt or reduced sperm count, females with male sexual characteristics, delayed sexual maturation, alterations in gonad structure, physical deformities, and altered plasma steroid hormone concentrations (Mills 2004). In some instances, environmentally relevant concentrations have been used along with an evaluation of vitellogenin production, which is a common test for endocrine disruption. A 21-day exposure of rainbow trout (*Oncorhynchus mykiss*) and roach (*Rutilus rutilus*) to 17β-estradiol and rainbow trout to estrone caused high levels of vitellogenin production in adult males (Routledge, Sheahan et al. 1998). The response threshold for 17β-estradiol in rainbow trout was a range from 1 to 10 ng/L and 100 ng/L for roach (Routledge, Sheahan et al. 1998). Responses in rainbow trout to estrone occurred between 25 and 50 ng/L (Routledge, Sheahan et al. 1998). Rainbow trout are more sensitive to 17β-estradiol than roach evidenced by 30 times greater vitellogenin production at 100 ng/L (Routledge, Sheahan et al. 1998). Rainbow trout were exposed to 25 ng/L of estrone and 17β-estradiol individually and combined. Individual responses were minor when compared to the significant increases in vitellogenin production due to the combination. The response to the combination was significantly greater than to 50 ng/L of estrone alone (Routledge, Sheahan et al. 1998). The study could not determine if the combined effect was synergistic, but stated that it was certainly additive (Routledge, Sheahan et al. 1998). Vitellogenin production occurred in Japanese medaka (*Oryzias latipes*) at 17β-estradiol concentrations of 5.0 ng/L and 31.6 ng/L of estrone (Flippin 2007). Fathead minnows (*Pimephales promelases)* caged downstream of a WWTP effluent had significantly higher expression of vitellogenin and estrogen receptor alpha than minnows caged above the effluent. The ecological significance of observed elevations of vitellogenin production in fish at environmentally relevant concentrations and demonstrated effects at higher concentrations is not well understood.

Non-Steroidal Anti-Inflammatory Drugs

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) include prescription and non-prescription drugs used to treat inflammation, pain, and fever. Examples of NSAIDs include diclofenac, naproxen, ketoprofen, and acetaminophen. Drugs in this class act by inhibiting the synthesis of prostaglandins, which are involved in several processes in the body including inflammation, regulation of vasoconstriction and vasodilatation in the kidney, coagulation, and protective gastric mucosa synthesis (Fent, Weston et al. 2006).

While little is known about the effect of NSAIDs on aquatic organisms, a few studies using environmentally relevant concentrations identified impacts to freshwater crustaceans and fish. Reduced activity was observed in the freshwater crustacean *Gammarus pulex* at concentrations as low as 10 ng/L of ibuprofen in a study that used concentrations ranging from 1 to 100 ng/L (De Lange 2006). Maximum and median concentrations of ibuprofen found during the USGS national reconnaissance study were 1.0 and 0.20 µg/L, respectively (Kolpin, Furlong et al. 2002). Diclofenac has been shown to result in liver, gill, and kidney cytopathology in rainbow trout (*Oncorhynchus mykiss*) at the lowest observed effect concentration (LOEC) of 1 µg/L (Triebskorn, Casper et al. 2004). A review of monitoring studies reported median and maximum concentrations of diclofenac at 0.81 µg/L and 2 µg/L, respectively, in surface waters (Fent, Weston et al. 2006). Inhibition of the cyclooxygenase (COX) enzyme occurred in Japanese medaka (*Oryzias latipes*) at concentrations of 1 µg/L of ibuprofen (Flippin 2007). The COX enzyme is targeted in humans to reduce inflammation. The ecological implication of COX enzyme response in Japanese medaka or other fish species is unknown. One notable instance of terrestrial ecological impacts is the 95% decline in the Oriental white-backed vulture (*Gyps bengalensis*) in Pakistan due to feeding on carrion of livestock medicated with diclofenac (Oaks 2004). Based on few existing studies, NSAIDs appear to influence more than one mechanism and result in chronic toxicity in the aquatic environment.

Caffeine

The effect of environmental concentrations of caffeine on aquatic species is essentially unknown. Caffeine is heavily consumed worldwide and often used as an indicator of human waste pollution because it persists in the environment. Maximum and median concentrations of caffeine found in the USGS nationwide study were 5.7 and 0.081 µg/L, respectively (Kolpin, Furlong et al. 2002). Tadpoles of the northern leopard frog (*Rana pipiens*) were evaluated by activity level, startle response, growth rate, and survival when exposed to 0.6 and 6.0 µg/L of caffeine (Fraker and Smith 2004). Caffeine decreased tadpole activity levels at 0.6 µg/L and increased tadpole activity at concentrations in excess of those found in the environment (Fraker and Smith 2004). Given the widespread presence and persistence of caffeine, additional studies are warranted.

Other PPCPs

The occurrence and toxicity of other major classes of PPCPs including lipid regulators, antiepileptics, analgesics, cardiac drugs, synthetic musks, and nicotine metabolites have not been thoroughly investigated. Published studies are few and have evaluated toxicity at concentrations much higher than found in the environment. The lipid regulator gemfibrozil is frequently detected in surface waters and relatively persistent in the environment. Two studies found that gemfibrozil bioaccumulated in rainbow trout (*O. mykiss*) and goldfish (*Carassius auratus*), but both sets of experiments used concentrations greater than those found in surface waters (Mimeault 2005; Brown 2007). Carbamazepine is an antiepileptic medication and very resistant to environmental degradation. Decreased survival of *Chironomus riparius* (Oetken 2005) was found when exposed to amounts greater than environmental concentrations. Similar studies of nicotine and synthetic musks identify adverse effects, but due to the concentrations used, the studies do not necessarily provide an accurate assessment of chronic toxicity (Passinoreader 1995; Wollenberger 2003). Due to the lack of information on the potential adverse effects of several classes of frequently detected PPCPs, a conclusion cannot be reached.

Environmental Degradation Products

Environmental degradation products of PPCPs, particularly products of photolysis, can be as or more toxic than the compound in the ingested or metabolite form although very little is known about the effects to aquatic organisms (Petrovic 2007). Prednisone has seven photoproducts, some of which were found to be highly toxic to the crustacean *Ceriodaphnia dubia* while chronic and acute toxicity of the parent compound were found to be low (DellaGreca, Fiorentino et al. 2003). While triclosan has been found to lose antibiotic function after photolysis and, therefore, the toxic effects exhibited in the studies described above, photoproducts of triclosan include 2,8-dichlorodibenzo-p-dioxin and 2,4-dichlorophenol (2,4-DCP), which are known toxins (Latch, Packer et al. 2005; Petrovic 2007). In the study described above that evaluated eight antibiotics used in intensive farming operations, photochemical degradation products were suspected contributors to toxicity though the ratio of parent compounds to photoproducts was not quantified (Halling-Sorensen 2000). Some photoproducts of tetracycline antibiotics were shown to have antibiotic properties comparable to tetracycline and be effective against tetracycline-resistant bacteria, which indicates that the photoproducts acted via a different mechanism than the parent compound (Halling-Sorensen, Sengelov et al. 2002). The limited information on the occurrence and effects of environmental degradation products of PPCPs suggests that some compounds are potentially as or more toxic than parent compounds.

Mixtures

Studies of PPCP mixtures have identified impacts to aquatic organisms. The importance of understanding the impacts of mixtures of PPCPs is widely acknowledged though mixture studies are rare. Certain mixtures have been found to be nontoxic at specific concentrations and are summarized above under PPCPs Nontoxic at Environmental Concentrations. However, other studies of mixture have identified impacts. Wild fathead minnows (*Pimephales promelas*) exposed to cattle feedlot effluent were collected and examined (Orlando 2004). Researchers discovered lower testicular testosterone synthesis, altered head morphometrics, and smaller testis in males and decreased estrogen to androgen ratio in females (Orlando 2004). A study found that when exposed to a mixture of the natural estrogen 17β-estradiol and the antiestrogens letrozole and tamoxifen, Japanese medaka (*Oryzias latipes*) exhibited impaired reproductive capability and vitellogenin production. The objective of the study was to determine if EDCs could balance in a manner that avoids impacts to fish species and concluded that while in some instances, abnormalities were less pronounced there were others in which a greater impact was incurred as a result of the mixture. Fathead minnows were exposed to a mixture of naproxen, gemfibrozil, diclofenac, ibuprofen, triclosan, salicylic acid, and acetaminophen at environmentally relevant concentrations of 10, 30, 100, and 300 ng/L (Parrott 2009). The minnows in this life cycle study exhibited no changes in growth, development, length, weight, liver weight, gonad weight, sex characteristics, egg production, or egg deformaties at 10 and 30 ng/L (Parrott 2009). However, egg deformities in the first generation of minnows occurred in the 100 and 300 ng/L treatment (Parrott 2009). Given that PPCPs exist in the environment in mixtures and that effects have been identified in both single compound and mixture studies, further mixture studies are required to understand the ecological implications of PPCPs in surface waters.

THE BAY-DELTA SYSTEM

Data on the presence of PPCPs in the Bay-Delta are very limited. None of the ongoing monitoring programs include PPCPs and occurrence data consists of results from a few short-term studies. The national reconnaissance study conducted by the USGS in 1999-2000 included four sites within or tributary to the Delta: the Sacramento River at Freeport, Mud Slough near Gustine, Orestimba Creek near Crows Landing, San Joaquin River near Vernalis, and French Camp Slough near Stockton (**Table 2**) (Kolpin, Furlong et al. 2002). As part of the San Francisco Estuary Regional Monitoring Program (SFERMP), surface water samples from 12 locations within the estuary, including one site in both the Sacramento and San Joaquin Rivers were screened for two common fragrances, an antipyretic, and a sunscreen (Oros, Jarman et al. 2003). Samples were taken in July of 1999 and 2000 (**Table 3**). A study by the Metropolitan Water District of Southern California and the Orange County Water District currently is investigating sources, fate and transport and PPCPs in California drinking water sources. This study includes monitoring sites along the Sacramento River in the vicinity of the Sacramento Regional Wastewater Treatment Plant.

A few university studies have analyzed the occurrence and effect on aquatic organisms of PPCPs in the Delta. In a study conducted by University of California, Berkeley, University of California, Riverside, and Applied Marine Sciences, 110 surface water samples from 16 locations in 2006 within the Delta and Napa River were evaluated for steroid hormones (17α-estradiol, 17β-estradiol, estrone, estriol, progesterone, medroxyprogesterone, testosterone, and androstenedione) and alkylphenol ethoxylates (APEs) (Lavado and Schlenk 2008). Bioassays, or measurements of the effects of the compounds on living organisms, were also conducted on rainbow trout (*O. mykiss*). The goal of the study was to evaluate estrogenicity of Delta surface waters as part of the effort to restore Chinook salmon and other populations. Steroid hormones were either not present in the samples or in concentrations that were detectable, but below quantitation limits, which is when results are considered to be reliably accurate. Concentrations of 17α-estradiol, 17β-estradiol, estrone, estriol, progesterone, and testosterone are consistent (less than 5 ng/L) with those found in the USGS study described above. APEs were found in all 110 samples, but concentrations were one or more orders of magnitude below those expected to cause effects in fish. A subset of samples was analyzed for PPCPs and all concentrations were less than 5 ng/L, below the concentration expected to cause effects in fish. In contrast, high estrogenic activity was found in the bioassay results at 6 of the 16 sites. The inconsistency between the water sample and bioassay results was attributed to the possibility that other compounds could be responsible for feminization of Delta fish species. Clams, mussels, and oysters were analyzed for synthetic musks as part of the SFERMP analytes in 2002 and 2003 (**Table 4**) (Hoenicke, Oros et al. 2007). A study by the Department of Environmental Toxicology at the University of California at Davis is currently underway and will evaluate the estrogenic or anti-androgenic response of the resident inland silverside

(*Menidia beryllina*) to the combination of prevalent pyrethroids and 17α-ethinylestradiol. Finally, a recent monitoring effort as part of a small pilot study conducted by the Aquatic Ecosystems Analysis Laboratory at the University of California at Davis found caffeine, trimethoprim, sulfamethoxazole, gemfibrozil, ibuprofen, carbamazepine, and fluoxetine in the Sacramento River downstream of the Sacramento Regional Wastewater Treatment Plant.

Recent agency documents acknowledge PPCPs as contaminants in the Bay-Delta and recommend further study. The CALFED Science Program document *The State of Bay-Delta Science, 2008* states that contaminants are stressors of concern and associated declines in native species populations have not been quantified. The document states that inputs of PPCPs are expected to increase with population and includes monitoring of and prediction of exposure to human and veterinary pharmaceuticals in a list of suggested components of an adaptive management strategy (CALFED 2008a). The CALFED *Water Quality Program Plan Year 9*, identifies pharmaceuticals and endocrine disrupters as contaminants of concern that could impact beneficial uses in the Bay-Delta (CALFED 2008b). The Ecosystem Conceptual Model, Chemical Stressors in the Sacramento-San Joaquin Delta, which is part of the Sacramento-San Joaquin Delta Regional Ecosystem Restoration Implementation Plan, includes PPCPs as one of many chemical stressors in the Delta. The Central Valley Regional Water Quality Control Board is developing a regional monitoring program for the Delta. As the process is in an early stage, a list of potential analytes is not available. Further research is necessary to determine the extent to which PPCPs are responsible for the decline of the Bay-Delta ecosystem. As described above, the few studies that have been conducted point to the presence of PPCPs that have been linked to adverse effects to aquatic organisms. Given these results, it is possible that the presence of PPCPs could be contributing to the ecological strain observed in the Delta and it may be appropriate to allocate study this problem.

Table 2
USGS Delta Monitoring Results (µg/L)

Site ID	**CA01**	**CA07**	**CA08**	**CA09**	**CA10**
Site Name	Sacramento River at Freeport, CA	Mud Slough near Gustine, CA	Orestimba Creek near Crows Landing, CA	San Joaquin near Vernalis, CA	French Camp Slough near Stockton, CA
Latitude	38°27'15"	37°15'45"	37°24'49"	37º40’34”	37º52’52”
Longitude	121°29'54"	120º54’20”	121º00’54”	120º15’55”	121º14’54”
Sulfamethoxazole (antibiotic)	<.023	<.023	<.023	<.023	<.023
Acetaminophen (antipyretic)	0.25	<.009	E.004	E.004	<.009
Caffeine[1] (stimulant)	<.014	<.014	<.014	<.014	<.014
Caffeine[2] (stimulant)	<.080	E.04	E.02	.08	<.060
Cimetidine (antacid)	<.007	<.007	<.007	<.007	<.007

Table 2 **USGS Delta Monitoring Results (µg/L)**					
Codeine (analgesic)	<.024	--	--	--	--
Cotinine (nicotine metabolite)	<.023	<.023	<.023	<.023	<.023
Dehydronifedipine (antianginal)	<.01	<.01	<.01	<.01	<.01
Digoxigenin (digoxin metabolite)	<.008	<.008	<.008	<.008	<.008
Digoxin (cardiac stimulant)	<.26	--	--	--	--
Diltiazem (antihypertensive)	<.012	<.012	<.012	<.012	<.012
1,7-Dimethylxanthine (caffeine metabolite)	<.018	<.018	<.018	<.018	<.018
Enalaprilat (antihypertensive metabolite)	<.152	<.152	<.152	<.152	<.152
Fluoxetine (antidepressant)	<.018	<.018	<.018	<.018	<.018
Gemfibrozil (antihyperlipidemic)	<.015	<.015	<.015	<.015	<.015
Ibuprofen (anti-inflammatory)	<.018	<.018	<.018	<.018	<.018
Metformin (antidiabetic)	<.003	<.003	<.003	<.003	<.003
Paroxetine metabolite (antidepressant metabolite)	<.26	<.26	<.26	<.26	<.26
Ranitidine (antacid)	<.01	<.01	<.01	<.01	<.01
Albuterol (antiasthmatic)	<.029	<.029	<.029	<.029	<.029
Trimethoprim (antibiotic)	<.014	<.014	<.014	<.014	<.014
Warfarin (anticoagulant)	<.001	<.001	<.001	<.001	<.001
Acetophenone (fragrance)	<.100	<.150	<.150	<.150	<.150
Cholesterol[2] (plant/animal steroid)	<1.500	E.5	E.2	<1.500	E.2
Cholesterol [3] (plant/animal steroid)	.383	--	--	--	--
Codeine (analgesic)	<.100	<.100	<.100	<.100	<.100
Coprostanol[2] (fecal steroid)	<.600	<.600	<.600	<.600	<.600
Coprostanol[3] (fecal steroid)	<.005	--	--	--	--
Cotinine (nicotine metabolite)	<.040	<.600	<.600	<.600	<.600
17-estradiol[2] (reproductive hormone)	<.500	<.500	<.500	<.500	<.500
17-estradiol[3] (reproductive hormone)	<.005	--	--	--	--
Stigmastanol (plant steroid)	<2.000	--	--	--	--
Triclosan (antimicrobial disinfectant)	<.040	.04	<.040	E.01	<.040
cis-Androsterone (urinary steroid)	<.005	--	--	--	--
Equilenin (estrogen replacement)	<.005	--	--	--	--
Equilin (estrogen replacement)	<.005	--	--	--	--
17-estradiol (reproductive hormone)	<.005	--	--	--	--
17-ethynyl estradiol (ovulation inhibitor)	<.005	--	--	--	--
Estriol (reproductive hormone)	<.005	--	--	--	--
Estrone (reproductive hormone)	<.005	--	--	--	--

Table 2 **USGS Delta Monitoring Results (µg/L)**					
Mestranol (ovulation inhibitor)	.011	--	--	--	--
19-norethisterone (ovulation inhibitor)	<.005	--	--	--	--
Progesterone (reproductive hormone)	<.005	--	--	--	--
Testosterone (reproductive hormone)	<.005	--	--	--	--

-- Data not collected E – estimated [2] Analysis by capillary-column GC/MS
[1] Analysis by HPLC [3] Analysis by GC/MS

Table 3 **Occurrence Data - San Francisco Estuary Regional Monitoring Program (ng/L)** [1]						
Compound	CASRN[2]	Delta	North Bay	Central Bay	South Bay	Golden Gate
acetaminophen (antipyretic)	103-90-2	102	182	14	390	1
Galaxolide (fragrance)	1222-05-5	8	28	3	131	nd
octylmethoxy cinnamate (sunscreen)	5466-77-3	91	963	6	117	3
Tonalide (fragrance)	88-29-9	1	2	1	8	nd

[1] Data was grouped into subregions and shown as published nd – not detected
[2] Chemical Abstracts Service Registry Number

Table 4 **Bivalve Monitoring - San Francisco Estuary Regional Monitoring Program (ng/g dry weight)**				
Compound	**Concentration (ng/L)**			**Detection Frequency (%)**
	Median	**Minimum**	**Maximum**	
Oysters (*Crassostrea gigas*)				
Celestolide (fragrance)	16.7	8.2	57.0	60
Galaxolide (fragrance)	386.0	116.0	855.0	100
Tonalide (fragrance)	157.0	106.0	516.0	80
Versalide (fragrance)	22.7	20.3	25.1	40
Table 4 **Bivalve Monitoring - San Francisco Estuary Regional Monitoring Program (ng/g dry weight)**				
musk ambrette (fragrance ingredient)	3.4	1.9	6.0	60
musk ketone (fragrance ingredient)	2.1	1.4	9.1	60
musk moskene (fragrance ingredient)	nd	nd	nd	0
musk xylene (fragrance ingredient)	3.6	2.6	7.1	80
Mussels (*Mytilus californianus*)				
Celestolide (fragrance)	31.9	7.1	93.4	43
Galaxolide (fragrance)	221.0	78.5	305.0	71
Tonalide (fragrance)	110.2	30.4	275.0	57
Versalide (fragrance)	nd	nd	nd	0
musk ambrette (fragrance ingredient)	3.3	0.8	4.9	71
musk ketone (fragrance ingredient)	3.8	1.3	4.8	71
musk moskene (fragrance ingredient)	nd	nd	nd	0

musk xylene (fragrance ingredient)	3.3	2.3	4.0	100
Clams (*Corbicula fluminea*)				
Celestolide (fragrance)	24.1	22.6	25.5	100
Galaxolide (fragrance)	246.0	243.0	249.0	100
Tonalide (fragrance)	nd	nd	nd	0
Versalide (fragrance)	56.3	56.3	56.3	50
musk ambrette (fragrance ingredient)	2.2	2.1	2.3	100
musk ketone (fragrance ingredient)	13.6	10.6	16.5	100
musk moskene (fragrance ingredient)	nd	nd	nd	0
musk xylene (fragrance ingredient)	4.2	4.1	4.2	100
nd – not detected				

CONCLUSION

Published studies do not provide enough information to thoroughly evaluate the ecological implications of the presence of PPCPs in surface waters. In addition to the innate complexities of investigating this topic, many experiments have evaluated acute toxicity or concentrations much greater than those detected in the environment. The extensive literature that has been developed in the last decade addresses all relevant aspects of PPCPs in the environment, but provides limited information on each. Worldwide studies of the occurrence of PPCPs have discovered widely used pharmaceuticals and other products in concentrations ranging from ng/L to the low µg/L in surface and groundwater. Many sources contribute to the presence of PPCPs in surface waters though WWTP effluent and runoff from factory farming and CAFOs are the most significant. No treatment technologies currently exist that can completely remove PPCP compounds from treatment plant effluent. Even if such a treatment option were available, the retrofit of the thousands of WWTPs would be of tremendous scale and cost. Impacts to aquatic organisms ranging from algae to fish have been demonstrated although information is lacking for the Bay-Delta system. Monitoring programs very rarely include analysis for PPCPs and occurrence data for important ecosystems such as the Bay-Delta are severely lacking. To address and further investigate the consequences of PPCPs in the environment, further research on the adverse effects of PPCPs, particularly in relevant mixtures, focused monitoring efforts, and treatment technology development are of the utmost importance.

REFERENCES

Andreozzi, R., M. Raffaele, et al. (2003). "Pharmaceuticals in STP effluents and their solar photodegradation in aquatic environment." Chemosphere **50**(10): 1319-1330.

Barnes, K. K., D. W. Kolpin, et al. (2008). "A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States - I) Groundwater." Science of the Total Environment **402**(2-3): 192-200.

Bendz, D., N. A. Paxeus, et al. (2005). "Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Hoje River in Sweden." Journal of Hazardous Materials **122**(3): 195-204.

Beulig, A. and J. Fowler (2008). "Fish on prozac: Effect of serotonin reuptake inhibitors on cognition in goldfish (vol 122, pg 426, 2008)." Behavioral Neuroscience **122**(4): 776-776.

Bolonga, N., A.F. Ismaila, M.R. Salimb, T. Matsuurad (2008). "A review of the effects of emerging contaminants in wastewater and options for their removal." Desalination **239**: 229-246.

Borgmann, U., D. T. Bennie, et al. (2007). "Effect of a mixture of seven pharmaceuticals on Hyalella azteca over multiple generations." Chemosphere **66**(7): 1278-1283.

Bradley, P. M., Barber, Larry B., Kolpin, Dana W., McMahon, Peter B., Chapelle, Francis H. (2007). "Biotransformation of caffeine, cotinine, and nicotine in stream sediments: Implications for use as wastewater indicators." Environmental Toxicology and Chemistry **26**(6): 1116 - 1121.

Brain, R. A., M. L. Hanson, et al. (2008). Aquatic plants exposed to pharmaceuticals: Effects and risks. Reviews of Environmental Contamination and Toxicology, Vol 192. **192:** 67-115.

Brain, R. A., D. J. Johnson, et al. (2004). "Microcosm evaluation of the effects of an eight pharmaceutical mixture to the aquatic macrophytes Lemna gibba and Myriophyllum sibiricum." Aquatic Toxicology **70**(1): 23-40.

Brett, M. T. and D. C. Muller-Navarra (1997). The role of highly unsaturated fatty acids in aquatic food web processes.

Brooks, B. W., C. K. Chambliss, et al. (2005). "Determination of select antidepressants in fish from an effluent-dominated stream." Environmental Toxicology and Chemistry **24**(2): 464-469.

Brown, J. N., Paxeus, Nicklas, Forlin, Lars, Larsson, D.G. Joakim (2007). "Variations in bioconcentration of human pharmaceuticals from sewage effluents into fish blood plasma." Environmental Toxicology and Pharmacology **24**: 267 - 274.

CALFED (2008a). The State of Bay-Delta Science 2008. Sacramento, Ca, The CALFED Science Program.

CALFED (2008b). Water Quality Program, Program Plan Year 9. T. C. S. Program. Sacramento, Ca.

Carballa, M., F. Omil, et al. (2004). "Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant." Water Research **38**(12): 2918-2926.

Chalew, T. E. A. and R. U. Halden (2009). "ENVIRONMENTAL EXPOSURE OF AQUATIC AND TERRESTRIAL BIOTA TO TRICLOSAN AND TRICLOCARBAN." Journal of the American Water Resources Association **45**(1): 4-13.

Clara, M., N. Kreuzinger, et al. (2005). "The solids retention time - a suitable design parameter to evaluate the capacity of wastewater treatment plants to remove micropollutants." Water Research **39**(1): 97-106.

Conley, J. M., S. J. Symes, et al. (2008). "Spatial and temporal analysis of pharmaceutical concentrations in the upper Tennessee River basin." Chemosphere **73**(8): 1178-1187.

Cordova, A. L., Scow, Kate M. (2007). "Effects of ciprofloxacin on salt marsh sediment microbial communities." The ISME Journal **1**: 585 - 595.

Danielsdottir, M. G., M. T. Brett, et al. (2007). "Phytoplankton food quality control of planktonic food web processes." Hydrobiologia **589**: 29-41.

Daughton, C. G. (2002). "Environmental stewardship and drugs as pollutants." Lancet **360**(9339): 1035-1036.

Daughton, C. G. and T. A. Ternes (1999). "Pharmaceuticals and personal care products in the environment: Agents of subtle change?" Environmental Health Perspectives **107**: 907-938.

De Lange, H. J., Noordoven, W., Murkc, A.J., L¨urling, M., Peeters, E.T.H.M. (2006). "Behavioural responses of Gammarus pulex (Crustacea, Amphipoda) to low concentrations of pharmaceuticals." Aquatic Toxicology **78**: 209 -216.

DellaGreca, M., A. Fiorentino, et al. (2003). "Identification of phototransformation products of prednisone by sunlight: Toxicity of the drug and its derivatives on aquatic organisms." Environmental Toxicology and Chemistry **22**(3): 534-539.

Dolar, D., K. Kosutic, et al. (2009). Removal of emerging contaminants of industrial origin by NF/RO - A pilot scale study.

Dussault, E. B., V. K. Balakrishnan, et al. (2008). "Toxicity of human pharmaceuticals and personal care products to benthic invertebrates." Environmental Toxicology and Chemistry **27**(2): 425-432.

Eganhouse, R. P., J. Pontolillo (2002). "Problems with physicochemical property data for hydrophobic organic compounds." Abstracts of Papers of the American Chemical Society **224**: 517.

Fent, K., A. A. Weston, et al. (2006). "Ecotoxicology of human pharmaceuticals." Aquatic Toxicology **76**(2): 122-159.

Flippin, J. L., Huggett, Duane, Foran, Christy M. (2007). "Changes in the timing of reproduction following chronic exposure to ibuprofen in Japanese medaka, Oryzias latipes." Aquatic Toxicology **81**: 73 -78.

Focazio, M. J., D. W. Kolpin, et al. (2008). "A national reconnaissance for pharmaceuticals and other organic wastewater contaminants in the United States - II) Untreated drinking water sources." Science of the Total Environment **402**(2-3): 201-216.

Fong, P. P. (1998). "Zebra Mussel Spawning is Induced in Low Concentrations of Putative Serotonin Reuptake Inhibitors." Biological Bulletin **194**: 143 - 149.

Fraker, S. L. and G. R. Smith (2004). "Direct and interactive effects of ecologically relevant concentrations of organic wastewater contaminants on Rana pipiens tadpoles." Environmental Toxicology **19**(3): 250-256.

Franza, S., Altenburger, Rolf, Heilmeierb, Hermann, Schmitt-Jansena, Mechthild (2008). "What contributes to the sensitivity of microalgae to triclosan?" Aquatic Toxicology **90**: 102 - 108.

Garric, J., B. Vollat, et al. (2007). "Effects of the parasiticide ivermectin on the cladoceran Daphnia magna and the green alga Pseudokirchneriella subcapitata." Chemosphere **69**(6): 903-910.

Halling-Sorensen, B. (2000). "Algal toxicity of antibacterial agents used in intensive farming." Chemosphere **40**(7): 731-739.

Halling-Sorensen, B., S. N. Nielsen, et al. (1998). "Occurrence, fate and effects of pharmaceutical substances in the environment - A review." Chemosphere **36**(2): 357-394.

Halling-Sorensen, B., G. Sengelov, et al. (2002). "Toxicity of tetracyclines and tetracycline degradation products to environmentally relevant bacteria, including selected tetracycline-resistant bacteria." Archives of Environmental Contamination and Toxicology **42**(3): 263-271.

Harwood, J. L. (1996). "Recent advances in the biosynthesis of plant fatty acids." Biochimica Et Biophysica Acta-Lipids and Lipid Metabolism **1301**(1-2): 7-56.

Heath, R. J., J. R. Rubin, et al. (1999). "Mechanism of triclosan inhibition of bacterial fatty acid synthesis." Journal of Biological Chemistry **274**(16): 11110-11114.

Heberer, T. (2002). "Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data." Toxicology Letters **131**(1-2): 5-17.

Henry, T. B., Black, M.C. (2008). "Acute and Chronic Toxicity of Fluoxetine (Selective Serotonin Reuptake Inhibitor) in Western Mosquitofish." Archives of Environmental Contamination and Toxicology **54**: 325 - 330.

Hoenicke, R., D. R. Oros, et al. (2007). "Adapting an ambient monitoring program to the challenge of managing emerging pollutants in the San Francisco Estuary." Environmental Research **105**(1): 132-144.

Huang, C. H. and D. L. Sedlak (2001). "Analysis of estrogenic hormones in municipal wastewater effluent and surface water using enzyme-linked immunosorbent assay and gas chromatography/tandem mass spectrometry." Environmental Toxicology and Chemistry **20**(1): 133-139.

Isidori, M., A. Nardelli, et al. (2006). "A multispecies study to assess the toxic and genotoxic effect of pharmaceuticals: Furosemide and its photoproduct." Chemosphere **63**(5): 785-793.

Johnson, D. J., Sanderson, Hans, Brain, Richard A., Wilson, Christian J., Bestari, Ketut (Jim) T., Solomon, Keith R. (2005). "Exposure assessment and microcosm fate of selected selective serotonin reuptake inhibitors." Regulatory Toxicology and Pharmacology **42**: 313 - 323.

Kidd, K. A., Blanchfield, Paul J., Mills, Kenneth H., Palace, Vince P., Evans, Robert E., Lazorchak, James M., Flick, Robert W. (2006). "Collapse of a fish population after exposure to a synthetic estrogen." Proceedings of the National Academy of Sciences of the United States of America **104**(21): 8897 -8901.

Kim, S. D., J. Cho, et al. (2007). "Occurrence and removal of pharmaceuticals and endocrine disruptors in South Korean surface, drinking, and waste waters." Water Research **41**(5): 1013-1021.

Kohler, H. R., Kloas, Werner, Schirling, Martin, Lutz, Ilka, Reye, Anna L., Langen, Jan-S., Triebskorn, Nagel, Roland, Schonfelder, Gilbert (2007). "Sex steroid receptor evolution and signaling in aquatic invertebrates." Ecotoxicology **16**: 131 - 143.

Kolpin, D. W., E. T. Furlong, et al. (2002). "Pharmaceuticals, hormones, and other organic wastewater contaminants in US streams, 1999-2000: A national reconnaissance." Environmental Science & Technology **36**(6): 1202-1211.

Kosaka, K., H. Yamada, et al. (2000). "The effects of the co-existing compounds on the decomposition of micropollutants using the ozone/hydrogen peroxide process." Water Science and Technology **42**(7-8): 353-361.

Kreke, N., Dietrich, D.R. (2008). "Physiological Endpoints for Potential SSRI Interactions in Fish." Critical Reviews in Toxicology **37**: 215 - 247.

Kummerer, K. (2009). "Antibiotics in the aquatic environment - A review - Part I." Chemosphere **75**(4): 417-434.

Kummerer, K. (2009). "Antibiotics in the aquatic environment - A review - Part II." Chemosphere **75**(4): 435-441.

Kunkel, U., Radke, Michael (2008). "Biodegradation of Acidic Pharmaceuticals in Bed Sediments: Insight from a Laboratory Experiment." Environmental Science & Technology **42**(19): 7273 - 7279.

Lam, M. W., C. J. Young, et al. (2004). "Aquatic persistence of eight pharmaceuticals in a microcosm study." Environmental Toxicology and Chemistry **23**(6): 1431-1440.

Latch, D. E., J. L. Packer, et al. (2005). "Aqueous photochemistry of triclosan: Formation of 2,4-dichlorophenol, 2,8-dichlorodibenzo-p-dioxin, and oligomerization products." Environmental Toxicology and Chemistry **24**(3): 517-525.

Lavado, R., Loyo-Rosales, Jorge E., Kolodziej, Edward P., Sedlak, David L. and D. Schlenk (2008). "Evaluation of steroid estrogen and estrogenic activity in surface waters from central California." Marine Environmental Research **66**: 121 - 125.

Lutzhoft, H. C. H., B. Halling-Sorensen, et al. (1999). "Algal toxicity of antibacterial agents applied in Danish fish farming." Archives of Environmental Contamination and Toxicology **36**(1): 1-6.

Maul, J. D., L. J. Schuler, et al. (2006). "Effects of the antibiotic ciprofloxacin on stream microbial communities and detritivorous macroinvertebrates." Environmental Toxicology and Chemistry **25**(6): 1598-1606.

Metcalfe, C. D., X. S. Miao, et al. (2003). "Distribution of acidic and neutral drugs in surface waters near sewage treatment plants in the lower Great Lakes, Canada." Environmental Toxicology and Chemistry **22**(12): 2881-2889.

Mills, L. J., Chichester, Clinton (2004). "Review of evidence: Are endocrine-disrupting chemicals in the aquatic environment impacting fish populations?" Science of the Total Environment **343**: 1 -34.

Mimeault, C., Woodhouse, A.J., Miao, X.-S., Metcalfe, C.D., Moon, T.W., Trudeau, V.L. (2005). "The human lipid regulator, gemfibrozil bioconcentrates and reduces testosterone in the goldfish, Carassius auratus." Aquatic Toxicology **73**: 44 - 54.

Oaks, J. L., Gilbert, Martin, Virani, Munir Z., Watson, Richard T., Meteyer, Carol U., Rideout, Bruce A., Shivaprasad (2004). "Diclofenac residues as the cause of vulture population decline in Pakistan." Nature **427**(6975): 630 - 633.

Oetken, M., Nentwig, G., Loffler, D., Ternes, T., Oehlmann, J. (2005). "Effects of Pharmaceuticals on Aquatic Invertebrates. Part I. The Antiepileptic Drug Carbamazepine." Archives of Environmental Contamination and Toxicology **49**: 353 - 361.

Onesios, K. M., J. T. Yu, et al. (2009). "Biodegradation and removal of pharmaceuticals and personal care products in treatment systems: a review." Biodegradation **20**(4): 441-466.

Orlando, E. F., Kolok, A.S., Binzcik, G.A., Gates, J.L., Horton, M.K., Lambright, C.S., Gray, L.E., Soto, A.M., Guillette, L.J. (2004). "Endocrine-disrupting effects of cattle feedlot effluent on an aquatic sentinel species, the fathead minnow." Environmental Health Perspectives **112**(3): 353 - 358.

Oros, D. R., W. M. Jarman, et al. (2003). "Surveillance for previously unmonitored organic contaminants in the San Francisco Estuary." Marine Pollution Bulletin **46**(9): 1102-1110.

Parrott, J. L., Bennie, D.T. (2009). "Life-Cycle Exposure of Fathead Minnows to a Mixture of Six Common Pharmaceuticals and Triclosan." Journal of Toxicology and Environmental Health **72**(10): 633 - 641.

Parrott, J. L. and B. R. Blunt (2005). "Life-cycle exposure of fathead minnows (Pimephales promelas) to an ethinylestradiol concentration below 1 ng/L reduces egg fertilization success and demasculinizes males." Environmental Toxicology **20**(2): 131-141.

Passinoreader, D. R., Berlin, W.H., Hickey, J.P. (1995). "Chronic Bioassays of Rainbow-Trout Fry with Compounds Representative of Contaminants in Great-Lakes Fish." Journal of Great Lakes Research **21**(3): 373 - 383.

Pérez, S., Barceló, Damià (2006). "Fate and occurrence of X-ray contrast media in the environment." Analytical and Bioanalytical Chemistry **387**: 1235 - 1246.

Petrovic, M., Barcelo, Damia Ed. (2007). Analysis, Fate and Removal of Pharmaceuticals in the Water Cycle, 50. Comprehensive Analytical Chemistry. Amsterdam, Elsevier Science.

Petrovic, M., A. Diaz, et al. (2003). "Occurrence and removal of estrogenic short-chain ethoxy nonylphenolic compounds and their halogenated derivatives during drinking water production." Environmental Science & Technology **37**(19): 4442-4448.

Poiger, T., H. R. Buser, et al. (2001). "Photodegradation of the pharmaceutical drug diclofenac in a lake: Pathway, field measurements, and mathematical modeling." Environmental Toxicology and Chemistry **20**(2): 256-263.

Radjenovic, J., M. Petrovic, et al. (2009). "Fate and distribution of pharmaceuticals in wastewater and sewage sludge of the conventional activated sludge (CAS) and advanced membrane bioreactor (MBR) treatment." Water Research **43**(3): 831-841.

Routledge, E. J., D. Sheahan, et al. (1998). "Identification of estrogenic chemicals in STW effluent. 2. In vivo responses in trout and roach." Environmental Science & Technology **32**(11): 1559-1565.

Sanderson, H., B. Laird, et al. (2007). "Assessment of the environmental fate and effects of ivermectin in aquatic mesocosms." Aquatic Toxicology **85**(4): 229-240.

Segner, H., K. Caroll, et al. (2003). "Identification of endocrine-disrupting effects in aquatic vertebrates and invertebrates: report from the European IDEA project." Ecotoxicology and Environmental Safety **54**(3): 302-314.

Simazaki, D., J. Fujiwara, et al. (2008). "Removal of selected pharmaceuticals by chlorination, coagulation-sedimentation and powdered activated carbon treatment." Water Science and Technology **58**(5): 1129-1135.

Smith, G. R. and A. A. Burgett (2005). "Effects of three organic wastewater contaminants on American toad, Bufo americanus, tadpoles." Ecotoxicology **14**(4): 477-482.

Snyder, S. A., P. Westerhoff, et al. (2003). "Pharmaceuticals, personal care products, and endocrine disruptors in water: Implications for the water industry." Environmental Engineering Science **20**(5): 449-469.

Swann, M., Blaxter KL, Field HI, Howie JW, Lucas IAM, Millar ELM, Murdoch JC, Parsons JH, White EG (1969). Report of the joint committee on the use of antimicrobials in animal husbandry and veterinary medicine, Her Majesty's Stationery Office, London, UK.

Ternes, T. (1999). "Preface - Drugs and hormones as pollutants of the aquatic environment: determination and ecotoxicological impacts." Science of the Total Environment **225**(1-2): 1-2.

Ternes, T. A. (1998). "Occurrence of drugs in German sewage treatment plants and rivers." Water Research **32**(11): 3245-3260.

Ternes, T. A., M. Meisenheimer, et al. (2002). "Removal of pharmaceuticals during drinking water treatment." Environmental Science & Technology **36**(17): 3855-3863.

Tixier, C., H. P. Singer, et al. (2003). "Occurrence and fate of carbamazepine, clofibric acid, diclofenac, ibuprofen, ketoprofen, and naproxen in surface waters." Environmental Science & Technology **37**(6): 1061-1068.

Triebskorn, R., H. Casper, et al. (2004). "Toxic effects of the non-steroidal anti-inflammatory drug diclofenac Part II. Cytological effects in liver, kidney, gills and intestine of rainbow trout (Oncorhynchus mykiss)." Aquatic Toxicology **68**(2): 151-166.

USEPA (2000). Clean Watersheds Needs Survey 2000. Washington DC, US Environmental Protection Agency, Office of Wastewater Management.
USEPA (2004). Clean Watersheds Needs Survey 2004. Washington DC, US Environmental Protection Agency, Office of Wastewater Management.
USEPA (2009a). Pharmaceuticals and Personal Care Products (PPCPs): Relevant Literature, US Environmental Protection Agency, Las Vegas, NV**:** http://www.epa.gov/ppcp/lit.html.
USEPA. (2009b). "Pharmaceuticals and Personal Care Products, Basic Information." Retrieved 10 June 2009, 2009, from http://www.epa.gov/ppcp/.
Vandenbergh, G. F., D. Adriaens, et al. (2003). "Effects of 17 alpha-ethinylestradiol on sexual development of the amphipod Hyalella azteca." Ecotoxicology and Environmental Safety **54**(2): 216-222.
Veldhoen, N., R. C. Skirrow, et al. (2006). "The bactericidal agent triclosan modulates thyroid hormone-associated gene expression and disrupts postembryonic anuran development." Aquatic Toxicology **80**(3): 217-227.
Watts, M. M., D. Pascoe, et al. (2003). "Exposure to 17 alpha-ethinylestradiol and bisphenol A-effects on larval moulting and mouthpart structure of Chironomus riparius." Ecotoxicology and Environmental Safety **54**(2): 207-215.
Westerhoff, P., Y. Yoon, et al. (2005). "Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes." Environmental Science & Technology **39**(17): 6649-6663.
Wilson, B. A., V. H. Smith, et al. (2003). "Effects of three pharmaceutical and personal care products on natural freshwater algal assemblages." Environmental Science & Technology **37**(9): 1713-1719.
Wollenberger, L., Breitholtz, Magnus, Kusk, Kresten Ole, Bengtsson, Bengt-Erik (2003). "Inhibition of larval development of the marine copepod *Acartia tonsa* by four synthetic musk substances." Science of the Total Environment **305**: 53 -64.
Wollenberger, L., B. Halling-Sorensen, et al. (2000). "Acute and chronic toxicity of veterinary antibiotics to Daphnia magna." Chemosphere **40**(7): 723-730.
Yoon, Y., P. Westerhoff, et al. (2006). "Nanofiltration and ultrafiltration of endocrine disrupting compounds, pharmaceuticals and personal care products." Journal of Membrane Science **270**(1-2): 88-100.
Yoon, Y., P. Westerhoff, et al. (2007). Removal of endocrine disrupting compounds and pharmaceuticals by nanofiltration and ultrafiltration membranes.
Yu, Z. R., S. Peldszus, et al. (2008). "Adsorption characteristics of selected pharmaceuticals and an endocrine disrupting compound - Naproxen, carbamazepine and nonylphenol - on activated carbon." Water Research **42**(12): 2873-2882.
Zhou, J. L., Z. L. Zhang, et al. (2009). "Pharmaceutical residues in wastewater treatment works effluents and their impact on receiving river water." Journal of Hazardous Materials **166**(2-3): 655-661.