Chapter 8

Environmental Emission of Pharmaceuticals from Wastewater Treatment Plants in the U.S.A.

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The residual drugs, drug bioconjugates, and their metabolites, mostly from human and veterinary usage, are routinely flushed down the drain, and enter wastewater treatment plants (WWTP). Increasing population, excessive use of allopathic medicine, continual introduction of novel drugs, and existing inefficient wastewater treatment processes result in the discharge of large volumes of pharmaceuticals and their metabolites from the WWTPs into the environment. The effluent from the WWTPs globally contaminate ~25% of rivers and the lakes. Pharmaceuticals in the environment, as contaminants of emerging concerns, behave as pseudo-persistent despite their relatively short environmental half-lives in the environment. Therefore, residual levels of pharmaceuticals in the environment not only pose a threat to the wildlife but also affect human health through contaminated food and drinking water. This chapter highlights WWTPs as point-sources of their environmental emissions and various effects on the aquatic and terrestrial ecosystem.

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Introduction

Pharmaceuticals are typically designed to retain their chemical identities long enough after administration for their targeted therapeutic action in the human body (*1*). Administered drugs are excreted as either unchanged parent drugs and/or conjugated forms (such as glucuronides and glycines) or as metabolites. Pharmaceuticals, down-the-drain contaminants of emerging concern, eventually reach wastewater treatment plants (WWTPs). Existing wastewater treatment processes are incapable of complete removal of pharmaceutical compounds (*1*, *2*); therefore, discharge of WWTP effluents and sewage sludge are considered as the point sources of environmental contamination from drugs (*3*, *4*).

There were 14,591 publicly owned WWTPs in the U.S.A. serving 226.4 million people in 2012 (*5*). In the U.S.A., thousands of prescribed and over-the-counter as well as illicit drugs are discharged annually into the environment through ~35300 million gallons of wastewater, >8 million of dry biosolids, and ~500 million tons of animal manure (*6–8*). Many different classes of pharmaceuticals including psychoactives, antihypertensives, analgesics, antibiotics as well as illicit drugs and artificial sweeteners were reported in wastewater (*1*, *9–11*), sewage sludge (*9*, *12*), receiving waters (*13*), and drinking water (*14*) in the U.S.A..

Understanding the overall fate, distribution, and short and long-term effects of environmental exposure of pharmaceuticals is important to minimize exposure and to protect the aquatic ecosystem and human health. It is particularly critical in the fast-growing southwest region of the U.S.A. where reclaimed water consumption is being commonly practiced (*15*). Pharmaceuticals in the environment have the potential to bioaccumulate (*16*); for example, a report found that the diclofenac and gemfibrozil were bioaccumulated by biofilm and aquatic invertebrates (*17*). However, very little is known about the potential ecological risks of most pharmaceuticals and their metabolites/transformed products in the environment (*18*). Pharmaceuticals discharged from WWTPs not only pose a direct ecological risk, but can also turn onto the precursors of hazardous substances. For instance, methadone forms *N*-nitrosodimethylamine, a carcinogenic disinfectant byproduct, during the drinking water treatment process (*19*). Overall, very little is known about the potential chronic effects of pharmaceutical contaminants on environmental biota and human health, particularly with the exposure to a "cocktail" of pharmaceutical contaminants (*20*). In this chapter, we discuss the occurrence and mass loading of pharmaceuticals into WWTPs, their removal, environmental emission, and their effects on ecosystems.

Mass Loading of Pharmaceuticals into the WWTPs

Wastewater Influent

Various classes of pharmaceuticals including antibiotics, analgesics, antihypertensives, illicit drugs, and psychoactives were reported at ng/L to µg/L levels that enter WWTPs (Table 1 and Figure 1) (*1*, *4*, *7*, *9–11*, *20–33*). WWTPs in the U.S.A. typically treat millions of gallons of domestic and/or industrial sewage every day (*34*); a WWTP that treats 25 MGD wastewater would daily receive milligrams to several grams of the individual pharmaceutical compounds. These statistics appear daunting when thousands of prescription, over-the-counter, illicit, veterinary drugs, their metabolites, and their conjugates enter into the WWTPs.

Pharmaceutical prioritization for the research on environmental occurrence as well as their effects on the environment and human health should subject to geographical regions, climates, demographics, and cultural backgrounds (*18*). In 2011, 262.5 million of antibiotic prescriptions were dispensed in the U.S.A., that equivalents to >5 prescriptions to every 6 people (*35*). Azithromycin, sulfamethoxazole, and trimethoprim are among the top prescribed antibiotics in the U.S.A. (*36*); and are also the most frequently detected antibiotics in wastewater (*1*, *22–25*). Sulfamethoxazole and trimethoprim were loaded at 0.71 kg/d and 0.39 kg/d, respectively, into a WWTP serving ~650,000 people in Las Vegas, NV, U.S.A. (*22*). Diphenhydramine, a first generation antiallergenic drug, was found at 530 ng/L of diphenhydramine in wastewater influent during elevated seasonal allergies in Texas, U.S.A. (*24*).

A recent large-scale study (from 50 large WWTPs from 20 states in the U.S.A. that treat ~17% of total wastewater produced in the U.S.A.) found antihypertensives and antipsychotics in wastewater more frequently at higher concentrations than other classes of prioritized pharmaceuticals (*7*). Psychoactives are among the most widely prescribed pharmaceuticals globally (*37*). In the U.S.A., the total usage of psychoactive pharmaceuticals increased from 1998 to 2008 by 78% (*38*), and were the top-selling classes of prescription medications, with $14.6 billion in sales in 2009 (*39*). Twenty-two pharmaceuticals listed in Table 1 are among the top 100 prescribed pharmaceuticals in the U.S.A. in 2011 (www.rxlist.com). A wide range of psychoactive drugs including antischizophrenics, sedatives-hypnotics-anxiolytics, and antidepressants was found in wastewater influent in the U.S.A. (Table 1). The mass loading of aripiprazole, the most prescribed drug in the U.S.A. (www.drugs.com), to a WWTP was found to be 6.46 mg/d/1000 people in NY (*9*). Alprazolam, quetiapine, sertraline, lorazepam, fluoxetine, bupropion were the top psychoactive drugs sold in the U.S.A. in 2013 (www.psycentral.com); and were found at a loading of 1.66-78.9 mg/d/1000 people in a WWTP in NY (*9*). Carbamazepine and selective serotonin reuptake inhibitors (SSRI) such as sertraline, citalopram, and fluoxetine were the most frequently detected antipsychotic drugs in wastewater in the U.S.A. (*3*, *9*, *22*, *24*, *25*, *40*). Venlafaxine was found at 0.93 µg/L in a WWTP serving 1.8 million people and ~800 industries in St. Paul, MN that equivalents to 669 g/d load of venlafaxine into a WWTP.

Table 1. Occurrence of pharmaceuticals in wastewater influent, effluent, and sludge in the U.S.A.

Analytes	*Influent*	*Effluent*	*Sludge*
	Concentration (ng/L)	*Concentration (ng/L)*	*Concentration (ng/g dw)*
Psychoactives			
Aripiprazole	5.43 (*9*), 5.58 (*9*)	1.69 (*9*), 10.3 (*9*)	16.8 (*9*), 115 (*9*)
Dehydro-aripiprazole	-	-	1.49 (*9*), 2.93 (*9*)
Quetiapine	15.5 (*9*), 24.4 (*9*)	0.98 (*9*), 4.60 (*9*)	17.7 (*9*), 21.1 (*9*)
Nor-quetiapine	66.1 (*9*), 71.0 (*9*)	74.3 (*9*), 82.3 (*9*)	133 (*9*), 196 (*9*)
Lorazepam	16.2 (*9*), 20.3 (*9*)	64.2 (*9*), 78.4 (*9*)	0.26 (*9*)
Alprazolam	5.89 (*9*), 6.24 (*9*)	4.59 (*9*), 6.20 (*9*)	0.28 (*9*), 0.61 (*9*), 1.56 (*21*)
α-hydroxy alprazolam	17.4 (*9*), 21.4 (*9*)	9.2 (*9*), 12.7 (*9*)	0.37 (*9*), 1.43 (*9*)
Diazepam	3.38 (*9*), 3.79 (*9*)	1.73 (*9*), 2.58 (*9*), 3.70 (*22*)	0.48 (*9*)
Oxydiazepam	6.52 (*9*), 8.43 (*9*)	7.72 (*9*), 9.87 (*9*)	0.86 (*9*), 1.60 (*9*)
Nordiazepam	4.04 (*9*), 5.30 (*9*)	3.69 (*9*), 4.53 (*9*)	0.96 (*9*), 1.08 (*9*)
Carbamazepine	145 (*9*), 241 (*9*), 232 (*22*), 100 (*23*) 147.5 (*24*), 137 (*25*), 115 (*26*), 102 (*27*)	310 (*9*), 268 (*9*), 187 (*22*), 65 (*23*), 119.5 (*28*), 156 (*25*), 97 (*7*), 21.3 (*26*), 175 (*27*)	83.1 (*9*), 118 (*9*), 66.5 (*26*)
Sertraline	43.1 (*9*), 80.8 (*9*), 60 (*4*)	82.8 (*9*), 24.5 (*9*), 55.2 (*4*), 21 (*7*)	862 (*9*), 1490 (*9*), 458 (*21*)
Norsertraline	65.3 (*9*), 71.1 (*9*), 14.3 (*4*)	54.4 (*9*), 16.4 (*9*), 37.5 (*4*), 9.9 (*7*)	394 (*9*), 688 (*9*)
Venlafaxine	336 (*9*), 415 (*9*), 930 (*4*)	480 (*9*), 339 (*9*), 873 (*4*)	84.2 (*9*), 129 (*9*)
Bupropion	110 (*9*), 147 (*9*), 72.5 (*4*)	67.4 (*9*), 34.1 (*9*), 221 (*4*)	12.5 (*9*), 23.7 (*9*)

Analytes	*Influent*	*Effluent*	*Sludge*
	Concentration (ng/L)	*Concentration (ng/L)*	*Concentration (ng/g dw)*
Citalopram	59.4 (*9*), 133 (*9*), 78.9 (*4*)	280 (*9*), 150 (*9*), 125 (*4*)	170 (*9*), 283 (*9*)
Desacetyl citalopram	12.8 (*9*), 55.4 (*9*)	79.3 (*9*), 118 (*9*)	130 (*9*), 222 (*9*)
Paroxetine	10.5 (*4*)	15.8 (*4*)	41.6 (*21*)
Fluoxetine	27.1 (*4*), 17 (*22*), 600 (*23*),	45.3 (*4*), 25 (*22*), 560 (*23*), 8.6 (*7*), 20 (*27*), 60 (*29*), 56 (*29*)	-
Norfluoxetine	14.2 (*4*), 9.9 (*22*)	13.6 (*4*), 3.9 (*22*), 7.1 (*7*), 20 (*29*), 26 (*29*)	-
Anti-hypertensions			
Atenolol	1220 (*9*), 606 (*9*), 3060 (*22*), 1172.5 (*24*)	594 (*9*), 426 (*9*), 879 (*22*), 940 (*7*), 281 (*27*)	23.0 (*9*), 27.6 (*9*)
Propranolol	24.5 (*9*), 24.1 (*9*), 7.5 (*24*)	74.2 (*9*), 82.2 (*9*), 33 (*7*)	83.3 (*9*), 49.7 (*9*), 107.4 (*21*)
Diltiazem	105 (*9*), 168 (*9*), 1019.4 (*24*)	194 (*9*), 53 (*23*), 85 (*7*)	48.5 (*9*), 61.9 (*9*)
Desacetyl diltiazem	473 (*9*), 483 (*9*)	294 (*9*), 327 (*9*)	84.9 (*9*), 179 (*9*), 7.4 (*21*)
Verapamil	7.30 (*9*), 18.5 (*9*)	38.5 (*9*), 49.2 (*23*), 26 (*7*)	218 (*9*), 170 (*9*), 551.4 (*21*)
Nor-verapamil	8.88 (*9*), 14.8 (*9*)	8.29 (*9*), 20.3 (*9*), 5.8 (*7*)	385 (*9*), 175 (*9*), 458 (*21*)
Analgesics			
Hydrocodone	70 (*9*), 130 (*30*), 210 (*30*), 13 (*30*), 80 (*30*), 14 (*30*), 30 (*30*),	8.6 (*23*), 22 (*7*), 910 (*20*), 330 (*20*)	21.7 (*21*)
Oxycodone	80 (*30*), 210 (*30*), 58 (*30*), 15 (*30*), 220 (*30*), 29 (*30*)	53 (*7*)	157 (*21*)

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Table 1. (Continued). Occurrence of pharmaceuticals in wastewater influent, effluent, and sludge in the U.S.A.

Analytes	*Influent*	*Effluent*	*Sludge*
	Concentration (ng/L)	*Concentration (ng/L)*	*Concentration (ng/g dw)*
Diclofenac	116 (*22*), 104.75 (*24*), 277 (*22*), 83 (*27*)	12 (*26*), 83 (*27*)	48.4 (*26*)
Naproxen	22500 (*22*), 35700 (*22*), 11772 (*27*)	30.0 (*26*), 13 (*27*)	19.1 (*26*)
Acetaminophen	6100 (*23*), 18775 (*24*), 45726 (*27*), 99498 (*29*), 113281 (*29*)	860 (*23*), 79 (*7*), 354 (*29*), 152 (*29*)	-
Ibuprofen	22300 (*26*), 13481 (*27*), 24317 (*29*), 24033 (*29*)	460 (*7*), 55.8 (*22*), 9 (*27*), 928 (*29*), 2600 (*29*)	109 (*22*)
Codeine	170 (*23*), 205 (*24*)	170 (*23*)	
Antihistamine			
Diphenhydramine	462 (*9*), 227 (*9*), 367.5 (*24*)	194 (*9*), 85.7 (*9*), 588.8 (*28*)	293 (*9*), 444 (*9*)
2-(diphenylmethoxy) acetic acid	3.70 (*9*), 3.79 (*9*)	4.14 (*9*), 4.50 (*9*)	-
Antiplatelet			
Clopidogrel	31.4 (*9*), 35.5 (*9*)	21.8 (*9*), 23.7 (*9*)	29.0 (*9*), 31.4 (*9*)
Clopidogrel carboxylic acid	124 (*9*), 160 (*9*)	116 (*9*), 194 (*9*)	2.26 (*9*), 3.24 (*9*)
Anticholesterolemic			
Gemfibrozil	4770 (*22*), 1500 (*24*), 934 (*25*), 4670 (*25*), 791 (*27*)	9.0 (*22*), 41 (*25*), 420 (*7*), 151 (*26*)	93.3 (*26*)
Anti-biotics			

Analytes	*Influent*	*Effluent*	*Sludge*
	Concentration (ng/L)	*Concentration (ng/L)*	*Concentration (ng/g dw)*
Sulfamethoxazole	2060 (*22*), 360 (*23*), 2625 (*24*), 1786 (*25*), 2252 (*27*)	5.0 (*22*), 140 (*23*), 141.4 (*28*), 304 (*25*), 910 (*7*), 313 (*27*)	-
Trimethoprim	1140 (*22*), 300 (*23*), 417.5 (*24*), 913 (*27*)	120 (*23*), 170 (*7*), 115 (*27*)	-
Azithromycin	28.2 (*1*)	690.4 (*28*), 15 (*31*), 66 (*32*), 17 (*25*), 56 (*7*), 20.2 (*1*), 510 (*20*), 150 (*20*), 1416 (*20*), 560 (*20*)	-
Illicit Drugs			
Cocaine	74.2 (*10*), 77.6 (*10*), 35 (*30*), 230 (*30*), 56 (*30*), 66 (*30*), 72 (*30*), 10 (*30*), 860 (*30*), 769 (*32*)	1.75 (*10*)	3.6 (*21*), 1.7 (*10*), 4.48 (*10*)
Benzoylecgonine	6100,(33) 71023 (*10*), 1793 (*10*), 2800 (*30*), 2100 (*30*), 370 (*30*), 620 (*30*), 420 (*30*), 110 (*30*), 1500 (*30*), 1573 (*32*)	98.1 (*10*), 18.5 (*10*)	1.05 (*10*)
Norcocaine	2.92 (*10*), 5.64 (*10*), 15 (*30*), 9 (*30*), 4 (*30*), 50 (*30*), 17.9 (*32*)	1.02 (*10*), 5.07 (*10*)	-
Cocaethylene	3.94 (*10*), 4.84 (*10*)	-	-
Amphetamine	92.3 (*10*), 92.1 (*10*), 220 (*30*), 550 (*30*), 80 (*30*), 120 (*30*), 250 (*30*), 90 (*30*), 130 (*30*), 309 (*32*)	3.5 (*7*)	-

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Table 1. (Continued). Occurrence of pharmaceuticals in wastewater influent, effluent, and sludge in the U.S.A.

Analytes	*Influent*	*Effluent*	*Sludge*
	Concentration (ng/L)	*Concentration (ng/L)*	*Concentration (ng/g dw)*
Methamphetamine	3.82 (*10*), 6.22 (*10*), 920 (*30*), 2000 (*30*), 10 (*30*), 920 (*30*), 150 (*30*), 1494 (*32*), 25.3 (*1*)	350.1 (*28*), 4.98 (*10*), 22.3 (*10*), 13 (*31*), 0.8 (*32*), 355 (*20*), 230 (*20*), 270 (*20*), 227 (*20*), 318 (*20*), 190 (*20*), 570 (*20*), 110 (*20*)	-
Morphine	158 (*10*), 203 (*10*), 647 (*32*)	33.9 (*10*)	18.4 (*10*), 21.6 (*10*)
Methadone	5.41 (*10*), 20.6 (*10*), 33 (*30*), 59 (*30*), 4.9 (*30*), 16 (*30*), 62 (*30*), 14 (*30*), 47 (*30*)	17.3 (*10*), 18.2 (*10*)	13.9 (*10*), 20.3 (*10*)
EDDP	22.6 (*10*), 45.6 (*10*)	38.2 (*10*), 110 (*10*)	21.5 (*10*), 49.8 (*10*)
MDMA	10.1 (*10*), 25.4 (*10*), 70 (*30*), 30 (*30*), 2.7 (*30*), 10 (*30*), 3.5 (*30*), 185 (*32*)	2.88 (*10*), 23.2 (*10*), 0.5 (*31*), 96 (*20*)	3.95 (*10*)
MDEA	2.33 (*10*), 3.29 (*10*)	0.27 (*10*), 1.12 (*10*)	0.68 (*10*)
MDA	118 (*10*), 491 (*10*), 6 (*30*), 2 (*30*), 7 (*30*), 45.5 (*32*)	12.8 (*10*), 34.4 (*10*)	23.2 (*10*), 42.4 (*10*)
Artificial Sweeteners			
Sucralose	47500 (*24*), 33000 (*11*), 25900 (*11*)	20500 (*11*), 38800 (*11*)	423 (*11*), 651 (*11*)
Saccharin	13800 (*11*), 16400 (*11*)	420 (*11*), 2340 (*11*)	180 (*11*), 286 (*11*)
Aspartame	80 (*11*), 180 (*11*)	80 (*11*), 140 (*11*)	80 (*11*), 448 (*11*)
Acesulfame	920 (*11*), 1230 (*11*)	1520 (*11*), 2140 (*11*)	117 (*11*), 119 (*11*)
Stimulants			

Analytes	*Influent*	*Effluent*	*Sludge*
	Concentration (ng/L)	*Concentration (ng/L)*	*Concentration (ng/g dw)*
Caffeine	42000 (*23*), 27700 (*10*), 26900 (*10*), 5700 (*30*), 120000 (*30*), 14979 (*27*), 66400 (*29*), 82882 (*29*)	15200 (*23*), 535.3 (*28*), 37.9 (*10*), 129 (*10*)	-
Paraxanthine	55000 (*23*),14700 (*10*), 9650 (*10*)	25000 (*23*), 112 (*28*), 39.4 (*10*), 16.4 (*10*)	-
Nicotine	17000 (*23*), 3670 (*10*), 3800 (*10*), 1177 (*27*)	21000 (*23*), 27.5 (*10*), 19.6 (*10*)	-
Cotinine	1980 (*10*),1430 (*10*), 2000 (*30*), 2700 (*30*), 1461 (*29*)	14.1 (*10*), 34 (*10*)	-

In a WWTP Murray, KY serving 15100 people and treats 5 MGD (*1*)*; In a WWTP in St. Paul, MN serving 1.8 M people and ~800 industries* (*4*)*; In 50 WWTPs from 20 States across the U.S.A. served over 46 M people and treats 6000 MGD* (*7*)*; In In 2 WWTPs in Albany, NY serving 15,000 and 100,000 people* (*9*)*; In 2 WWTPs in Albany, NY serving 15,000 and 100,000 people* (*10*)*; In 2 WWTPs in Albany, NY serving 15,000 and 100,000 people* (*11*)*; In 10 WWTPs in AZ, CO, NV, and UT* (*20*)*; In 94 WWTPs from 32 states and the DC under USEPA's National Sewage Sludge Survey Program* (*21*)*; In a WWTPs in Las Vegas, NV serving 650,000 people and treats 91 MGD* (*22*)*; In a WWTP in Jamaica Bay, NY that treats 81 MGD* (*23*)*; In a WWTP in Waco, TX serving ~100,000 people and treats ~25 MGD wastewater inflow* (*24*)*; In 3 WWTPs in Mississippi serving 26000 to 299000 people and treats 3.5-47 MGD* (*25*)*; In 5 WWTPs in Southern California serving 100000-195000 people and treat 42-68 MGD* (*26*)*; In 2 WWTPs in Southeast U.S.A. 100000-195000 people and treat 20 and 36 MGD* (*27*)*; In a WWTP in Omaha, NE serving population of 419,545 and treats 27.2 MGD wastewater inflow* (*28*)*; In 2 WWTPs in Charleston, SC treating 20 and 5.1 MGD* (*29*)*; In 7 WWTPs across the U.S.A. serving population ranged from 27300 to 841000* (*30*)*; In 3 WWTPs in NV, UT, and SC* (*31*)*; In a WWTP serving ~1,000,000 people and treats 100 MGD* (*32*)*; In a reclamation plant in Lubbock, TX serving 269,140 people and treats ~21 MGD wastewater inflow* (*33*)*.*

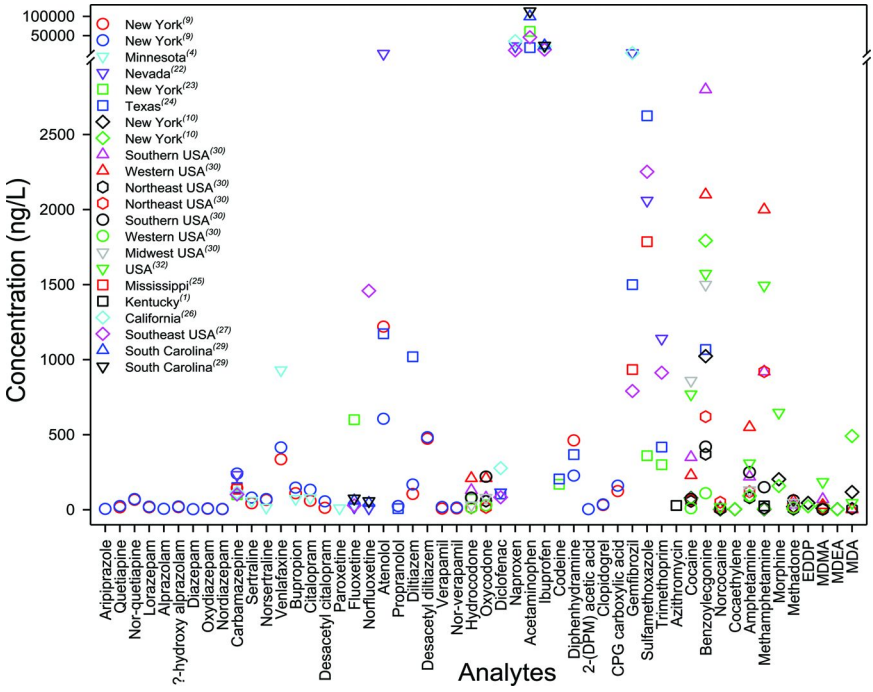

Figure 1. Concentration of pharmaceuticals and their select metabolites in wastewater influents from the WWTPs in the U.S.A.

The regional distribution patterns of the select pharmaceuticals are different in the U.S.A. (*41*). Despite the relatively higher usage of oxycodone in the Northeast and that of hydrocodone in the Midwest, South, and the Western U.S.A. among major narcotic analgesics (*41*); Chiaia et al. (*30*) reported higher concentrations of oxycodone than hydrocodone across the U.S.A.. The usage and availability of analgesics in prescription and over-the-counter forms are increasing; aggregate production quotas of hydrocodone and oxycodone in the U.S.A. was increased by ~300% to ~90,000 kg and ~55,000 kg, respectively, from 2000 to 2010 (*42*). Acetaminophen was reported highest (61.0 µg/L) in wastewater influent from a WWTP in NY that treats 81 MGD (*23*) that is equivalent to a mass loading of 18.7 kg/d of acetaminophen into the WWTP. Similarly, 7.75 kg/d mass loading of naproxen into a municipal WWTP serving ~650,000 people in Las Vegas, NV, U.S.A. was found (*22*). The hydrocodone-acetaminophen combination medication was not only the most frequent opioid analgesic prescribed in the United States but was also the overall top prescribed drug with 3995.2 million prescriptions being dispensed in 2010 (*43*).

The United Nations Office on Drugs and Crime (UNODC) estimated that there were over 165-315 million illicit-drug users globally (*44*); and 9.4% of the population ≥12 years of age used illicit drugs in the U.S.A. in 2013 (*45*).

Cocaine is one of the major illicit drugs second only to cannabis in the U.S.A.; and 94 tons of cocaine (~10.5% of the total global production) seizures were reported in 2011 (*44*). Cocaine was found in 93% of wastewater influent samples (*10*). Individual illicit drugs including cocaine, methamphetamine, morphine, methadone, MDMA, and their metabolites were loaded at 0.07 to 149 g/d into the WWTPs in NY (serving ~100,000 people). Subedi and Kannan (*10*) also utilized the concentrations of illicit drugs in influent, so-called sewage epidemiology, to estimate community usage of illicit drugs. The consumption rate of illicit drugs in Albany, NY ranged from 1.67 to 3510 mg/d/1000 people. An estimate of daily consumption of cocaine in Lubbock, TX was 1152 ± 147 g; young adults (15-34 years) alone consume 13.1 ± 1.7 g/d/1000 individuals in Lubbock, TX (*33*). Methamphetamine users in the U.S.A. increased by 68.6% to 595,000 users from 2010 to 2013 (*45*); and several studies reported methamphetamine in influent across the U.S.A. (*1*, *10*, *25*, *30*).

With the availability of isotopically labeled standards of parent drugs and their metabolites, as well as the recent analytical improvements capable of simultaneous analysis of pharmaceuticals and their metabolites, fate studies are increasingly determining metabolites along with their parent analogs. The ratio of degradates/metabolites to their parent compounds in wastewater can provide additional sources of contaminants. For instance, the metabolite to parent drug ratio for sertraline and fluoxetine of <1 in influent suggested either direct disposal of unused parent drug in wastewater or transformation/degradation of conjugated forms of drug into their parent drug during wastewater treatment process (*3*, *4*). Moreover, drug metabolites such as norfluoxetine are as pharmacologically active as the parent fluoxetine. The concentration of clopidogrel carboxylic acid, a metabolite of clopidogrel, was ~4 times higher than its parent drug (*9*) and methadone in influent was ~3 times lower than its metabolite [(2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)] (*10*). The overall concentrations of a parent drug and its transformed product/metabolite provide a better estimate of the total mass loading of a drug into the WWTPs.

It is also important to recognize potential seasonal variations of pharmaceutical loading into the WWTP for the evaluation of wastewater treatment process and overall performance of WWTPs. For example, a load of antipyretics such as ibuprofen can be higher in winter while that of an antihistamine such as diphenhydramine can be relatively higher in summer due to their increased usage in respective seasons (*7*). Cocaine consumption on weekends was found higher than on weekdays while monitoring a reclamation plant for a 5-month period in Lubbock, TX using sewage epidemiology (*33*). Moreover, special events in WWTP network coverage such as sporting events can increase the mass loading of prescribed and illicit drugs into the WWTPs (*32*).

Suspended Particulate Matter

Very few studies of the fate of pharmaceuticals in WWTPs have incorporated the pharmaceutical concentrations in suspended particulate matter (SPM) to estimate the mass loading of pharmaceuticals into the WWTPs in the U.S.A. (*9–11*). The available literature estimated the mass loading only based on the

dissolved fraction of pharmaceuticals; which can be near an accurate mass loading of the highly water soluble pharmaceuticals to the WWTPs. However, select parent drugs and their metabolites having a relatively higher organic carbon-water partitioning coefficient (*K*oc) can significantly partition onto SPM. For example, the estimation of a mass loading of methadone based only on the aqueous concentration of methadone and its metabolite (EDDP*;* log *K*oc = 5.673) in wastewater can underestimate the total methadone loading by 40% (*10*). Similarly, a ~50.4% mass loading of aspartame to the WWTP was found to sorb in SPM unlike sucralose, saccharin, and acesulfame, which have >90% of their mass loading in filtered wastewater (*11*).

Removal of Pharmaceuticals from WWTPs

Wastewater treatment processes in the U.S.A. typically is comprised of preliminary treatment (screening and grit removal), primary treatment (sedimentation), and secondary treatment (biological treatments using activated sludge/trickling filters/facultative lagoon). Secondary treatment is a national standard of the U.S.A. to discharge treated wastewater to surface water (*46*). While conventional activated sludge (CAS) is the most common biological treatment system in use, advanced or tertiary treatment may be required at specific sites to comply with the regulations set to protect human health and the ecosystem. The dominant mechanism of removal of pharmaceuticals having higher sorption coefficient (K_d > 300 kg L^{-1}) is the adsorption to sludge whereas more acidic drugs including most of the pharmaceutical metabolites undergo biodegradation (*47*). The removal of pharmaceutical from WWTPs depends on the physiochemical properties of the drug, treatment process, capacity, microbial environment, season (temperature), precipitation, pH, etc. However, the removal of pharmaceuticals from WWTPs is barely complete with the existing conventional wastewater treatments in use despite the multi-step treatments (*2*).

Overall, inconsistent removal efficiencies of most of the pharmaceuticals were reported from the WWTPs in the U.S.A. (Figure 2) (*1*, *4*, *9*, *23*, *25–27*, *29*). Select psychoactives such as venlafaxine, fluoxetine, citalopram, carbamazepine, alprazolam, and lorazepam had very low (usually <25%) removal from WWTPs (*4*, *9*). Complex removal mechanisms during wastewater treatment can be responsible for no or negative removal of select pharmaceuticals such as deconjugation of carbamazepine glucuronide (*48*), deconjugation of morphine glucuronide (*10*), and polyhalogenated structural rigidity of sucralose (*11*, *24*). Unlike psychoactives, analgesics such as hydrocodone, diclofenac, naproxen, acetaminophen, and ibuprofen were significantly (57-100%) removed from WWTPs employing CAS in the U.S.A. (*22*, *23*, *26*, *27*, *29*). Azithromycin was barely removed from a WWTP in KY(*1*) but 60-100% mass loading of sulfamethoxazole and trimethoprim were removed from WWTPs in different states in the U.S.A. (*22*, *23*, *25*, *27*). Similarly, ~70-90% mass loading of cocaine, benzoylecgonine, amphetamine, and MDA were removed from WWTPs in NY while methamphetamine and methadone had negative WWTP removal (*10*).

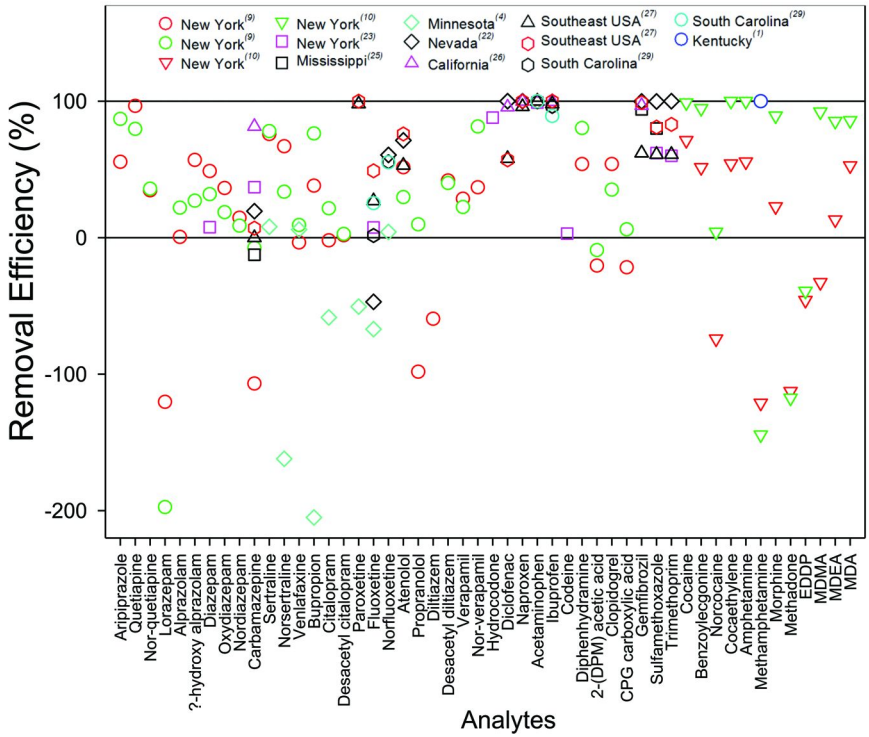

Figure 2. Removal efficiency of pharmaceuticals from WWTPs in the U.S.A.

Environmental Emission of Pharmaceuticals from WWTPs

Wastewater Effluent

Treated wastewater effluent is a point source of pharmaceuticals into the aquatic environment (*3*, *4*). Typically, the effluent discharge is a "cocktail" of unchanged parent drugs, metabolites, their conjugates, and potentially several other WWTP-derived transformed products (Table 1, Figure 3) (*1*, *4*, *7*, *9*, *10*, *20*, *22*, *23*, *25–29*, *31*, *32*). Pharmaceutical discharge into the environment was apparent as early as 1977 when 28.69 kg of salicylic acid was reported to discharge daily to the Missouri River in Kansas City through wastewater effluent from a WWTP that served 600,000 people treating 300 MLD wastewater (*49*). After more than two decades, ng/L to µg/L levels of psychoactives, antihypertensives, antibiotics, analgesics, and their select metabolites are reported in 139 sewage-impacted streams in 32 states in the U.S.A. (*13*). Above-mentioned pharmaceuticals were also found at ng/L in Boulder Basin of Lake Mead, a source of drinking water for the Las Vegas Metropolitan area (*22*) and in 19 drinking water utilities across the U.S.A. (*14*). Once discharged into the environment, pharmaceuticals can be transported significantly long distances

in surface water (*3*); venlafaxine was found as high as 102 ng/L even at 8.4 km downstream from a single-source effluent-impacted streams. Recently, several pharmaceuticals including carbamazepine, atenolol, sulfamethoxazole, diphenhydramine, gemfibrozil, and cocaine, were found in near shore sites of San Francisco Bay, CA (*50*) and Muir Beach to Monterey Bay, U.S.A. (*51*).

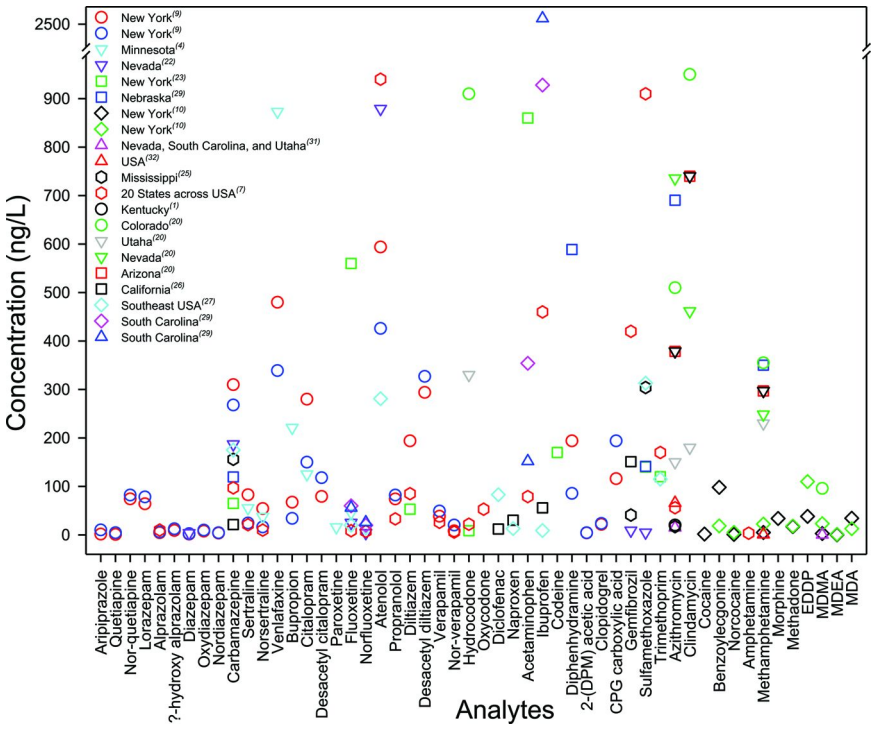

Figure 3. Concentration of pharmaceuticals and their select metabolites in wastewater effluents from the WWTPs in the U.S.A.

Psychoactives and antihypertensives were the most frequently detected among 63 pharmaceuticals at highest concentrations in effluents from 50 large WWTPs across the U.S.A. (*7*). Total discharge of 16 psychoactive pharmaceuticals and their select metabolites from a WWTP in Albany, NY was found at 1542 mg/d/1000 inhabitants, which is equivalent to an annual discharge of 56.3 kg psychoactives into the river (*9*). Annual discharge of azithromycin and methamphetamine from a WWTP to receiving water in Nevada was 1-4 kg and 0.05-0.11 kg, respectively, whereas that of MDMA in South Carolina was 0.02 kg (*31*). However, 6.5 kg of illicit drugs including cocaine, methamphetamine, morphine, methadone, MDMA, and their metabolites were discharged into the river from a WWTP in NY (*10*). The pharmaceutical discharge through wastewater effluent also varies with the seasons, similar to that was described

earlier for influent. The concentrations of pharmaceuticals in effluent during winter can be higher than in summer due to relatively higher human-consumption of drugs and inefficient biodegradation of drugs in winter (*26*).

Wastewater contamination in the environment has shown to be traceable with select chemical tracers. Chemical traceability of wastewater contamination depends on its dynamic reserve (i.e. the ratio between highest measured concentration and its method detection limit) and the detection frequency. High dynamic reserve and detection frequency of contaminants qualify for the contaminant's stability and potential of being detected under highly diluted conditions (*9*). Due to their ubiquitous occurrence and persistence, sucralose (*52*), acesulfame (*53*), and caffeine (*54*) were used as chemical tracers of wastewater contamination. Benotti et al. (*14*) also suggested atenolol and trimethoprim as indicator compounds for wastewater contamination and to estimate the efficacy of wastewater treatment.

Sewage Sludge

About 6.5 million metric tons of dry sewage sludge is produced annually in the U.S.A., and >60% of treated sewage sludge is applied to land in the U.S.A. in 2004 (*55*). The US EPA also estimated that ~0.1% of agricultural land in the U.S.A. is annually applied with biosolids (*56*). The U.S.A. regulates the use or disposal of sewage sludge through the Code of Federal Regulation Title 40, Part 503; the US EPA currently has establishes regulatory limits for select toxic chemical contaminants; however, limits are not yet established for pharmaceuticals. Pharmaceuticals were the dominant class of organics determined, second to alkylphenols and their ethoxylates, in National Sewage Sludge Repository samples that encompassed digested municipal sewage samples from 164 WWTPs across the U.S.A. (*57*). More frequent large-scale screening to identify and prioritize the potential toxic pharmaceuticals is warranted. In a nationwide study determining pharmaceuticals in composite biosolid samples from 94 WWTPs in 32 States and the District of Columbia in the U.S.A. (Figure 4), it was estimated that 210-250 tons of 72 pharmaceuticals including psychoactives, antihypertensives, and antibiotics reside annually in US soils from biosolids land application (*12*).

Select pharmaceuticals and their metabolites preferentially adsorb onto the sludge, which depends primarily on their organic carbon-water partitioning coefficient (K_{oc}) values. The environmental discharge of sertraline, nor-sertraline (a metabolite of sertraline), verapamil, and norverapamil through sewage sludge was significantly higher than other psychoactives and antihypertensives (*9*). However, the partitioning kinetics can vary with seasons; antibiotics' partitioning was higher in winter and lowest in autumn (*58*).

Previously the fraction of contaminants partitioned into sewage sludge was considered as "removed"; however, contaminants cannot be considered "removed" unless eliminated from treated sludge prior to their discharge or land-application (*37*). Pharmaceuticals can be bioavailable in the soil for an extended period after sludge application; norfluoxetine was measured at 0.29-0.32 mg/kg dw in the top soil after 8 months of sludge application (*59*). In fact,

many studies report the uptake of sludge-derived contaminants by plants (*60*) and soil-dwelling organisms (*6*). Nevertheless, the discharged pharmaceuticals can be deposited at the bed-sediments (*3*) or bioaccumulated by the aquatic organism (*16*, *61*, *62*).

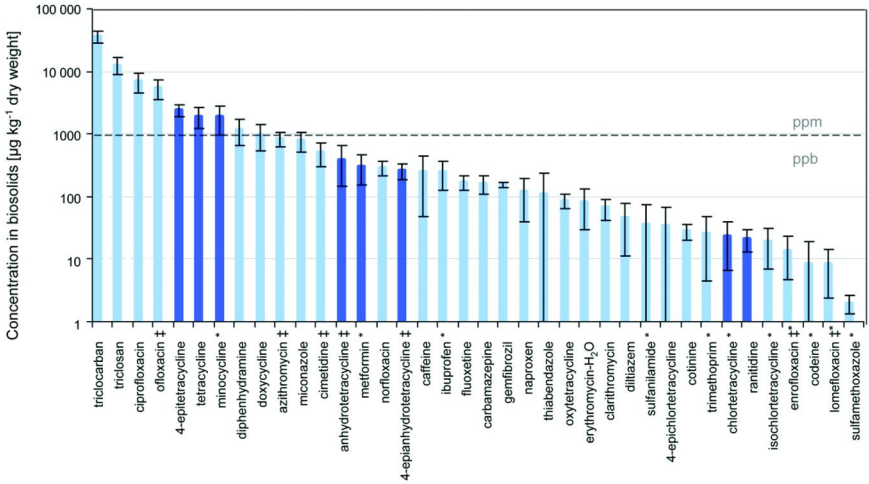

Figure 4. Rank order of Mean concentrations of Pharmaceuticals in composites of a total of 110 biosolid samples from 94 WWTPs in 32 States and the District of Columbia in the U.S.A. Newly detected pharmaceuticals are shown in darker hue. (Reproduced with permission from Ref. (12): Copyright 2010 Elsevier).

Effect of Pharmaceuticals in Environment

Pharmaceuticals in the environment are relatively short-lived compared to classic persistent organic pollutants; however, daily used of pharmaceuticals and our modern sanitary practices result in their continual discharge into the environment, making pharmaceuticals pseudo-persistent contaminants in the environment (*2*). Therefore, aquatic organisms are exposed over their lifetime to a "cocktail" of discharged pharmaceuticals, their conjugates, and metabolites. Pharmaceuticals have been shown to accumulate in lettuce (*Lactuca sativa*) (*63*), periphyton and snails (*64*), in mussels (*65*), fish tissues (*61*), and sharks (*66*).

Toxicological consequences of chronic exposure of a pharmaceutical blend in the environment are likely more appropriate to consider but have not been implicit yet (*14*). However, low-level exposure to an individual drug over time has caused physiological and behavioral alternations. For example, venlafaxine, one of the depressants found at µg/L levels in the environment, significantly decreased serotonin concentration in the fish brain (*67*). Similarly, diazepam altered the swimming behavior of zebrafish embryos exposed to 235 ng/L for 14 days (*68*), while reproductive behavior was not significantly altered by exposure

of fathead minnow to as high concentration as 13 μg/L. Nevertheless, the effective environmental effect can be substantial if organisms exposed to multiple pharmaceuticals with the same modes of action are present in the ecosystem (*2*).

Typically, risk quotient (RQ), the ratio between the concentration of pharmaceutical and its predicted no-effect concentration (PNEC), is used to determine the potential risk associated with the environmental occurrence (*69*). A significant ecotoxicological risk (RQ >1) to human health was reported from a psychoactive in sewage sludge (*26*), from antibiotics, analgesics, and antihypertensives in digested sludge (*69*), and antibiotics in digested sludge-amended soil (*12*). Alternatively, the ecological risk associated with the pharmaceutical exposure in the environment can be estimated by comparing the effluent concentration of drugs with minimum therapeutic daily dose rate (Dd_{min}) or free plasma concentration after therapeutic dose (C_{max}). The effluent concentrations of all 43 individual pharmaceuticals detected from 50 large WWTPs across the U.S.A. were well below their Dd_{min} (*7*). The ratio of the effluent concentration to the corresponding C_{max} was <0.1; however, sertraline (0.71), propranolol (0.65), and valsartan (0.18) levels suggested the immediate risks to the fish and other aquatic organisms.

In addition to direct ecological risk, the potential of antibiotic residues in the environment to emerge as human pathogens resistant to specific antibiotics has recently been considered a global concern. The global consumption of antibiotics has increased >30% from 2000 to 2010; the U.S.A. annually produces >50,000,000 lbs of antibiotics that are extensively used in human therapy and veterinary (*70*). Survival of the fittest at the bacterial level of antibiotic-resistant bacteria (ARBs) depends on the volume of antibiotics used and the patterns of infectious disease. In the U.S.A., antibiotic resistance annually causes 2 million infections and 23,000 deaths that cost $20 billion in direct health care and $35 billion of productivity loss (*70*, *71*). In the U.S.A., antibiotics are frequently detected in wastewater effluent (*72*) and surface water at ng/L to μg/L levels; and antibiotics at these concentrations in the environment were reported to influence the proliferation of ARBs in the environment (*73*). Moreover, the biological treatment during wastewater treatment can even increase the ARBs and antibiotic-resistant genes (ARGs), which are eventually discharged into the surface water (*12*). A recent study showed that the ARGs in the river were significantly correlated with upstream capacities of WWTPs (*73*). In addition, pharmaceuticals in the environment not only pose an immediate ecological risk but can also transform into more toxic substances. For example, methadone can form a carcinogenic disinfectant byproduct, *N*-nitrosodimethylamine, during the drinking water treatment process (*19*).

Insights and Future Perspectives

Despite thousands of drugs on the market and >30 new drugs annually approved by US FDA, very few (~100) pharmaceutical contaminants are reported in the U.S.A.. Some of the most prescribed and sold classes of drugs in the U.S.A. such as anticholesterols, bronchodilators, proton pump inhibitors

Loganathan et al.; Persistent Organic Chemicals in the Environment: Status and Trends in the Pacific Basin Countries II ...
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were scarcely reported in the environment. Therefore, the fate studies of a diverse class of prescribed drugs, illicit drugs, and designer drugs as well as their environmental emission are critical. As discussed earlier, mass loading calculations should incorporate the fraction of drugs in SPM while the estimation of environmental emission should incorporate the fraction partitioned on sewage sludge. It is particularly important for the pharmaceuticals having relatively higher solid-liquid partitioning coefficients. Similarly, the mass loading of pharmaceutical metabolites into the WWTPs can be as high as their parent drugs while the environmental emission of metabolites of select drugs from WWTPs has been found more than their parent drugs (*9*, *10*, *37*). In addition, biochemical degradation of pharmaceuticals during wastewater treatment process should not always be considered as "removal" since they can be transformed into the hazardous products and/or still have enough biochemical activity to pose ecological toxicity.

On another hand, pharmaceutical prioritization for the fate and toxicological investigation should depend on regional usage patterns, sewage treatment strategies, and the drug's potential toxicological effects in the environment. For instance, the number of *Klebsiella pneumoniae*, antibacterial-resistant bacteria, infections was increased ~10% from 2008 to 2014 in the U.S.A. while increasing ~100% in India (*74*), where ~67% patients purchase medication without a prescription and ~70% of the total sewage produced is discharged into the environment without any treatment (*75*). The U.S. Food and Drug Administration implementing the voluntary plan with industries to phase out concerned antibiotics in the U.S.A. (*76*), however, the need-based administration, recycling unused drugs, and development of next-generation antibacterial drugs are inevitable.

There are very few reports on environmental contamination from pharmaceuticals discharged from on-site wastewater treatment (septic) systems despite 25% of the U.S. population being served by the septic systems (*77*, *78*). Therefore, more investigations on pharmaceutical contamination from septic systems would reveal their effects in suburban and rural areas. The potential of pharmaceuticals and illicit drugs to contaminate the sources of drinking water, as well as their potential of escaping degradation during drinking water treatment process should be addressed.

There are increasing reports of acute aquatic toxicity from the exposure of residual levels of pharmaceuticals in the environment (*16*, *78*); however, the chronic aquatic toxicity and the mechanism-of-action based toxicity studies are rarely available. The aquatic organism is continually exposed not only to an environmental cocktail of diverse pharmaceuticals but also to a diverse group of persistent contaminants. Potential different modes of efficacy including synergism can exist and would assist to evaluate the mechanism-of-action as well as mode-of-action based aquatic toxicity. Further evaluation of toxicity associated with the uptake of WWTP-derived pharmaceuticals from biosolids-applied farmland is warranted since ~2/3 of the total sewage sludge produced is applied to farmland in the U.S.A..

Overall, the need for a sustainable solution is becoming increasingly critical and one of the important challenges of the 21st century, that could somehow address the environmental contamination by pharmaceuticals and their health

effects in wildlife and humans. Sustainable solutions for this global problem require innovative research in this area, that necessitates ample resources including research funding. Federal and pharmaceutical agencies may consider funding for novel and innovative ideas that have potential to provide sustainable and global solutions.

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