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Pharmaceuticals in the Surface Water of the USA: A Review

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Abstract This review investigates the occurrence of pharmaceuticals in the surface waters (including rivers, lakes, oceans, and aquifers) of the USA, discusses various pathways of pharmaceutical contamination from different point sources, assesses the potential risk of pharmaceutical contamination for aquatic organisms, and provides a discussion on the opportunities for a sustainable management of pharmaceutical contamination. We found a total of 93 pharmaceuticals that have been reported to contaminate the surface water, including: 27 antibiotics; 15 antidepressants; 9 antihypertensives; 7 analgesics; 7 anticonvulsants; 6 antilipidemics; 3 contraceptives; 3 stimulants; and 2 each of antihistamines, blood thinners, disinfectants, antacids, antitussives, anti-anxiety, anti-inflammatory, and diuretic agents. The pharmaceuticals that are assessed to be at high risk (risk quotient RQ ≥1.0) include acetaminophen (analgesic), caffeine (stimulant), sulfadimethoxine (antibiotic), as well as triclocarban and triclosan (both used in disinfectants). Such drugs require detailed evaluation as to the frequency of their occurrence and the risks for aquatic organisms and humans. Opportunities for sustainable control of pharmaceutical contamination include source control (proper disposal of leftover pharmaceuticals; careful monitoring of hospital wastes), and improvements to treatment facilities for the efficient removal and safe transformation of pharmaceutical contaminants.

Keywords Risk assessment · Surface water · Biosolids · Pharmaceuticals · Review · Antibiotics · Effluents · Fate · Antibiotics · Antidepressants · Contraceptives · Disinfectants · Sustainable · Management

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Introduction

A significant volume of pharmaceuticals are used by humans for the treatment of diseases, injuries, or illnesses, in addition to their use as personal care products [1]. At the consumer level, we are mostly concerned about the use of pharmaceuticals and personal care products (PPCPs) in making our lives healthier, and are less concerned about the fate of PPCPs after consumption. However, the occurrence of PPCPs in our water environment [2–5, 6•, 7] opens up new discussions on the fate of PPCPs post-consumption, and the repercussions of their presence in water.

A number of studies have investigated the impact of pharmaceutical contamination of the water environment on aquatic organisms [8–13]. For example, Gelsleichter and Szabo [8] in a recent study found that synthetic estrogens used as human contraceptives (17α-ethynylestradiol), as well as six of the selective serotonin/norepinephrine reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine) used as human antidepressants, were observed at detectable levels in the plasma of neonate bull sharks (*Carcharhinus leucas*) residing in the wastewater-impacted Caloosahatchee River in Florida. In another study, Fair et al. [10] reported detectable levels of anthropogenic triclosan (a chemical commonly found in household disinfectants) in blood plasma of wild bottlenose dolphins (*Tursiops truncatus*).

Such unwanted exposure and accumulation may pose potential health risks for aquatic organisms, as has been documented in a number of reports [14–25]. Fent et al. [16] reviewed the ecotoxicity of human pharmaceuticals and suggested that, while acute effects on aquatic organisms are most unlikely (except for large volume spills), very little is however known about the long-term effects of these pharmaceuticals on aquatic organisms. Oliveira et al. [25] investigated the effects of oxytetracycline and amoxicillin on the development and

biomarker activities of zebrafish, and indicated that short-term effects on physiological impairment in the zebrafish population is unlikely to occur, but suggested that chronic long-term exposures from low doses must also be investigated. In another study, Nietch et al. [17] suggested that the effects of chronic lower range exposure of triclosan may play an important role towards a shift in the stream mesocosm community, including bacteria and macro-invertebrates.

Since chronic (long-term) pharmaceutical toxicity data is limited, a common method of assessing environmental risk is by calculating a risk quotient (RQ). This is a ratio of the measured or predicted pharmaceutical environmental concentration (PEC), and the predicted no-effect concentration (PNEC), the environmental concentration at which no adverse effect on aquatic ecosystem function is to be expected [23, 24, 26–28]. The PNEC values are estimated on the basis of available acute or chronic toxicity data for several aquatic organisms: bacteria, algae, invertebrates, and fish; where the toxicity data is adjusted with an appropriate assessment factor [23, 29•]. The calculated RQ value is then used to prioritize pharmaceuticals that are likely to pose a high risk ($RQ \geq 1.0$); medium risk ($1.0 > RQ \geq 0.1$); or low risk ($RQ < 0.1$); to the aquatic ecosystem [21, 29•, 30].

The unwanted exposure to pharmaceuticals may also pose health risks for humans, either indirectly through bioaccumulation in the food chain, or directly through consumption of drinking water tainted with pharmaceutical contaminants (measured or estimated) [15, 20, 31–33]. For example, Leung et al. [33] investigated the occurrence of pharmaceuticals in tap water and assessed the health risks to humans at different life stages. They concluded that the risk to humans from exposure to pharmaceutical contaminants is low based on current toxicity data, although a long-term monitoring framework is proposed [33]. Similarly, other studies have concluded that, based on current knowledge, the presence of trace levels of pharmaceuticals poses negligible or only minor risks to humans [15, 20, 31, 32].

Given the significance of pharmaceutical contamination in the water environment, this review examines the maximum levels of pharmaceuticals reported in the surface waters (exclusively of the USA), discusses various pathways of pharmaceutical contamination from different point sources, assesses the potential risk of pharmaceuticals contamination for aquatic organisms, and identifies opportunities for sustainable management of pharmaceutical contamination. In this review, 'pharmaceuticals' are defined as prescription and non-prescription drugs that are either ingested, inhaled, or topically applied for prevention and/or cure of diseases, illnesses, and injuries. Thus, two of the antimicrobial compounds (triclosan and triclocarban) commonly used in household disinfectants are included; however, all of the naturally occurring hormones, as well as synthetic flavors and fragrances, cosmetics, and personal care products were excluded. Where maximum or highest levels of pharmaceuticals were not available, average or mean values were used as maximum levels. The literature search was conducted using the Web of Science database, using the keyword "pharmaceutical(s)" in natural or surface water, which includes rivers, lakes, oceans, and aquifers. The database was searched for all the years up to January 2014, but only those references that reported maximum concentrations of the same pharmaceutical were included.

Fate of Pharmaceuticals Post-consumption

Figure 1 shows a schematic of the various pathways by which pharmaceuticals can enter the surface water, which includes rivers, lakes, oceans, and aquifers. The major point sources of pharmaceuticals are: (1) industry (mainly from manufacture of pharmaceuticals) [34]; (2) household [35, 36]; and (3) hospitals [37]. The contribution from household and hospitals is mainly the result of the excretion of un-metabolized or metabolized consumed (ingested, injected, inhaled) pharmaceuticals; the washing away of topically applied personal care products [36, 38]; and the disposal (flushed down the toilet or solid waste) of expired and unwanted (leftover) pharmaceuticals [39, 40]. A significant volume of pharmaceutical waste also ends up as solid waste, including waste from Concentrated Animal Feeding Operations (CAFO).

Pharmaceutical wastewater from the aforementioned point sources, including other liquid waste from industry, hospitals, and household (washing, bathing, showering, and kitchen use), form a complex mixture of raw wastewater (Raw WW), which is treated in wastewater treatment plants (WWTP). Although the primary goal of a WWTP is to treat wastewater through a combination of physical, biological and chemical treatment [35]; the ability to treat pharmaceuticals and personal care products (PPCPs) is widely evaluated [41], particularly the persistence of pharmaceuticals post-WWTP, in the treated wastewater (Treated WW) [20], and Biosolids [42]. The latter is an unwanted byproduct of WWTP that results from municipal wastewater residuals or sewage sludge after additional treatment processes, including aerobic and/or anaerobic digestion, lime stabilization, and dewatering [43].

Persistent pharmaceuticals in Treated WW is either discharged into surface waters (especially in coastal settings) or reclaimed for land irrigation and farming [44], which may also enter surface water via direct leaching or surface runoffs [2, 45]. Biosolids, on the other hand, are applied on land as fertilizer or soil conditioner. However, persistent pharmaceuticals in biosolids, including pharmaceuticals from solid waste, may also enter surface water through leaching or surface runoffs [46]. Additional pathways by which pharmaceutical contaminants can enter surface water are from sewer overflow or the leakage of sewer distribution lines [47–49].

Pharmaceutical contaminants may also enter groundwater via infiltration from surface water, or leachate of solid waste,

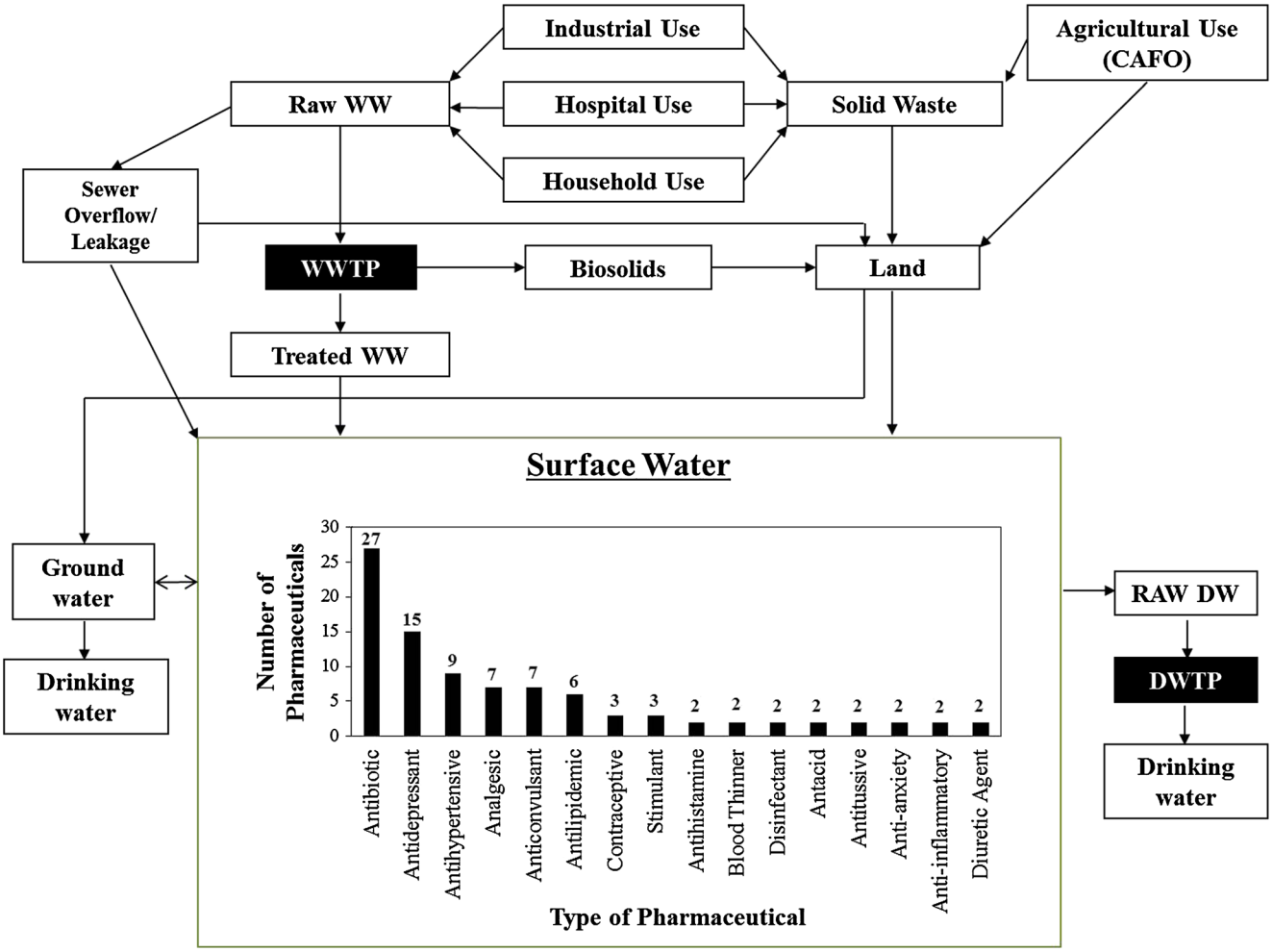

Fig. 1 Schematic showing various pathways by which pharmaceuticals enter surface water, and distribution of the types of pharmaceuticals found in surface water of the USA. WW (wastewater); DW (drinking water); CAFO (Concentrated Animal Feeding Operation); WWTP (wastewater treatment plant); DWTP (drinking water treatment plant)

or pharmaceutical-tainted irrigation water. The occurrence of pharmaceuticals in groundwater is problematic, especially since groundwater may be used for drinking water, especially in rural settings where remote treatment facilities are limited [50], thus posing potential health risks for humans. In contrast, human exposure to pharmaceutical contaminants in surface water is mostly indirect, including accidental ingestion, topical exposure, and biomagnification through the food chain. Surface water drawn in for raw drinking water (Raw DW) is subject to extreme treatment before distribution as drinking water. However, pharmaceutical contaminants in surface water may pose potential health risks for aquatic organisms [46].

Occurrence and Risk Assessment of Pharmaceuticals in Surface Water

Figure 1 (inset) also shows the number of pharmaceuticals (per pharmaceutical type) reported to occur in the surface water of the USA. A total of 93 pharmaceuticals have been reported to be present and contaminate the surface water, including: 27 antibiotics; 15 antidepressants; 9 antihypertensives; 7 analgesics; 7 anticonvulsants; 6 antilipidemics; 3 contraceptives; 3 stimulants; and 2 each of antihistamines, blood thinners, disinfectants, antacids, antitussives, anti-anxiety, anti-inflammatory, and diuretic agents. Table 1 groups the pharmaceuticals included in this study by type and identity (CAS #), with a brief description on the uses of the different types, and also indicates metabolites of the original pharmaceuticals used. Only one veterinary medicine, tylosin (CAS# 1401-69-0) categorized under antibiotics, was included in this study. Additionally, the occurrence of cotinine (CAS# 486-56-6), which is a metabolite of nicotine, is most likely linked to exposure from cigarette smoke. A recent study by Levine et al. showed elevated levels of cotinine in urine samples of smokers compared to nonsmokers (through passive smoking) [51]. The suggested pathway for cotinine contamination is from urine samples to Raw WW to Treated WW to surface water.

Table 1 List of pharmaceuticals, categorized as per their usage, included in this study

Type of pharmaceutical and usage	Pharmaceuticals	CAS number
Analgesic - *pain killer*	Acetaminophen	103-90-2
	Codeine	76-57-3
	Gabapentin	60142-96-3
	Hydrocodone	125-29-1
	Ibuprofen	15687-27-1
	Indomethacin	53-86-1
	Naproxen	22204-53-1
Antihypertensive - *lowers high blood pressure*	Atenolol	29122-68-7
	Dehydronifedipine[1]	67035-22-7
	Desmethyldiltiazem[2]	86408-45-9
	Diltiazem	42399-41-7
	Enalapril	75847-73-3
	Enalaprilat[3]	76420-72-9
	Metoprolol	37350-58-6
	Metoprolol Acid[4]	56392-14-4
	Propranolol	525-66-6
Antilipidemic - *reduces lipid levels in blood*	Atorvastatin	134523-00-5
	Clofibric Acid	882-09-7
	Gemfibrozil	25812-30-0
	o-hydroxy atorvastatin[5]	214217-86-6
	p-hydroxy atorvastatin[6]	214217-88-6
	Simvastatin-hydroxy acid[7]	12009-77-6
Antidepressant - *treats major depressive disorder*	Bupropion	34841-39-9
	Citalopram	59729-33-8
	Cotinine[8]	486-56-6
	Desvenlafaxine	93413-62-8
	Duloxetine	116539-59-4
	Erythrohydrobupropion[9]	292055-72-2
	Fluoxetine	54910-89-3
	Fluvoxamine	54739-18-3
	Hydroxy—bupropion[10]	357399-43-0
	Norcitalopram[11]	144025-14-9
	Norfluoxetin[12]	83891-03-6
	Norsertraline[13]	91797-58-9
	Paroxetine	61869-08-7
	Sertraline	79617-96-2
	Venlafaxine	93413-69-5
Anticonvulsant (antiepileptic) - *treats epileptic seizures*	Carbamazepine	298-46-4
	10,11-Dihydroxy-carbamazepine[14]	NA
	10-Hydroxy-carbamazepine[15]	NA
	Dilantin	57-41-0
	Lamotrigine	84057-84-1
	Lamotrigine-2N-Glucuronide[16]	135288-68-5
	Primidone	125-33-7
Antihistamine	Cetirizine	83881-51-0
- *treats allergic reactions*	Diphenhydramine	58-73-1
Blood Thinner	Pentoxifylline	6493-05-6
Antibiotic (antibacterial/ antifungal) - *fights against bacterial infections*	Azithromycin	83905-01-5
	Chlortetracycline	57-62-5
	Clarithromycin	81103-11-9
	Clindamycin	18323-44-9
	Ciprofloxacin	85721-33-1
	Demeclocycline	127-33-3
	Doxycycline	564-25-0
	Enrofloxacin	93106-60-6
	Erythromycin	114-07-8
	Erythromycin-H_2O[17]	NA
	Erythromycin anhydrate[18]	NA
	Lincomycin	154-21-2
	Norfloxacin	70458-96-7
	Ofloxacin	82419-36-1
	Oxytetracycline	79-57-2
	Roxithromycin	80214-83-1
	Sulfachloropyridazine	80-32-0
	Sulfadimethoxine	122-11-2
	Sulfamerazine	127-79-7
	Sulfamethazine	57-68-1
	Sulfamethizole	144-82-1
	Sulfamethoxazole	723-46-6
	Sulfathiazole	72-14-0
	Tetracycline	60-54-8
	Trimethoprim	738-70-5
	Thiabendazole	148-79-8
	Tylosin (veterinary medicine)	1401-69-0
Disinfectant (antibacterial/ antifungal) - *used in soaps and other household products*	Triclocarban	101-20-2
	Triclosan	3380-34-5
Antacid - *reduces acidity in the stomach*	Cimetidine	51481-61-9
	Ranitidine	66357-35-5
Antitussive - *medication against coughs*	Demethyl-dextrorphan[19]	NA
	Dextrorphan	125-73-5
Anti-anxiety - *inhibits anxiety*	Diazepam	439-14-5
	Meprobamate	57-53-4
Anti-inflammatory - *reduces inflammation*	Diclofenac	15307-79-6
	Salicylic acid	69-72-7
Contraceptive - *birth control pills*	17-α-ethinylestradiol	57-63-6
	Mestranol	72-33-3
	19-norethisterone	68-22-4

Table 1 (continued)

Type of pharmaceutical and usage	Pharmaceuticals	CAS number
Diuretic agent	Hydrochlorothiazide	58-93-5
- *treats fluid retention, increases urine output*	Triamterene	396-01-0
Stimulant	Caffeine	58-08-2
- *stimulates central nervous system*	Methamphetamine	537-46-2
	Paraxanthine	611-59-6

CAS = Chemical Abstracts Service

CAS Registry Number is a Registered Trademark of the American Chemical Society

NA = Not Available

[1] Metabolite of Nifedipine; [2] Metabolite of Diltiazem; [3] Metabolite of Enalapril; [4] Metabolite of Metoprolol; [5,6] Metabolites of Atorvastatin; [7] Metabolite of Simvastatin; [8] Metabolite of Nicotine; [9,10] Metabolites of Bupropion; [11] Metabolite of Citalopram; [12] Metabolite of Fluoxetine; [13] Metabolite of Sertraline; [14,15] Metabolites of Carbamazepine; [16] Metabolite of Lamotrigine; [17,18] Metabolites of Erythromycin; [19] Metabolite of Dextrorphan

It is important to note here that the total number of 93 pharmaceuticals is only a fraction of the total number of pharmaceuticals used by humans and by animal farms. Thus, more pharmaceuticals are expected to occur in the surface water, given the physical-chemical properties of pharmaceuticals favoring persistence, and the inefficiency of the WWTPs. Furthermore, data on more pharmaceuticals occurring in surface waters of the USA could perhaps be found with different search keywords, such as naturally occurring hormones, synthetic flavors and fragrances, cosmetics, personal care products, and the aforementioned specific types of pharmaceuticals (e.g., antibiotics).

In order to assess the risks posed by the pharmaceuticals detected in surface water to living organisms, we calculated the risk quotient (RQ) values, a ratio of the highest concentrations of pharmaceuticals detected in surface water and predicted no-effect concentration (PNEC) values. The PNEC values were estimated by dividing the pharmaceutical's chronic toxicity values towards fish (obtained from PBT Profiler [52]) with an assessment factor of 100 [27], which is required to extend the chronic toxicity values for fish to other aquatic organisms [30, 53, 54]. Table 2 shows highest concentrations of pharmaceuticals detected in surface water, their estimated PNEC, and calculated RQ values. We subcategorized the RQ values into low risk (RQ<0.1); medium risk (0.1≤RQ<1); and high risk (RQ≥1.0) [21, 29•, 30, 55]. The levels of pharmaceuticals at medium risk are: azithromycin; carbamazepine; cimetidine; citalopram; codeine; cotinine; diltiazem; diphenhydramine; 17-α-ethinylestradiol; fluoxetine; mestranol; paraxanthine; sertraline; sulfamethoxazole; thiabendazole; and venlafaxine. The

Table 2 Maximum concentrations of pharmaceuticals detected in surface water (SW), their predicted no-effect concentration (PNEC), and their calculated risk quotient (RQ)

Chemical	PNEC[a] (ng/L)	SW (ng/L)	RQ (SW/PNEC)
Acetaminophen	4.8×10^5	10,000 [76]	2.08^{HR}
Atenolol	1.1×10^6	859 [77]	0.08
Atorvastatin	9,000	7.3 [77]	0.08
Azithromycin	820,000	2,356 [78]	0.29^{MR}
Bupropion	NA	227 [79]	-
Carbamazepine	900,000	1,238 [80]	0.14^{MR}
10,11-Dihydroxy-carbamazepine	NA	80 [81]	-
10-Hydroxy-carbamazepine	NA	255 [81]	-
Caffeine	490,000	7,110 [82]	1.45^{HR}
Cetirizine	5.2×10^9	70 [81]	<0.01
Chlortetracycline	3,900,000	690 [76]	0.02
Cimetidine	410,000	580 [76]	0.14^{MR}
Ciprofloxacin	1.3×10^9	116 [78]	<0.01
Citalopram	140,000	219 [79]	0.16^{MR}
Clarithromycin	930,000	72 [80]	<0.01
Clindamycin	220,000	11 [80]	<0.01
Clofibric acid	3.3×10^7	10 [83]	<0.01
Codeine	290,000	1,000 [76]	0.34^{MR}
Cotinine	520,000	900 [76]	0.17^{MR}
Dehydronifedipine	2,899,000	30 [76]	<0.01
Demeclocycline	6,200,000	440 [84]	<0.01
Desmethyl-dextrorphan	NA	10 [81]	-
Desmethyl-diltiazem	NA	65 [85]	-
Desvenlafaxine	NA	84 [81]	-
Dextrorphan	72,000	50 [81]	0.07
Diazepam	70,000	2.6 [77]	<0.01
Diclofenac	3.9×10^9	42 [77]	<0.01
Dilantin	180,000	170 [77]	0.09
Diltiazem	92,000	130 [80]	0.14^{MR}
Diphenhydramine	360,000	1,410.6 [86]	0.39^{MR}
Doxycycline	7,600,000	80 [84]	<0.01
Duloxetine	125,000	2 [87]	<0.01
Enalapril	1,200,000	0.35 [77]	<0.01
Enalaprilat	3.9×10^7	46 [76]	<0.01
Enrofloxacin	3.7×10^8	15 [88]	<0.01
Erythrohydrobupropion	NA	180 [81]	-
Erythromycin	3,200,000	438 [80]	0.01
Erythromycin-H_2O	NA	1,700 [76]	-
Erythromycin anhydrate	NA	62 [81]	-
17-α-ethinylestradiol	180,000	831 [76]	0.46^{MR}
Fluoxetine	25,000	65 [81]	0.26^{MR}
Fluvoxamine	3,051,000	4.6 [79]	<0.01
Gabapentin	1.0×10^{10}	54 [81]	<0.01
Gemfibrozil	890,000	790 [76]	0.09
Hydroxy-bupropion	NA	150 [81]	-
Hydrochlorothiazide	1,400,000	75 [85]	<0.01
Hydrocodone	2,500,000	10 [85]	<0.01
o-hydroxy atorvastatin	NA	6.9 [77]	-
p-hydroxy atorvastatin	NA	9.2 [77]	-

Table 2 (continued)

Chemical	PNEC[a] (ng/L)	SW (ng/L)	RQ (SW/PNEC)
Ibuprofen	4,900,000	2796 [80]	0.06
Indomethacin	370,000	26 [80]	<0.01
Lamotrigine	1.5×10^8	455 [81]	<0.01
Lincomycin	1,300,000	730 [76]	0.06
Meprobamate	1.1×10^7	594 [77]	<0.01
Mestranol	130,000	407 [76]	0.31[MR]
Metformin	8.4×10^9	150 [76]	<0.01
Methamphetamine	1,100,000	62.6 [86]	<0.01
Metoprolol	5,300,000	237 [81]	<0.01
Metoprolol acid	NA	74 [81]	-
Lamotrigine-2N-Glucuronide	NA	95 [81]	-
Naproxen	2.1×10^7	107 [89]	<0.01
Norcitalopram	NA	74 [81]	-
19-norethisterone	3,500,000	872 [76]	0.02
Norfloxacin	2.3×10^9	120 [76]	<0.01
Norfluoxetine	NA	13.6 [79]	-
Norsertraline	NA	26.7 [79]	-
Ofloxacin	2.2×10^9	281 [78]	<0.01
Oxytetracycline	4.0×10^7	1,340 [90]	<0.01
Paraxanthine	800,000	3,100 [76]	0.39[MR]
Paroxetine	576,000	90 [80]	0.02
Pentoxifylline	460,000	2.8 [91]	<0.01
Primidone	430,000	62 [92]	0.01
Propranolol	950,000	53 [81]	<0.01
Ranitidine	8.5×10^7	10 [76]	<0.01
Roxithromycin	2,300,000	180 [76]	<0.01
Salicylic acid	6,900,000	47 [93]	<0.01
Sertraline	39,000	49 [87]	0.13[MR]
Simvastatin-hydroxy acid	NA	0.74 [77]	-
Sulfachloropyridazine	870,000	10 [78]	<0.01
Sulfadimethoxine	380,000	15,000 [90]	3.95[HR]
Sulfamerazine	890,000	1.5 [94]	<0.01
Sulfamethazine	530,000	220 [76]	0.04
Sulfamethizole	740,000	130 [76]	0.02
Sulfamethoxazole	640,000	1,900 [76]	0.30[MR]
Sulfathiazole	500,000	80 [90]	0.02
Tetracycline	7,300,000	140 [84]	<0.01
Thiabendazole	74,000	188 [81]	0.25[MR]
Triamterene	1,400,000	12 [85]	<0.01
Triclocarban	13,000	5,600 [95]	43[HR]
Triclosan	71,000	2,300 [76]	3.24[HR]
Trimethoprim	1,800,000	710 [76]	0.04
Tylosin	4.7×10^8	280 [76]	<0.01
Venlafaxine	280,000	1,310 [87]	0.47[MR]

NA = Not available

[a] PNEC values estimated using chronic toxicity for fish values (obtained from PBT Profiler [52]) divided by an assessment factor of 100 [27]

[HR] High risk

[MR] Medium risk

occurrence of these pharmaceuticals in surface water needs further monitoring. Acetaminophen (analgesic), caffeine (stimulant), sulfadimethoxine (antibiotic), triclocarban (used in disinfectants), and triclosan (used in disinfectants) levels in surface water are at high risk, which suggests detailed evaluation of their potential risk for aquatic organisms [21].

Opportunities for Sustainable Management of Pharmaceuticals

A total of 93 pharmaceuticals have been reported to occur in the surface water of the USA. It is important to evaluate the potential health risks of prioritized pharmaceuticals for humans and aquatic organisms, to design strategies for their removal from surface water, evaluate the pathways by which these pharmaceuticals enter surface water, and highlight their point sources. Such a comprehensive undertaking will give us an opportunity to explore sustainable strategies for managing and controlling pharmaceutical contamination in the environment.

The aforementioned text on "Fate of pharmaceuticals post-consumption" discusses the pathways by which pharmaceuticals enter the surface water. The first opportunity for minimizing pharmaceutical contamination is at the consumer level [39, 40, 56•, 57, 58], especially with respect to disposal of unwanted or leftover pharmaceuticals through the sink, toilet, or garbage. Wieczorkiewics et al. recently investigated the use, storage, and disposal of prescription and nonprescription medications by the residents of Cook County, Illinois. The study revealed that 59 % of respondents reported disposing of medications in the household garbage, and 31 % flushed them down the toilet or sink. More interestingly, over 80 % of respondents stated that they had never received information about proper medication disposal [56•]. It is evident from this study that public education on proper disposal of pharmaceuticals is lacking or not "prescribed" at the drug stores. Viable solutions for minimizing pharmaceutical contamination at consumer level include: (1) state or federal-funded collection bins at the local grocery or drug stores for collecting leftover (unwanted, unused or expired) pharmaceuticals; (2) public education on proper disposal of leftover drugs through schools, flyers, and television advertisements.

Another opportunity for controlling pharmaceuticals at the source would be to address waste from pharmaceutical industries [34] and hospitals [26, 29•, 37, 59, 60]. In a recent study Verlicchi et al. found consistent differences in the levels of some antibiotics, analgesics and lipid regulators in the effluent directly from the hospital with that mixed with the local urban effluent, thereby suggesting that hospital effluents represent one of the main sources of pollutants, in particular antibiotics, receptor antagonists and lipid regulators [29•]. Thus, wastewater from the pharmaceutical industry and hospitals should

be more carefully monitored for elevated levels of pharmaceuticals and perhaps have their own treatment units; further, the pharmaceutical industries could invest in manufacturing greener pharmaceuticals [61] that are more conducive to degradation post-consumption and safe for the environment [46].

Furthermore, wastewater treatment facilities should be more carefully evaluated for the efficiency of their treatment of pharmaceutical contaminants [38, 62–65]. Progress has been made towards the more efficient removal and transformation of pharmaceuticals using advanced treatments, employing processes of physical [66, 67], chemical [62, 68–71], and biological nature [72–75]. In addition to evaluating the treatment efficiency, it is also important to investigate whether pharmaceuticals are transformed into safer metabolites [46].

Conclusions

Given the significance of pharmaceutical contamination in the water environment, this review assessed the occurrence and risk of pharmaceuticals in the surface waters of the USA. A total of 93 pharmaceuticals have been reported to occur in the surface water, the most common being of the type antibiotic (total of 27) and antidepressant (total of 15). The pharmaceuticals that are assessed to be at high risk (RQ≥1.0) include acetaminophen (analgesic); caffeine (stimulant); sulfadimethoxine (antibiotic); triclocarban (used in disinfectants); and triclosan (used in disinfectants). Given the high ecological risk, these pharmaceuticals require detailed evaluation, which means that their levels in surface water must be continuously monitored, and the risks for aquatic organisms must be carefully evaluated (both for chronic and acute toxicity), and any opportunities for their removal from the surface water and sustainable management opportunities must be explored. The following recommendations can be used as a guide for sustainable management of pharmaceutical contaminants:

(1) State or federal-funded collection bins at the local grocery or drug stores for collecting leftover (unwanted, unused or expired) pharmaceuticals;
(2) Public education on proper disposal of leftover drugs through schools, flyers, or television advertisements;
(3) Stringent monitoring of pharmaceutical contaminants in the wastewater from pharmaceutical industry and hospitals;
(4) Investment in manufacture of greener pharmaceuticals more conducive to degradation post-consumption;
(5) Careful evaluation of WWTPs for efficiency of pharmaceutical contaminant removal;
(6) Regulation of the use of biosolids as fertilizer or soil conditioner;
(7) Regulation of the use of Treated WW for recreational use;
(8) Conduct research on chronic (long-terms) effects of pharmaceuticals (and their metabolites) on aquatic organisms.

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Compliance with Ethics Guidelines

Conflict of Interest Randhir P. Deo declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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