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Global scanning of selective serotonin reuptake inhibitors: occurrence, wastewater treatment and hazards in aquatic systems☆

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ABSTRACT

As the global population becomes more concentrated in urban areas, resource consumption, including access to pharmaceuticals, is increasing and chemical use is also increasingly concentrated. Unfortunately, implementation of waste management systems and wastewater treatment infrastructure is not yet meeting these global megatrends. Herein, pharmaceuticals are indicators of an urbanizing water cycle; antidepressants are among the most commonly studied classes of these contaminants of emerging concern. In the present study, we performed a unique global hazard assessment of selective serotonin reuptake inhibitors (SSRIs) in water matrices across geographic regions and for common wastewater treatment technologies. SSRIs in the environment have primarily been reported from Europe (50%) followed by North America (38%) and Asia-Pacific (10%). Minimal to no monitoring data exists for many developing regions of the world, including Africa and South America. From probabilistic environmental exposure distributions, 5th and 95th percentiles for all SSRIs across all geographic regions were 2.31 and 3022.1 ng/L for influent, 5.3 and 841.6 ng/L for effluent, 0.8 and 127.7 ng/L for freshwater, and 0.5 and 22.3 ng/L for coastal and marine systems, respectively. To estimate the potential hazards of SSRIs in the aquatic environment, percent exceedances of therapeutic hazard values of specific SSRIs, without recommended safety factors, were identified within and among geographic regions. For influent sewage and wastewater effluents, sertraline exceedances were observed 49% and 29% of the time, respectively, demonstrating the need to better understand emerging water quality hazards of SSRIs in urban freshwater and coastal ecosystems. This unique global review and analysis identified regions where more monitoring is necessary, and compounds requiring toxicological attention, particularly with increasing aquatic reports of behavioral perturbations elicited by SSRIs.

1. Introduction

The presence of pharmaceutical compounds in the environment has increasingly led to concern over potential adverse outcomes in aquatic organisms, and when antibiotics influence development of resistant microorganisms, risks to public health. Unprecedented global population growth and concentration in urban areas, particularly in megacities of developing regions, has heightened these concerns. As more of the world population becomes concentrated in and around urban centers, resource consumption and chemical use, including pharmaceuticals, will rise and sustainable water management will become increasingly important. In regions of the world that face water scarcity challenges, this trend lead to more attention as water reuse increases and urban water cycle is realized (Ankley et al., 2007; Postel, 2010; Brooks, 2014; Brooks and Conkle 2019). Unfortunately, in developing countries where chemical and waste infrastructure development has been outpaced by population growth, water and wastewater management is not advanced enough to meet growing needs (Burket et al., 2018). In these regions, there is increased concern over the risks of pharmaceuticals and other contaminants of emerging concern (CECs) to the aquatic environment along with public health due to raw to poorly treated sewage discharges (Vörösmarty et al., 2010; Arnold et al., 2014; Kookana et al., 2014).

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Pharmaceuticals are primarily released to the environment by wastewater treatment plant (WWTP) effluent or untreated sewage after consumption and excretion by humans. WWTPs were not designed to remove CECs, therefore treated wastewater effluent still contains trace amounts of steroidal hormones, synthetic hormones, personal care products, pharmaceuticals and other inorganic and organic contaminants (Ternes, 1998; Kolpin et al., 2002). Though acute effects of pharmaceuticals on aquatic organisms are unlikely to be observed at environmentally relevant concentrations, at least in developed regions, chronic sublethal response are increasingly reported because pharmaceuticals are continually released via wastewater effluent (Brooks et al., 2005). In certain regions of the world, surface waters are either partially or fully dependent on wastewater discharges for instream flows (Brooks et al., 2006; Ankley et al., 2007), which represent worse case scenarios for exposure to down the drain consumer chemicals. Specifically, Rice and Westerhoff (2017) reported that for over 900 streams in the United States, effluent discharge contributes 50% of instream flow; further, 25% of streams receiving reclaimed wastewater inputs had less than a ten-fold dilution factor of effluent (Rice & Westerhoff, 2017), a regulatory default factor commonly employed during environmental assessments of human pharmaceuticals (Brooks et al., 2003) that underestimates environmental exposures and risks in effluent-dominated and dependent systems (Brooks et al., 2006).

As reclaimed water discharges and untreated sewage continue to influence surface water systems, developments in environmental analytical chemistry have increased ability to detect and monitor pharmaceuticals and other CECs in the environment. Subsequently, numerous studies have been published on pharmaceuticals in the environment, beginning primarily in the mid-to-late 1990s. The greatest growth in this area is research occurred during the period of 2000–2015 where the number of journal articles and books published on pharmaceuticals in the environment increased from a rate of 200 per year to 1800 per year (Brooks et al., 2012; Daughton, 2016). However, certain classes of pharmaceuticals have received more attention than others. Early on, research focused on endocrine disrupting compounds (Brooks, 2018), but more recently focus has shifted to other compounds such as antihistamines (Kristofco & Brooks, 2017), calcium channel blockers (Saari et al., 2017) and antibiotics (Schafhauser et al., 2018; Kelly and Brooks, 2018). Another class of pharmaceuticals that has received extensive attention are antidepressants, including selective serotonin reuptake inhibitors (SSRIs), which were the first human pharmaceuticals identified to accumulate in fish collected from the field (Brooks et al., 2005). Such observations stimulated considerable attention to understand exposure, hazards risks and management of pharmaceuticals in the environment (Brooks, 2014).

SSRIs have been highly prescribed since the 1980s to patients diagnosed with clinical depression. These antidepressants elicit therapeutic responses by binding to the serotonin re-uptake transporter in neurons to increase levels of serotonin in the synapse of nerve cells (Hyman & Nestler, 1996). In 2010, SSRIs were among the most prescribed drugs in the United States for adolescents aged 12–18 and the top prescribed pharmaceuticals for persons aged 20 to 59 (Gu et al., 2010). In Canada, from 2005 to 2009, SSRI prescriptions from pediatricians increased by 39% with fluoxetine being the most commonly prescribed (Lam et al., 2013). Due to their widespread use and their incomplete removal during wastewater treatment, SSRIs are commonly found in wastewater effluents around the globe (Oakes et al., 2010; Metcalfe et al., 2010; Monteiro & Boxall, 2010; Lajeunesse et al., 2012). As a result, SSRIs are detected in many surface water systems and have been shown to cause biological effects in various aquatic organisms (Brooks, 2014). Subsequently, as surface water systems become increasingly influenced by WWTP discharges, it is important to understand the global aquatic hazards of SSRIs, which are routinely included in prioritization exercises for pharmaceuticals in the environment (Burns et al., 2018). In fact, identifying geographic regions where pharmaceuticals present elevated environmental risks was recently identified as a priority research need for effective management of water resources (Boxall et al., 2012; Rudd et al., 2014).

In the present study, a novel global scanning exercise forM SSRIs in the environment was performed across multiple water matrices and geographic regions. We aimed to understand the current knowledge on the occurrence and associated hazards of SSRIs in water systems around the world, specifically employing approaches previously reported (James et al., 2011; Corrales et al., 2015; Kristofco and Brooks. 2017; Saari et al., 2017; Schafhauser et al., 2018; Kelly and Brooks, 2018). Environmental exposure distributions (EEDs) were created for each SSRI when data was sufficient and probabilistic environmental hazard assessments (PEHA) were performed with therapeutic hazard values (THVs; Brooks, 2014) for each SSRI to identify potential exceedances in various water matrices across different geographic regions. The THV approach, which builds from initial plasma modeling efforts by Huggett et al. (2003), appears particularly useful for SSRIs and fish as previously demonstrated for sertraline by Valenti et al. (2012) and fluoxetine by Margiotta-Casaluci et al. (2014). Further, we examined different types of wastewater treatment technologies to explore whether SSRIs and associated hazards in effluent varied by wastewater treatment processes.

2. Materials and methods

2.1. Literature review of SSRIs

A comprehensive list of SSRIs was created from the Mammalian Pharmacokinetic Prioritization For Aquatic Species Targeting (MaPPFAST) database developed by Berninger et al. (2016) and is described in Table 1. Literature searches using specific search terms (see Supplemental Information) through April 2018 of the occurrence of antidepressants in effluent returned approximately 288 relevant publications from around 1700 total hits (Supplemental Information). In the present study, effluent was specifically selected as the matrix search term due to wastewater effluents being the primary source of SSRIs to aquatic systems. Further refinement yielded 152 relevant publications used for data collection (Supplemental Information). Quantitative occurrence data was collected from these publications along with study parameters, analytical methodologies, and geographic region: Africa, Asia-Pacific, Europe, North America, and South America (Supplemental Information).

Table 1
List of selective serotonin reuptake inhibitors and metabolites examined in the current study.

Compound	Molecular Weight	CAS
Citalopram	324.3	59729-33-8
Desmethyl citalopram[a]	310.4	62498-67-3
Desmethyl fluvoxamine[a]	304.3	192876-02-1
Escitalopram	324.3	128196-01-0
Fluoxetine	309.3	56296-78-7
Fluvoxamine	318.2	54739-18-3
Norfluoxetine[a]	295.3	126924-38-7
Norsertraline[a]	292.2	87875-41-8
Paroxetine	329.4	61869-08-7
Sertraline	306.2	79617-96-2

[a] Metabolites.

For publications where specific wastewater treatment plants were studied and information was available, the type of technology used at each specific plant was noted. Specific wastewater treatment approaches were grouped into one of the five categories: primary, secondary, disinfection processes, filtration processes, and advanced wastewater treatment processes. Treatment technologies used in addition to traditional secondary treatment are generally referred to as tertiary treatment processes. Tertiary treatment options include filtration and other advanced processes. Filtration processes are those in which wastewater passes through natural filters, such as sand, or more advanced filters such as membranes. These processes can remove bacteria and viruses in addition to reducing suspended solids and other organic matter in effluent. Advanced treatment processes are typically only used in areas where there are sensitive receiving systems and particularly where various water reuse applications are occurring. Advanced treatment options include processes such as reverse osmosis, ultrafiltration, and advanced oxidation (Asano, 1998; Bastian & Murray, 2012; Metcalfe & Eddy, 2014). When data was available, PEHAs were conducted by matrix for specific geographic regions, specific SSRIs, and among wastewater treatment processes.

2.2. Probabilistic environmental hazard assessments

After SSRI data was collected and organized, maximum measured environmental concentrations (MECs) in each water matrix were used to create EEDs when there were greater than five occurrence observations available (Wheeler, 2002). Consistent with previously reported methods (Corrales et al., 2015; Kristofco and Brooks, 2017; Saari et al., 2017; Schafhauser et al., 2018; Kelly and Brooks, 2018), maximum MECs were used because these values were consistently reported, and nondetects were not included because minimum detection limits (MDLs) inherently different among studies. Sigmaplot 13.0 was used to generate environmental occurrence probability distributions, which were then used to perform PEHAs. This approach again followed methods previously described (Solomon and Takacs, 2001) and recently employed by our research team (Corrales et al., 2015; Kristofco and Brooks, 2017; Saari et al., 2017; Schafhauser et al., 2018; Kelly and Brooks, 2018). MECs were ranked in ascending order, and percent ranks were assigned using a Weibull formula (Eq. (1)):

$$j = (i^{*}100) / (n+1) \quad (1)$$

Where j is the percent probability, i is the numerical rank assigned to a MEC, and n is the total number of data points. A linear regression was then fit to the plot of Percent Rank vs. MECs (probability and log common scales, respectively; Sigmaplot 13.0) and analyzed. The slope and y-intercept were subsequently used to calculate centile values (Microsoft Excel, 2016 Microsoft Corp, Richmond, WA, USA) to estimate the probabilities of observing MECs at given concentrations using the equation:

$$Centile\ value = NORMDIST\left((m^{*}\log_{10}(x)) + b\right) \quad (2)$$

Which can be rearranged to identify a concentration at a specific centile value:

$$x = 10^{(\mathrm{NORMDIST}\ (Centile\ value)\ -\ b/m)} \quad (3)$$

The *NORMDIST* function returns a standard normal cumulative distribution function of the selected value, and m and b represent the slope and intercept, respectively, from the regression. To examine whether SSRIs in diverse water matrices may present therapeutic hazards to fish, THVs were calculated for each SSRI and compared to distributions of MECs using a PEHA approach. A THV is the concentration of a pharmaceutical in water that is predicted to bioaccumulate in fish plasma to a level equivalent of a minimum human therapeutic plasma dose (C_{min}): Eq. (3) (Brooks, 2014);

$$THV = C_{min} / P_{Blood:Water} \quad (4)$$

Where C_{min} is the minimum human blood plasma concentration that a drug achieves to elicit a therapeutic response, and $P_{Blood:Water}$ is the partitioning relationship for a compound in blood versus water. Log $P_{Blood:Water}$ was reported by Fitzsimmons et al. (2001) to predict hydrophobic organic chemical partitioning in rainbow trout (Eq. (5)):

$$\log P_{Blood:Water} = \log\left[(10^{0.73\ \log KOW\ *}\ 0.16) + 0.84\right. \quad (5)$$

Where log K_{ow} is the octanol:water partition coefficient. Huggett et al. (2003) initially proposed this plasma modeling concept to prioritize pharmaceuticals of environmental concern by estimating fish plasma levels of a pharmaceutical at a specific aqueous concentration (Eq. (6)):

$$\text{Fish plasma concentration} = [\text{Aqueous}]\ \text{x}\ \log P_{Blood:Water} \quad (6)$$

It is also important to note that Huggett et al. (2003) recommended use of an uncertainty factor of 1000. Despite a number of uncertainties that remain for fish plasma modeling and THVs (Brooks, 2014), we chose not to include this uncertainty factor in the current study because the THV approach appears particularly useful for SSRIs, as evidenced by previous fish studies with sertraline (Valenti et al., 2012) and fluoxetine (Margiotta-Casalucci et al., 2014). Plasma modeling approaches have been frequently used by our research team (Berninger et al., 2011; Valenti et al., 2012; Du et al., 2014; Scott et al., 2016; Kristofco et al. 2016) and others (Fick et al., 2010; Margiotta-Casaluci et al. 2014; 2016) to examine potential internal fish doses of pharmaceutical compounds in environmental systems (Kristofco and Brooks, 2017; Saari et al., 2017). Percent exceedances of the calculated THV were then derived for each EED for various water matrices, geographic regions, individual compounds, and wastewater treatment type.

3. Results and discussion

3.1. Global occurrence of SSRIs

Over the past 18 years, the number of peer reviewed published articles on the occurrence of SSRIs in different aquatic matrices has increased with the majority of articles published since 2010 (Fig. S1). The majority of publications are from Europe (77), North America (58), and Asia-Pacific (15), with only two studies from South Africa (Fig. S1). Regions where there was little to no occurrence data found included some areas of Europe, the Middle East, and parts of Asia-Pacific (e.g., Japan, Vietnam, South Korea). More broadly, there were limited to no studies from the large geographic regions, including Africa (and Antarctica). For these locations around the world, environmental risks of SSRIs should be considered in the future, particularly in the rapidly growing urban areas of Asia-Pacific, where the majority of people already cities and over one third of the global population will reside by 2050. It is thus not surprising that understanding environment and health risks, including through food web transfers, of pharmaceuticals was recently identified as a prior research need for Latin America (Furley et al., 2018). Across these geographic regions, occurrence of SSRIs has been studied in a range of matrices including wastewater influent sewage, wastewater effluent, freshwater, saltwater,

drinking water, and ground water. Similar SSRIs have been detected in influent, effluent, freshwater, and saltwater (Table 2), which allowed for direct comparisons among matrices (Table 3). Subsequently, EEDs were examined and PEHAs performed for each matrix among geographic regions (Fig. S2).

3.2. SSRIs in influent sewage

Six SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four metabolites (desmethyl citalopram, desmethyl fluvoxamine, norfluoxetine, norsertraline) were studied in wastewater influents. All of these SSRIs were detected; however, desmethyl citalopram, desmethyl fluvoxamine, escitalopram, and fluvoxamine were not detected in sewage with enough frequency to create EEDs (Tables 2 and 3). The most frequently detected SSRIs in influent were fluoxetine (34), citalopram (26), and sertraline (19). Of the SSRI metabolites that were studied, norfluoxetine (11) and norsertraline (8) were the most frequently reported from sewage. Most publications on SSRI occurrence in influent were from Europe (77), followed by North America (42), and Asia-Pacific (21), with no publications from South America during the literature search. Fluoxetine was the most frequently detected SSRI in Asia-Pacific, Europe, and North America followed by citalopram. Geographically, citalopram differed from other SSRIs with almost three quarters of studies coming from Europe. In Europe, almost equal study frequency was observed for citalopram compared to fluoxetine, whereas in North America fluoxetine was studied twice as frequently as citalopram. MECs in influent were not dependent on detection frequencies, with concentrations ranging from no detects (ND) to 32,228 ng/L and 39,732 ng/L (escitalopram and paroxetine, respectively; Salgado et al., 2011). Both of these values came from the same study examining influent sewage to a wastewater treatment plant in Seixal, Portugal (Table 2). Such differential occurrence information among SSRIs and geographic regions in sewage represents a research need for environmental surveillance and monitoring programs to more robustly define aquatic risks, particularly in regions where pharmaceutical consumption is increasing faster than implementation of sewage treatment technologies.

3.3. SSRIs in effluent

Five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and five metabolites (desmethyl fluvoxamine,

Table 2
Detection frequency and geographic distribution of selective serotonin reuptake inhibitors in wastewater influent sewage, effluent, freshwater and saltwater.

	Influent detection (ng/L)					Geographic distribution			
Compound	Times Studied	Times Detected	Ratio	Min[a]	Max[a]	Asia-Pacific	Europe	North America	South America
Citalopram	27	26	(26/27)	ND	17100	3	19	5	–
Desmethyl citalopram	6	4	(4/6)	ND	209	1	3	2	–
Desmethyl fluvoxamine	1	1	(1/1)	ND	12	–	–	1	–
Escitalopram	1	1	(1/1)	ND	32228	–	1	–	–
Fluoxetine	38	34	(34/38)	ND	3465	6	22	10	–
Fluvoxamine	4	3	(3/4)	ND	435	2	–	2	–
Norfluoxetine	12	11	(11/12)	ND	10400	–	8	4	–
Norsertraline	10	8	(8/10)	ND	386	2	2	6	–
Paroxetine	19	15	(15/19)	ND	39732	2	11	6	–
Sertraline	22	19	(19/22)	<0.13	997	5	11	6	–
Compound	Effluent detection (ng/L)					Geographic distribution			
	Times Studied	Times Detected	Ratio	Min[a]	Max[a]	Asia-Pacific	Europe	North America	South America
Citalopram	42	42	(42/42)	ND	9200	5	28	9	–
Desmethyl fluvoxamine	1	1	(1/1)	ND	9.3	–	–	1	–
Desmethyl citalopram	7	5	(5/7)	ND	425.7	1	4	2	–
Didesmethyl citalopram	1	1	(1/1)	0.9	20	–	1	–	–
Fluoxetine	70	57	(57/70)	ND	2700	7	36	27	–
Fluvoxamine	5	3	(3/5)	ND	3.9	2	1	2	–
Norfluoxetine	21	18	(18/21)	ND	9810	–	12	9	–
Norsertraline	11	9	(9/11)	ND	423	2	3	6	–
Paroxetine	26	20	(20/26)	ND	740	3	12	11	–
Sertraline	30	22	(22/30)	ND	1930	6	13	11	–
Compound	Freshwater detection (ng/L)					Geographic distribution			
	Times Studied	Times Detected	Ratio	Min[a]	Max[a]	Asia-Pacific	Europe	North America	South America
Citalopram	31	30	(30/31)	ND	426.6	–	19	11	1
Desmethyl citalopram	3	2	(2/3)	ND	2.41	–	1	1	–
Fluoxetine	44	25	(25/44)	ND	330	2	15	26	1
Fluvoxamine	1	0	(0/1)	ND	ND	–	–	1	–
Norfluoxetine	11	3	(3/11)	ND	80.5	–	5	6	–
Norsertraline	1	0	(0/1)	ND	ND	–	1	–	–
Paroxetine	14	7	(7/14)	ND	40	–	8	6	–
Sertraline	20	13	(13/20)	ND	75	1	10	8	1
Compound	Saltwater detection (ng/L)					Geographic distribution			
	Times Studied	Times Detected	Ratio	Min[a]	Max[a]	Asia-Pacific	Europe	North America	South America
Citalopram	2	2	(2/2)	0.9	5.4	–	2	–	–
Fluoxetine	4	2	(2/4)	ND	36	1	3	–	–
Norfluoxetine	1	0	(0/1)	ND	ND	–	1	–	–
Paroxetine	1	0	(0/1)	ND	ND	–	1	–	–
Sertraline	1	0	(0/1)	ND	ND	–	1	–	–

[a] Values reported directly from literature, converted to ng/L as needed.

Table 3
Equations for regressions lines and values corresponding to various centile values for environmental exposure distributions (EEDs) of maximum reported measured environmental concentrations (MECs) for selective serotonin reuptake inhibitors (SSRI); ng/L) in influent sewage, effluent, freshwater, and saltwater. For each distribution, 'n' represents the number of SSRI MECs reported and used in that specific matrix and region. EEDs were developed for specific geographic regions and individual SSRIs when data was sufficient ($n \geq 5$).

Matrix	Compound	Region	n	r^2	Slope	Intercept	Centile Value (ng/L)						
							1	5	10	20	50	95	99
Influent	All compounds	All regions	114	0.92	1.06	−2.03	0.5	2.3	5.1	13.3	83.6	3022.1	1.34×10^4
	Citalopram	All regions	22	0.90	1.31	−2.58	1.6	5.2	9.8	21.3	93.7	1693.7	5619.5
		Europe	17	0.93	1.32	−2.64	1.7	5.6	10.6	22.8	98.6	1732.1	5678.7
	Fluoxetine	All regions	47	0.83	1.18	−1.90	0.4	1.6	3.3	7.9	41.0	1023.3	3881.5
		Asia-Pacific	6	0.96	1.21	−1.64	0.3	1.0	2.0	4.6	22.6	516.3	1887.5
		Europe	36	0.75	1.04	−1.69	0.2	1.1	2.5	6.6	43.0	1663.2	7562.5
		N. America	5	0.83	1.47	−2.62	1.6	4.6	8.1	16.2	60.1	783.5	2270.4
	Norfluoxetine	All regions	12	0.90	0.67	−1.90	0.2	2.4	8.4	38.0	683.5	1.94×10^5	2.01×10^6
		Europe	11	0.89	0.74	−2.23	0.7	6.2	19.1	75.4	1040.6	1.76×10^5	1.47×10^6
	Paroxetine	All regions	11	0.79	0.65	−1.34	0.0	0.3	1.2	5.8	114.3	3.86×10^4	4.3×10^5
		Europe	7	0.91	0.61	−1.55	0.1	0.7	2.7	14.1	330.1	1.56×10^5	2.01×10^5
	Sertraline	All regions	14	0.96	2.17	−3.82	4.9	10.0	14.8	23.5	57.5	330.1	680.8
		Europe	7	0.90	2.54	−4.23	5.6	10.4	14.5	21.5	46.2	204.7	379.3
Effluent	All compounds	All regions	174	0.94	1.49	−2.72	1.8	5.3	9.2	18.1	66.5	841.6	2409.4
	Citalopram	All regions	59	0.89	1.90	−3.91	6.8	15.6	24.2	41.2	114.3	839.9	1918.8
		Europe	39	0.95	1.92	−3.75	5.5	12.5	19.3	32.8	90.0	648.7	1470.6
		N. America	18	0.97	5.46	−12.89	86.3	115.0	134.1	161.4	230.3	461.0	614.7
	Desmethyl citalopram	All regions	5	0.91	3.81	−8.37	38.6	58.2	72.5	94.6	157.4	425.4	642.4
		N. America	5	0.91	3.81	−8.37	38.6	58.2	72.5	94.6	157.4	425.4	642.4
	Fluoxetine	All regions	58	0.87	1.89	−3.04	2.4	5.5	8.5	14.6	40.6	300.7	689.4
		Europe	32	0.88	1.52	−2.57	1.4	4.0	7.0	13.6	48.5	581.3	1627.4
		N. America	25	0.96	3.07	−4.67	5.8	9.7	12.7	17.7	33.2	114.1	190.2
	Norfluoxetine	All regions	13	0.85	0.58	−1.42	0.0	0.4	1.7	9.7	272.5	1.84×10^5	2.73×10^6
		Europe	10	0.83	0.59	−1.67	0.1	1.1	4.6	25.4	685.1	4.28×10^5	6.15×10^5
	Norsertraline	All regions	6	0.93	2.31	−3.94	5.0	9.9	14.2	22.0	50.9	261.9	516.4
		N. America	6	0.93	2.31	−3.94	5.0	9.9	14.2	22.0	50.9	261.9	516.4
	Paroxetine	All regions	9	0.95	1.38	−2.04	0.6	1.9	3.5	7.3	29.9	464.2	1446.7
		Europe	5	0.94	1.40	−2.54	1.4	4.4	8.0	16.5	65.9	992.6	3052.9
	Sertraline	All regions	24	0.96	2.05	−3.07	2.3	5.0	7.5	13.4	31.9	202.9	437.1
		N. America	17	0.99	3.02	−4.74	6.3	10.6	14.0	19.5	37.1	130.2	219.1
Fresh-water	All compounds	All regions	170	0.98	1.50	−1.51	0.3	0.8	1.4	2.8	10.2	127.7	364.4
	Citalopram	All regions	115	0.98	1.42	−1.60	0.3	0.9	1.7	3.4	13.5	194.5	588.2
		Europe	61	0.96	1.89	−1.70	0.5	1.1	1.7	2.8	7.9	58.9	135.4
		N. America	54	0.86	1.21	−1.71	0.3	1.1	2.3	5.2	26.0	593.3	2169.1
	Fluoxetine	All regions	19	0.95	1.78	−1.55	0.4	0.9	1.4	2.5	7.4	61.8	149.2
		Europe	8	0.98	2.16	−1.91	0.6	1.3	2.0	3.1	7.7	44.6	92.4
		N. America	9	0.88	1.38	−1.21	0.2	0.5	0.9	1.9	7.6	119.4	373.8
	Norfluoxetine	All regions	5	0.68	0.88	−0.59	0.0	0.1	0.2	0.5	4.7	342.1	2021.9
	Sertraline	All regions	26	0.91	2.01	−1.24	0.3	0.6	1.0	1.6	4.1	27.2	59.3
		Europe	21	0.90	2.53	−1.78	0.5	0.9	1.2	1.8	3.8	17.2	31.9
Salt-water	All compounds	All regions	13	0.87	2.00	−1.06	0.2	0.5	0.8	1.3	3.4	22.3	48.8
	Citalopram	All regions	12	0.97	3.20	−1.42	0.5	0.9	1.1	1.5	2.8	9.0	14.8
		Europe	12	0.97	3.20	−1.42	0.5	0.9	1.1	1.5	2.8	9.0	14.8

desmethyl citalopram, didesmethyl citalopram, norfluoxetine, norsertraline) were identified in treated wastewater effluent (Table 2). All compounds were also detected at least once, and EEDs were developed for all except desmethyl fluvoxamine and didesmethyl citalopram (Table 3). Similar to influent sewage, the most frequently detected SSRIs in effluent were fluoxetine (70), citalopram (42), sertraline (22), and paroxetine (20), and norfluoxetine (18) and norsertraline (9) were the most frequently reported metabolites. Geographically, most publications studying SSRIs in effluent were from Europe (110), followed by North America (78), and then Asia-Pacific (26). No publications were found for SSRIs in effluents of South America, which again represents an environmental monitoring research need. Across Asia-Pacific, Europe, and North America, the most frequently studied SSRI was fluoxetine. Similar to influent sewage, citalopram was more commonly studied in effluents from Europe. Fluoxetine, sertraline, and paroxetine publications are more evenly distributed between Europe and North America with a few studies from Asia-Pacific. In North America, fluoxetine was studied three times more frequently than other SSRIs. However, the highest reported MEC in effluent for an SSRI and a metabolite was citalopram (9200 ng/L; Suárez et al., 2012) and norfluoxetine (9810 ng/L; Shraim et al., 2017), respectively (Table 2).

3.4. SSRIs in surface water

In global freshwater systems, five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and three metabolites (desmethyl citalopram, norfluoxetine, norsertraline) were studied, and fluvoxamine and norsertraline were the only two not detected in surface waters (Table 2). However, norsertraline has been commonly observed in aquatic life (e.g., Du et al., 2014) since its first report in fish (Brooks et al., 2005). Sufficient data allowed EED construction for citalopram, fluoxetine, norfluoxetine, and sertraline (Table 3). Unlike wastewater influent and effluent, the most commonly detected SSRI in surface waters was citalopram (30), followed by fluoxetine (25), sertraline (13), and paroxetine (7). Desmethyl citalopram and norfluoxetine were only detected two and three times, respectively. It is interesting to note that fluoxetine was the most frequently studied SSRI, but was only detected in

about half of publications, compared to citalopram that was detected in 30 out of the 31 publications studying its occurrence.

Geographically, the highest number of studies came equally from Europe and North America (59 each) with only six publications from Asia-Pacific and South America (3 each). From Europe, the most frequently studied SSRI was citalopram, in contrast to North America where fluoxetine was the most frequently studied SSRI. Out of all freshwater detections, citalopram was reported at the highest concentration in Iowa, USA (426.6 ng/L; Bradley et al., 2016) followed by fluoxetine, which was observed at the highest concentration in North Carolina, USA (330 ng/L; McEachran et al., 2018) (Table 2). Not surprisingly, the maximum concentrations detected for the majority of SSRIs was lower in freshwater systems than in either influent sewage or effluent wastewater (Table 2).

Whereas most of the global occurrence data of SSRIs in surface water systems are from freshwater studies, there were only nine publications studying SSRI occurrence in estuarine and marine systems. In these nine publications, there were four SSRIs studied (citalopram, fluoxetine, paroxetine, and sertraline) and one metabolite (norfluoxetine) (Table 2). Of these SSRIs, only citalopram and fluoxetine were detected, but only citalopram had enough detects to create an EED in this matrix. The maximum MEC in saltwater was fluoxetine in Australia (36 ng/L; Birch et al., 2015) (Table 2). Almost all studies came from Europe (8) with just one study from Australia. Such paucity of coastal and marine observations is concerning given the high density of human populations living on or immediate upstream from coastlines. Clearly, this represents an important research need, given increasing toxicological reports of SSRI influences on estuarine and marine organisms (Franzellitti et al., 2014, 2015).

3.5. Aquatic hazards of SSRIs

There was sufficient data for all SSRIs and some metabolites to create EEDs and perform PEHAs in various environmental matrices within specific geographic regions. For influent sewage, EEDs were developed for citalopram, fluoxetine, paroxetine, and sertraline (Fig. 1A–D) along with the metabolite norfluoxetine. We consider this exercise useful because pharmaceutical use appears to be increasing globally (Oldenkamp et al., 2019) and 80% of global sewage production remains untreated and is released to the environment (WWAP, 2017). Fluoxetine had the greatest number of occurrences (47), followed by citalopram (22), sertraline (14), and paroxetine (11). Comparing the 20th centile values across all geographic regions, sertraline was observed at the highest concentration (23.5 ng/L), despite not being one of the most frequently detected SSRIs. These 20th centile values for sertraline and citalopram (21.3 ng/L) were also about three times higher than fluoxetine and paroxetine (Table 3). Interestingly, the primary metabolite of fluoxetine, norfluoxetine, had almost a five times higher 20th centile value (37.9 ng/L) than fluoxetine (7.9 ng/L), yet again has not been as commonly studied. For fluoxetine in influent sewage, there were enough MECs to create EEDs across different geographic regions. In North America, the 20th centile for fluoxetine (16.2 ng/L) was about twice as high as Europe (6.6 ng/L) and four times as high as Asia-Pacific (4.6 ng/L). However, it is important to note for North America and Asia-Pacific that there were only 5 and 6 occurrences, respectively, compared to 36 from Europe (Table 3).

In effluent, EEDs were created for citalopram, fluoxetine, paroxetine, and sertraline (Fig. 2A–D). There was also enough

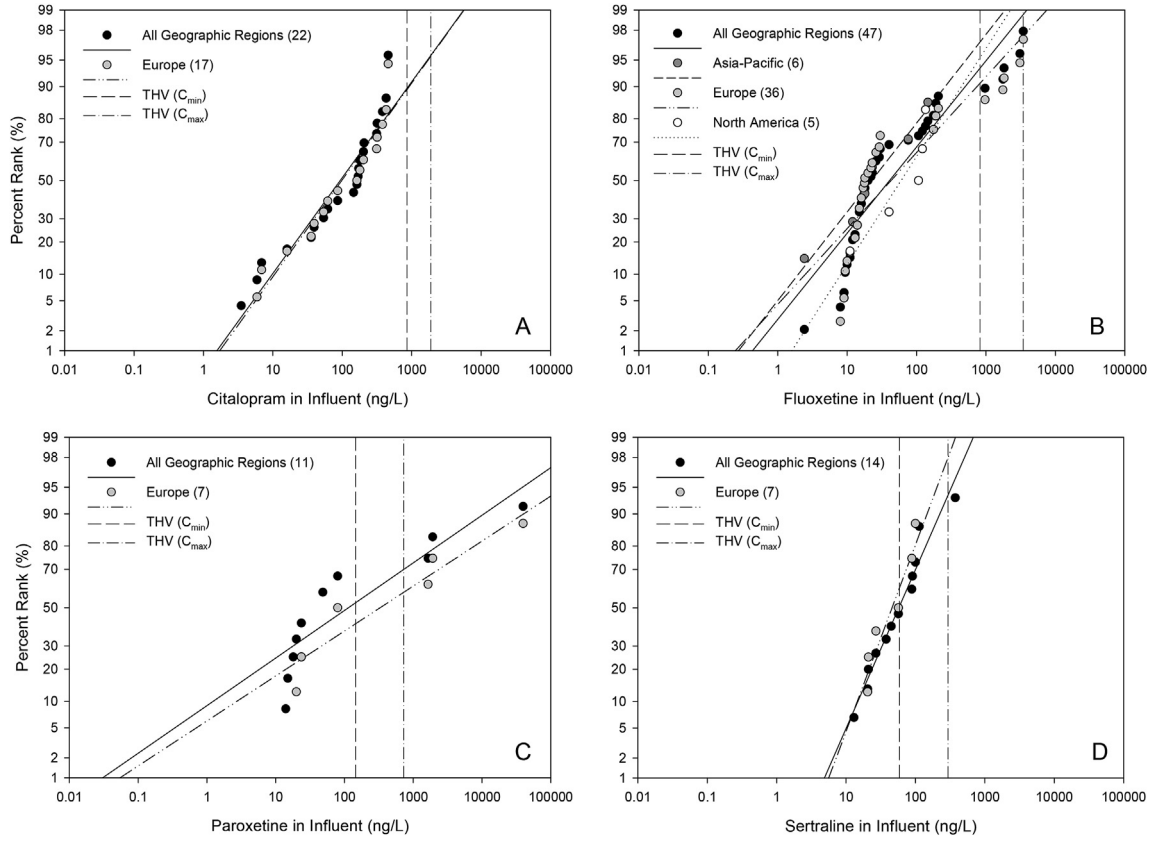

Fig. 1. Environmental exposure distributions for maximum measured influent concentrations for citalopram (A), fluoxetine (B), paroxetine (C), and sertraline (D) across all geographic regions. Numbers in parenthesis indicate the number of unique detections in each geographic region. Vertical dashed lines represent the therapeutic hazard value, predicted using either the human C_{min} or C_{max} without a safety factor of 1000 previously recommended by Huggett et al. (2003), for a specific selective serotonin reuptake inhibitor.

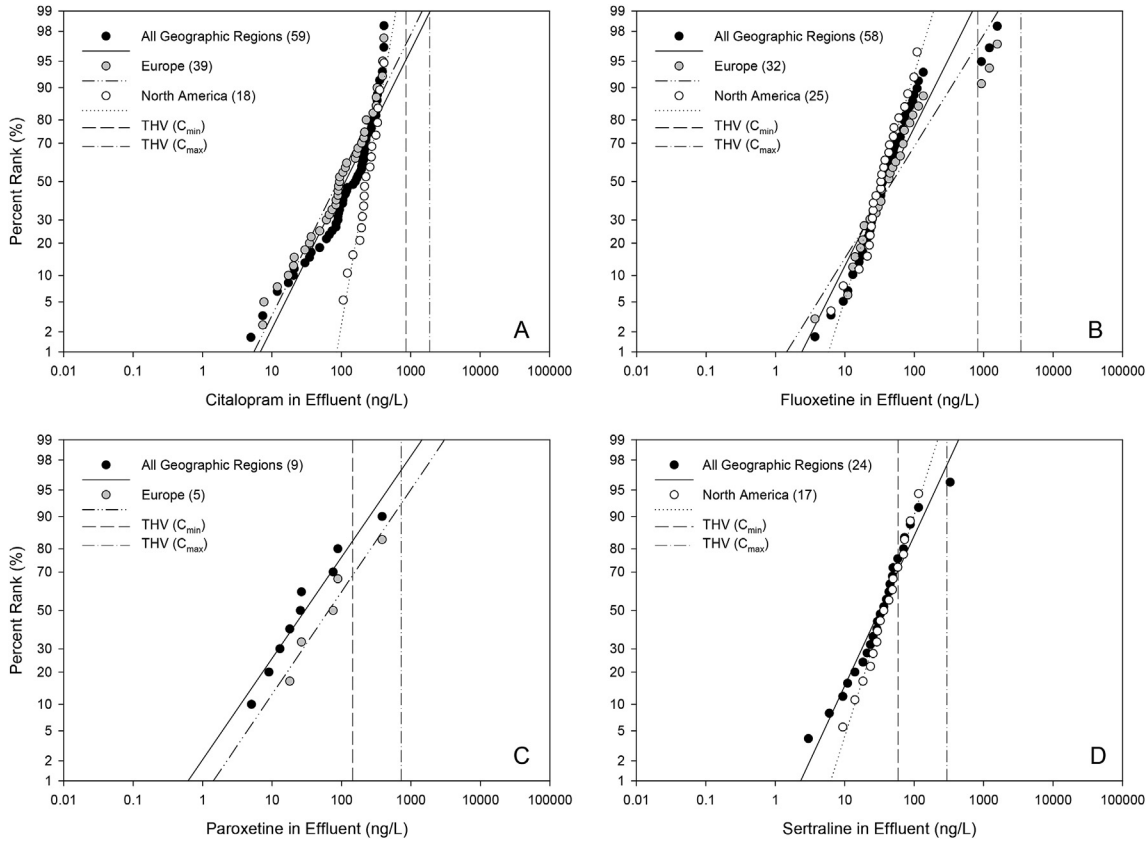

Fig. 2. Environmental exposure distributions for maximum measured effluent concentrations for citalopram (A), fluoxetine (B), paroxetine (C), and sertraline (D) across all geographic regions. Numbers in parenthesis indicate the number of unique detections in each geographic region. Vertical dashed lines represent the therapeutic hazard value, predicted using either the human C_{min} or C_{max} without a safety factor of 1000 previously recommended by Huggett et al. (2003), for a specific selective serotonin reuptake inhibitor.

occurrence data to create metabolite distributions for desmethyl citalopram, norfluoxetine, and norsertraline. The highest numbers of occurrences were for citalopram and fluoxetine (59 and 58, respectively) followed by sertraline (24) and paroxetine (9). Across all geographic regions, the 20th centile value for citalopram (41.2 ng/L) was about three times higher than the 20th centile value for fluoxetine (14.6 ng/L) despite having a similar number of measured occurrences. Whereas citalopram had the highest 20th centile value among parent SSRIs, its metabolite desmethyl citalopram had a 20th centile value two times higher (94.6 ng/L). Though similar to observations for other metabolites, there were only 5 occurrence points for desmethyl citalopram, which all came from the same study in North America (Supplementary Information). Geographically, similar to influent occurrences, the 20th centile for citalopram was significantly higher in North America (161.4 ng/L) compared to Europe (32.7 ng/L). However, similar 20th centile values were observed for both Europe and North America. Unlike we observed for influent sewage, the 20th centile value for fluoxetine (14.6 ng/L) was higher than its primary metabolite, norfluoxetine (9.7 ng/L). Elevated THV exceedances were observed for paroxetine in effluent (Table S1); however, fish toxicology studies incorporating plasma dose information has not been performed for this compound and thus represents a timely and important research need.

Despite the relatively limited information from coastal and marine regions, there was sufficient occurrence data for surface waters to create individual EEDs for both freshwater and marine systems (Table 3). Specifically, EEDs were made for citalopram, fluoxetine, and sertraline in freshwater, though there were only enough data points for citalopram to create an EED from saltwater (Fig. 3A–D). In freshwater systems, citalopram had the highest number of detections (115), followed by sertraline (26), and fluoxetine (19). Norfluoxetine was also detected in freshwater, but only 5 detections were recorded and all were from the same study (Supplementary Information). Such observations are concerning because norfluoxetine more readily crosses the blood brain barrier and is more potent than the parent compound, which is a prodrug. Among surface water detections, citalopram had the highest predicted 20th centile concentration (3.4 ng/L), and the lowest was sertraline (1.6 ng/L) so the range was much smaller than for influent or effluent. Further, when comparing the overall predicted 20th centile values for surface water, influent, and effluent, the surface water values were lower, which suggests instream dilution in those systems. Data was sufficient to perform geographic comparisons for citalopram and fluoxetine in freshwater systems. For citalopram specifically, the predicted 20th centile value in North America (5.2 ng/L) was higher than in Europe (2.8 ng/L). However, an opposite observation was made for fluoxetine with Europe having the higher 20th centile value (3.1 ng/L) compared to North America (1.9 ng/L).

To explore potential aquatic hazards of SSRIs among compounds, matrices, geographic regions and wastewater treatment technologies, we performed PEHAs with THVs (Table S1). As described previously, a THV is the predicted water concentration of a pharmaceutical that may be expected to bioaccumulate in a fish to a human therapeutic level, and is useful diagnostic tool to predict if certain pharmaceuticals present a risk to aquatic life and would therefore require further environmental research (Brooks, 2014).

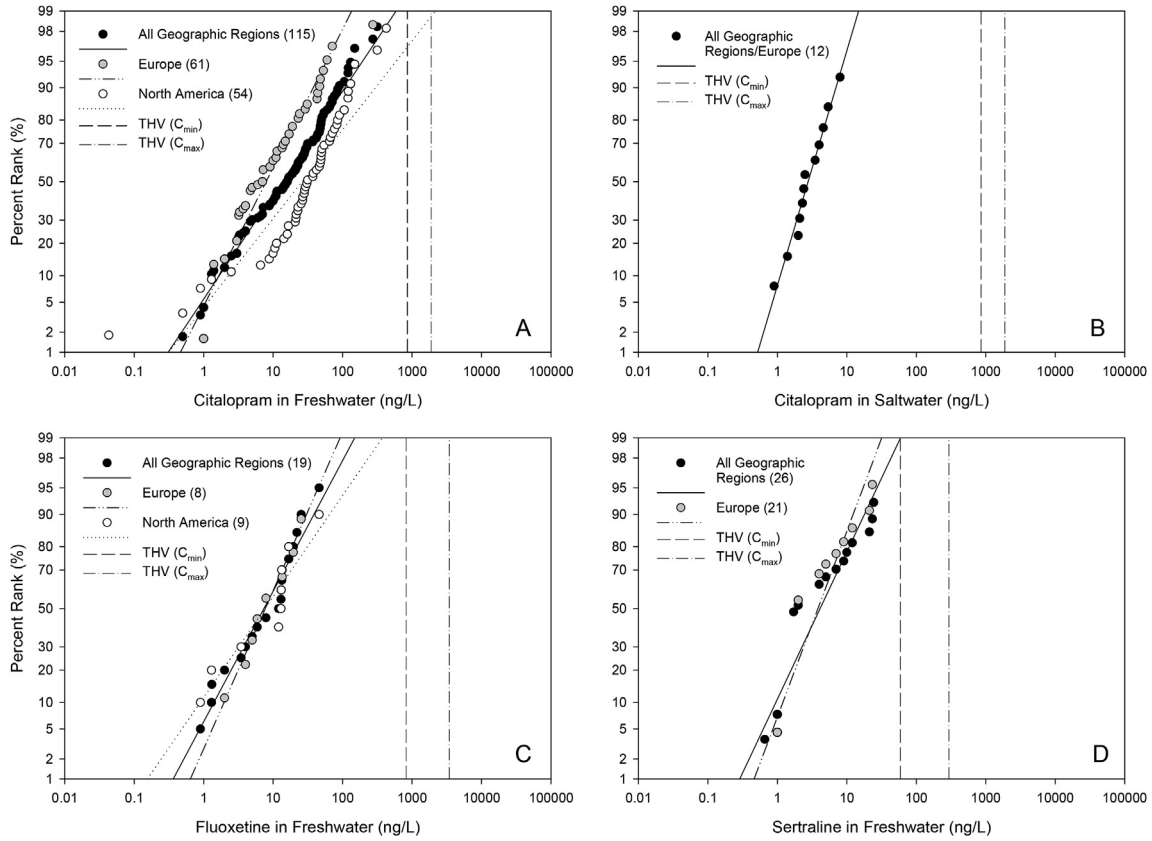

Fig. 3. Environmental exposure distributions for maximum measured surface water concentrations for citalopram in freshwater (A), citalopram in saltwater (B), fluoxetine in freshwater (C), and sertraline in freshwater (D) across all geographic regions. Numbers in parenthesis indicate the number of unique detections in each geographic region. Vertical dashed lines represent the therapeutic hazard value, predicted using either the human C_{min} or C_{max} without a safety factor of 1000 previously recommended by Huggett et al. (2003), for a specific selective serotonin reuptake inhibitor.

Specifically, our research team has employed THV modeling to select treatment levels for toxicology studies (Stanley et al., 2006, 2007; Berninger et al., 2011; Valenti et al., 2012), to examine whether aquatic hazards differ among wastewater treatment technologies (Du et al., 2014), to define spatiotemporal surface water quality in urban coastal systems (Scott et al., 2016, 2019), and to perform assessments with other pharmaceutical classes (Kristofco & Brooks, 2017; Saari et al., 2017). Fish plasma modeling approaches have further been included during various prioritization approaches for pharmaceuticals in the environment due to their advantages over descriptive assays commonly used for regulatory testing (Caldwell et al., 2014; Burns et al., 2018).

Among several considerations for the THV approach (Brooks, 2014), one limitation of THV modeling is that it does not consider pH influence on bioavailability. SSRIs are weak bases with pK_a values that result in ionization at environmentally relevant surface water pH, and are more bioavailable, and thus elicit more pronounced biological effects, at higher pH values (Nakamura et al., 2008; Valenti et al., 2009). For the present study, site-specific pH values were not consistently provided in literature, so this influence on bioavailability was not considered in fish plasma modeling. Further, for THV calculations the uncertainty factor of 1000 recommended by Huggett et al. (2003) was not used. This uncertainty factor was proposed to account for extrapolation from humans to fish, and for variation among fish species is terms of pharmacodynamics and metabolism (Huggett et al., 2003). If this uncertainty factor had been applied during the current study, elevated exceedances would be consistently observed among compounds, matrices, regions and treatment technologies. Clearly, future research is needed to advance mechanistic modeling for ionizables (Nichols et al., 2015; Armitage et al. 2017), including SSRIs, and to refine predictive toxicology of SSRIs across species (Brooks, 2014, 2018). These efforts will likely reduce uncertainties associated with SSRI endpoint sensitivities (Sumpter et al., 2014), including diverse behavior responses, among fish species (Martin et al. 2019a,b).

In the present study, THVs were calculated for each parent SSRI based on minimum (C_{min}) and maximum (C_{max}) human therapeutic plasma concentrations (Schulz et al., 2012). Using both the C_{min} and the C_{max} to predict THVs allows for examining potential exceedances across therapeutic windows in each matrix. Predicted THVs ranged from 858.1 to 59.1 ng/L for the C_{min}, and 1887.8 to 295.4 ng/L for the C_{max} (Table S1). Predicted percent exceedances were calculated across all geographic regions for all SSRIs in influent sewage and effluent; citalopram, fluoxetine, and sertraline in freshwater; and only citalopram in saltwater. In surface water systems there were minimal predicted exceedances, ranging from 0.5 to 1.0%, but again our approach in the present study did not employ the safety factor of 1000 recommended by Huggett et al. (2003) because information for sertraline (Valenti et al., 2012) and fluoxetine (Margiotta-Casalucci et al., 2014) identify the utility of fish plasma modeling for these SSRIs. Whether such approaches extend to other SSRI remains unknown, but mechanistically derived adverse outcome thresholds associated with internal dose clearly are advantaged compared to morphometric responses not plausibly linked to molecular initiation events for biological active molecules (Ankley et al., 2007; Berninger and Brooks, 2010; Valenti et al., 2012; Brooks, 2014; Caldwell et al., 2014; Margiotta-Casaluci et al., 2014, 2016; Brooks, 2018).

Table 4
Equations for regressions lines and values corresponding to various centile values for environmental exposure distributions (EEDs) of maximum reported measured environmental concentrations (MECs) for selective serotonin reuptake inhibitors (SSRIs; ng/L) following primary, secondary, and tertiary wastewater treatment. For each distribution, 'n' represents the number of SSRI MECs reported for a specific treatment and region. EEDs were developed for specific geographic regions when data was sufficient ($n \geq 5$).

Treatment	Region	n	r^2	Slope	Intercept	Centile Value (ng/L)						
						1	5	10	20	50	95	99
Primary	All regions	86	0.98	1.46	−1.44	0.3	0.7	1.3	2.6	9.6	128.1	374.8
	Europe	73	0.98	1.49	−1.39	0.2	0.7	1.2	2.3	8.5	106.8	305.0
	N. America	9	0.89	1.51	−1.86	0.5	1.4	2.4	4.7	16.5	206.0	581.4
Secondary	All regions	204	0.97	1.10	−1.69	0.3	1.1	2.4	5.9	34.2	1061.3	4403.5
	Asia-Pacific	25	0.97	2.10	−2.75	1.6	3.4	5.0	8.1	20.4	124.3	262.7
	Europe	95	0.97	1.16	−1.68	0.3	1.1	2.2	5.3	27.9	720.2	2771.8
	N. America	84	0.92	0.92	−1.57	0.2	0.8	2.1	6.2	50.8	3113.6	1.71×10^4
Advanced	All regions	9	0.89	1.38	−1.02	0.1	0.4	0.7	1.4	5.5	85.7	267.2
	N. America	5	0.84	1.11	−0.98	0.1	0.3	0.5	1.3	7.3	231.6	953.0
Disinfection	All regions	55	0.96	1.18	−2.06	0.6	2.3	4.6	10.9	56.2	1398.3	5295.6
	Europe	17	0.93	1.25	−2.12	0.7	2.4	4.6	10.4	48.8	1001.0	3500.0
	N. America	37	0.94	1.07	−1.91	0.4	1.8	3.9	10.0	61.7	2157.7	9411.7
Filtration	All regions	5	0.96	1.30	−1.67	0.3	1.1	2.0	4.4	19.4	358.0	1197.8
	Europe	5	0.96	1.30	−1.67	0.3	1.1	2.0	4.4	19.4	358.0	1197.8

In influent sewage, all SSRIs were observed to exceed THVs using both the C_{min} and C_{max} calculations. In many developing counties were there is limited to no wastewater treatment capacity, influent exceedances represent direct sewage inputs to surface water systems. The highest predicted percent exceedances were for sertraline (49% (C_{min}), 6.2% (C_{max})) and paroxetine (47.3% (C_{min}), 30.1% (C_{max})) with almost half of environmental concentrations predicted to exceed C_{min} THVs. Despite having higher frequencies of detection, citalopram and fluoxetine only had overall lower predicted exceedances (10.4% (C_{min}), 7.4% (C_{max}); 6.2% (C_{min}), 1.2% (C_{max}); respectively), suggesting future research should examine less commonly studied SSRIs, such as paroxetine and sertraline. Similar observations were made for THV exceedances in effluent. Here again, paroxetine and sertraline had the highest predicted exceedances (17.1% (C_{min}), 2.8% (C_{max}); 29.2% (C_{min}), 2.4% (C_{max})) compared to citalopram and fluoxetine (4.8% (C_{min}), 2.7% (C_{max}); 0.6% (C_{min}), ~0% (C_{max})), which were the most frequently detected SSRIs in effluent. Collectively, effluent exceedances were lower than those observed for SSRIs in influent sewage, which suggests discharge reduction by wastewater treatment technologies.

3.6. Aquatic SSRI hazards among wastewater treatment technologies

To investigate whether different types of wastewater treatment differentially influence SSRIs occurrence in effluent, PEHAs were also performed for each SSRI following different wastewater treatment technologies. We also considered this a useful exercise given gradients of differential wastewater treatment implemented around the world. Levels of wastewater treatment were categorized in one of five types: primary, secondary, disinfection, filtration, and advanced. Primary treatment involves the removal of large constituents from raw influent by rudimentary processes such as bars and coarse screens. Secondary treatment processes include biological treatments to reduce biological oxygen demand, suspended solids, and excess nutrients. Examples of secondary treatment processes include trickling filters and activated sludge. Disinfection processes are sometimes included in secondary treatment steps to remove or inactivate pathogens that are harmful to human health; common disinfection processes are chlorination by hypochlorite, UV light, and ozonation. In the present study, disinfection was categorized as a separate treatment type (Metcalf & Eddy, 2014), again given global differences in treatment capacity, in an attempt to further examine SSRI occurrence among wastewater treatment processes.

Due to the structure of available datasets, mean MECs were used rather than maximum MECs to create EEDs and perform subsequent PEHAs for various levels of wastewater treatment processes. Across all geographic regions and all SSRIs, the most frequently reported type of wastewater treatment was secondary (204), followed by primary (86), and disinfection (55) (Table 4). Among geographic regions, Europe had the highest frequency of primary effluent detections (73) compared to North America (9) (Table 4). It is important to note, however, that in many developing regions of the world there was a lack of literature on SSRI occurrence. In these regions, typical wastewater treatment consisted only of primary screens; therefore, this data gap is important for future study. For secondary effluents, Europe had the highest number of detections (95), followed by North America (84), and Asia-Pacific (25). Finally, for the three more advanced treated effluents, generally more detects came from North America, indicating there may be a higher frequency of advanced treatment technologies in North America compared to Europe or other geographic regions (Table 4).

We then examined potential differences in SSRI occurrence based on treatment process for each treatment process among all SSRIs and within geographic regions when data was sufficient. When comparing 20th centile values across treatment types, observations were highest for disinfection treatment processes (10.8 ng/L) and lowest for advanced processes (1.4 ng/L). There were not distinct trends in such observations as treatment became more sophisticated (Table 4). To further examine the influence of wastewater treatment technologies, we employed EEDs for individual SSRIs to examine exceedances of THVs among the different treatment types (Fig. 4 A-D and Table S2). Comparing primary and secondary treatment, percent exceedance of the THV for every SSRI was higher after secondary treatment versus primary. One potential explanation for this observation is the metabolism of SSRIs. When a human excretes an SSRI, it is excreted as both the parent compound along with corresponding metabolites. During secondary treatment processes, microorganisms may be biotransforming this human metabolite and reactivating it to the parent form of the compound. No noticeable trends were observed in THV exceedance as treatments became more advanced. For example, citalopram showed higher predicted exceedances after treatment by disinfection (18.2% (C_{min}), 10.9% (C_{max})) versus primary treatment (5.8%

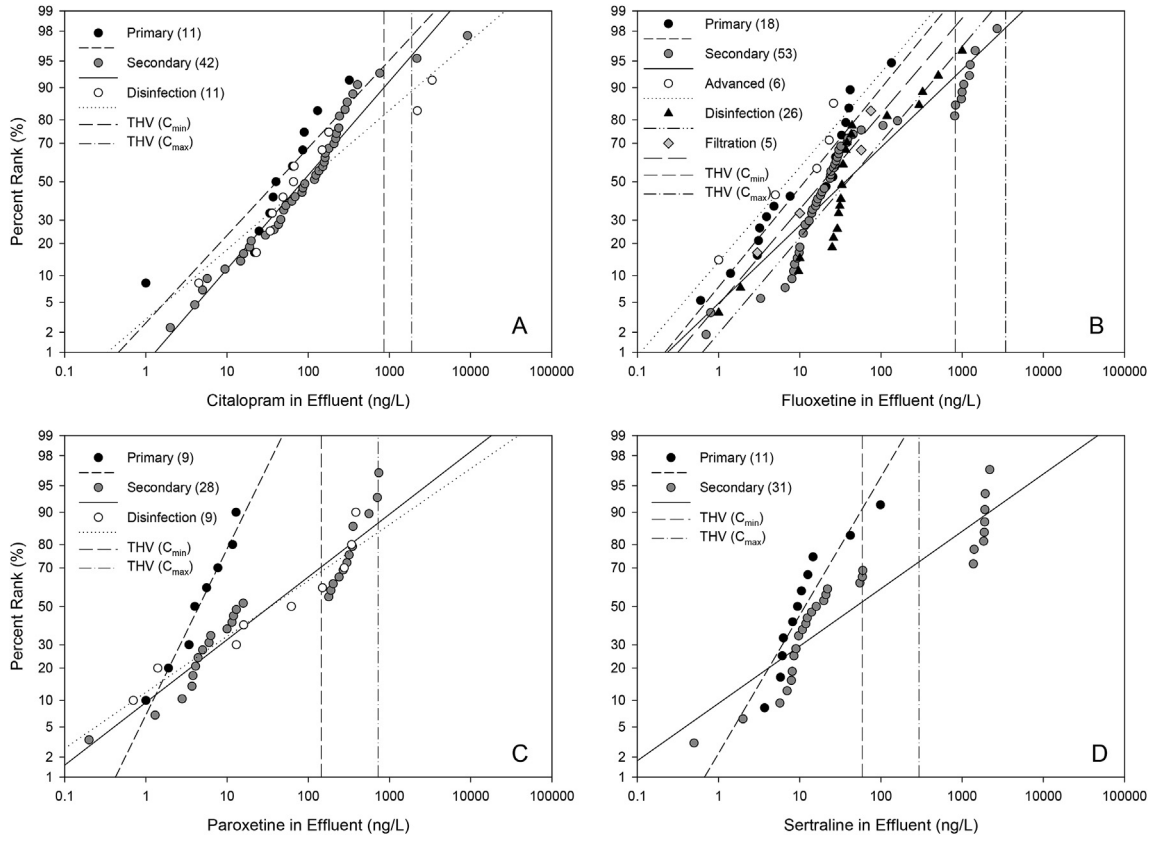

Fig. 4. Environmental exposure distributions for mean measured effluent concentrations for citalopram (A), fluoxetine (B), paroxetine (C), and sertraline (D) among different wastewater treatment types across all geographic regions. Numbers in parenthesis indicate the number of unique detections for each treatment type. Vertical dashed lines represent the therapeutic hazard value, predicted using either the human C_{min} or C_{max} without a safety factor of 1000 previously recommended by Huggett et al. (2003), for a specific selective serotonin reuptake inhibitor.

(C_{min}), 2.4% (C_{max})). Fluoxetine was the only SSRI that had enough available data to predict exceedances for all treatment types, but again with no clear pattern was observed with treatment sophistication.

Removal characteristics of various water and wastewater treatment technologies for pharmaceuticals, including SSRIs, have been described (Gerrity and Snyder, 2012). In addition, several site-specific studies demonstrate how different community consumption patterns of drugs and types of wastewater treatment processes and operations influence concentration of SSRIs in final effluent (Metcalfe et al., 2010; Lajeunesse et al., 2012; Lajeunesse et al., 2013; Silva et al., 2014). For example, Lajeunesse et al. (2012) demonstrated that SSRIs and selective norepinephrine reuptake inhibitors have higher removal efficiencies following secondary biological processes than primary treatment alone. These researchers further demonstrated that secondary treatment including biological nutrient removal had higher removal efficiencies of antidepressants compared to secondary processes with trickling filters. More advanced treatment processes have also been shown to impact antidepressant removal in effluents. Specifically, Snyder et al. (2006) found that ozone oxidation removed greater than 90% of fluoxetine in surface water and wastewater effluent samples in both field samples and bench-scale experiments. However, the present study was not designed to examine such site-specific influences on discharge concentrations of SSRIs, but rather provide a global perspective on SSRI occurrence in effluents from various treatment technologies. Future analysis should be performed to assess potential aquatic hazards of differentially treated wastewater effluents.

4. Conclusions

In the present study, we examined published literature on SSRIs in various aquatic matrices, among all geographic regions. One hundred and fifty two publications reported the occurrence of six parent SSRIs and four metabolites in water matrices. The majority of these publications came from Europe and North America, with minimal data from Asia-Pacific, a diverse region with elevated population growth and an increasing number of megacities near coastal regions. Data was scarce or nonexistent for South America and Africa, indicating that potential risks of SSRIs to aquatic life in those regions requires further attention. In fact, it appears critical that more research be focused on areas that will be experiencing the largest increases in population growth and concentration of these populations in cities over the coming years, particularly where wastewater treatment infrastructure and environmental management systems are limited. When data was sufficient, some geographic patterns were observed for specific SSRIs. In particular, fluoxetine has been studied more frequently in North America, compared to citalopram, which was more frequently reported from water matrices in Europe.

When data was available, PEHAs were performed for specific SSRIs among different water matrices, geographic regions and different types of wastewater treatment technologies. For surface water systems, there were limited exceedances of THVs, but in influent sewage and effluent, all SSRIs exceeded THVs using the C_{min}. The highest exceedance values were observed for paroxetine and sertraline in influent and effluent, despite not being the most frequently studied SSRIs. Specifically, Valenti et al. (2009) and

Margiotta-Casaluci et al. (2014) demonstrated that THV modeling provides high predictive utility for hazards to aquatic life for sertraline and fluoxetine, respectively. To our knowledge, similar mechanistic partitioning and toxicity work has not been done with citalopram and paroxetine indicating an area of imperative research need because citalopram was one of the most frequently detected SSRIs and paroxetine was predicted to exceed the THV (C_{min}) almost half of the time in influent detections. Among wastewater treatment technologies examined, THV exceedances for each SSRI were not observed among treatment type, though effluent levels and exceedances were consistently lower than influent sewage, which highlights the importance of extending monitoring efforts in regions with limited treatment capacity (Kookana et al., 2014).

It is important to note that fluoxetine, and potentially other SSRIs, exhibits appreciable binding (up to ~50%) to suspended particulates (Baker and Kasprzyk-Hordern, 2011), yet analytical methods for SSRIs in the aquatic matrices we examined here commonly prefilter water samples to remove these particles prior to extraction, a practice that likely has underestimated surface water levels of SSRIs. In fact, SSRI accumulation in filter feeding bivalves are consistently elevated compared to fish, suggesting particle bound SSRIs are an important dietary route of exposure in molluscs (Burket et al., 2019). Further, in the present study we employed a hazard assessment approach using THVs without a 1000 safety factor recommended by Huggett et al. (2003). If this safety factor had been used, then consistent exceedances would have been observed for these SSRIs across matrices, regions and treatment technologies. Future research with SSRIs is necessary to reduce uncertainties by improving predictive utility of models and approaches for cross-species extrapolations (Berninger et al., 2016; LaLone et al., 2016), particularly given diverse behavioral consequences increasingly reported for SSRIs (Stanley et al., 2007; Painter et al., 2009; Valenti et al., 2012; Brooks, 2014; Fong and Ford, 2014; Margiotta-Casaluci et al., 2014; Stewart et al., 2014; Weinberger and Klaper, 2014; Woodman et al., 2016; McDonald, 2017; Melvin, 2017; Pyle and Ford, 2017; Bertram et al., 2018; Martin et al., 2017, 2019; Saaristo et al., 2017, 2018; Brooks, 2018; Brooks and Steele, 2018; Steele et al., 2018; Martin et al. 2019a,b) and other neuroactive substances in aquatic systems.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2019.04.118.

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