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Pharmaceuticals in raw and treated water from drinking water treatment plants nationwide: Insights into their sources and exposure risk assessment

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ABSTRACT

Due to the large amounts of pharmaceuticals and personal care products (PPCPs) currently being consumed and released into the environment, this study provides a comprehensive analysis of pharmaceutical pollution in both raw and treated water from full-scale drinking water treatment plants nationwide. Our investigation revealed that 30 out of 37 PPCPs were present in raw water with mean concentrations ranging from 0.01–131 ng/L. The raw water sources, surface water (ND – 147 ng/L), subsurface water (ND – 123 ng/L) and reservoir sources (ND – 135 ng/L) exhibited higher mean concentration levels of pharmaceutical residues compared to groundwater sources (ND – 1.89 ng/L). Meanwhile, in treated water, 17 of the 37 analyzed PPCPs were present with carbamazepine, clarithromycin, fluconazole, telmisartan, valsartan, and cotinine being the most common (detection frequency > 40 %), and having mean concentrations of 1.22, 0.12, 3.48, 40.1, 6.36, and 3.73 ng/L, respectively. These findings highlight that, while water treatment processes are effective, there are some persistent compounds that prove challenging to fully eliminate. Using Monte Carlo simulations, risk assessment indicated that most of these compounds are likely to have negligible impact on human health, except for the antihypertensives. Telmisartan was identified as posing the highest ecological risk (RQ > 1), warranting further investigation, and monitoring. The study concludes by prioritizing specific 14 pharmaceuticals, including telmisartan, clarithromycin, lamotrigine, cotinine, lidocaine, tramadol, and others, for future monitoring to safeguard both ecological and human health.

1. Introduction

In the past two decades, there has been a growing global concern about the presence of pharmaceuticals and personal care products (PPCPs) in the aquatic environment (Ślósarczyk et al., 2021). Their presence in the aquatic environment primarily depends on their sales volume, pharmacokinetics (half-life, excretion, metabolism), the rate of disinfection in sewage systems and wastewater treatment plants (WWTPs) (Bayer et al., 2014; Huerta-Fontela et al., 2011; Romanucci et al., 2020). Additionally, they can also result from the improper disposal of expired pharmaceutical drugs and photodegradation of parent compounds (Ślósarczyk et al., 2021; Temussi et al., 2011). As a result, a large amount of PPCPs and their related metabolites have been detected in the aquatic environment, and the list is continuously increasing (Romanucci et al., 2020). While most PPCPs are not highly persistent, continuous addition of the parent PPCPs and their metabolites to the environment in small notable amounts, has led to their being considered as "pseudo-persistent" (Patel et al., 2019). They are biologically active even at low concentrations (Boxall et al., 2012; Vulliet and Cren-Olivé, 2011), hence their presence in treated drinking water may pose a significant threat to the drinking water quality (Jones et al., 2005). Despite the global increase in the manufacture, consumption, and environmental discharge of PPCPs, for a vast majority, there has been no environmental regulations (Čelić et al., 2019). In 2020, five PPCP compounds (amoxicillin, ciprofloxacin, sulfamethoxazole, trimethoprim, and venlafaxine) were included in the "Watch List" of the European Union (EU) (2020), Gómez-Regalado et al. (2023). And by 2022, two antibiotics (clindamycin and ofloxacin), and one PPCP compound (metformin and its degradation product) were proposed for inclusion in the 4th "Watch List" (Decision, 2015; Gomez Cortes et al., 2022).

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Antihypertensive drug, irbesartan, was moved from priority 3 to priority 2 in the EU commission's 4th watchlist in 2020 (JRC Technical Report, Selection of substances for the 4th watch list under the water framework directive, 2022).

PPCPs have been widely detected in water systems (Bai et al., 2018; Lee et al., 2019; Padhye et al., 2014) and suspect and nontarget studies have shed light on the consumption patterns and contamination status of new PPCPs in the Korean aquatic environment (Baek et al., 2022; Choi et al., 2021; Park et al., 2018; Park and Jeon, 2021) and globally (Čelić et al., 2021; Murrell and Dorman, 2020; Pinasseau et al., 2019). Although the specific PPCPs present in water environments may differ between countries, certain pollutants are widespread, and their potential interactions can pose risks related to the consumption of tap water (Kondor et al., 2021). In South Korea, about 20,800 different human pharmaceutical products are registered for use (Lee et al., 2024) and various PPCPs have been detected in drinking water sources (Cho et al., 2014; Im et al., 2020; Kim et al., 2020). The effectiveness of drinking water treatment plants (DWTPs) treatment processes varies significantly, leading to fluctuations in the concentrations of PPCPs in treated water. In a recent study, 6 PPCPs were detected in drinking water with maximum concentrations ranging from 2.3 to 46.8 ng/L (Kim et al., 2020). Furthermore, as the consumption and manufacture of active pharmaceutical ingredients (APIs) being produced changes and increases globally, with the introduction of new active pharmaceutical ingredients (APIs) annually (FDA website, https://www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda, accessed 30.07.24), there is a need to continuously monitor the concentrations and behavior of their residues in the aquatic environments. While most previous studies in Korea have focused on PPCPs in WWTPs and surface water, only two studies have focused on treated drinking water (Kim et al., 2020; Kim et al., 2007). Hence, there is still a limitation on the current contamination status of pharmaceutical residues in drinking water despite the continuous emergence of new APIs.

Therefore, the main objective of this study was to determine the nationwide occurrence and distribution of 37 PPCPs in raw and treated water from DWTPs and estimate their exposure risk to human health through Monte Carlo simulations. Additionally, the raw water concentrations were used to determine the ecological risks and a scoring system was used to prioritize PPCPs. This study will fill a crucial knowledge gap in understanding the quality of drinking water and source impacts, thereby guiding regulatory bodies in policy implementations.

2. Results and discussion

2.1. Occurrence of pharmaceutical residues in raw water and impact on sources

The overall detection frequencies, mean concentrations, minimum and maximum values of the detected pharmaceutical residues in raw and drinking water are summarized in Table 1. In raw water, 30 out of 37 different PPCPs were detected (> MDL) in at least one sampling site. Diltiazem, flumequine, ketoprofen, sulfachlorpyridazine, sulfadimethoxine, sulfathiazole, and triclocarban were not detected at any site. The mean concentrations of the 30 detected compounds ranged from

Table 1
Summary of PPCPs showing detection frequencies (DF%), minimum (Min), maximum (Max) and mean (Mean) concentrations.

Therapeutic Groups		PPCPs	Raw Water (n = 70)				Treated Water (n = 70)			
			DF% *	Min (ng/L)	Max (ng/L)	Mean (ng/L) *	DF% *	Min (ng/L)	Max (ng/L)	Mean (ng/L) *
Antibiotics (10)		Clarithromycin	81	ND	57.4	2.74	61	ND	0.46	0.12
		Roxithromycin	66	ND	38.5	1.46	4	ND	1.72	0.030
		Sulfamethoxazole	49	ND	1.49	0.42	ND	-	-	-
		Trimethoprim	41	ND	1.43	0.27	ND	-	-	-
		Sulfamethazine	19	ND	5.83	0.36	ND	-	-	-
		Flumequine	ND	-	-	-	ND	-	-	-
		Sulfamonomethoxine	3	ND	0.85	0.021	ND	-	-	-
		Sulfachlorpyridazine	ND	-	-	-	ND	-	-	-
		Sulfadimethoxine	ND	-	-	-	ND	-	-	-
		Sulfathiazole	ND	-	-	-	ND	-	-	-
Antidepressants (5)		Sulpiride	87	ND	234	22.0	7	ND	2.13	0.072
		Venlafaxine	51	ND	5.18	0.44	ND	-	-	-
		Citalopram	43	ND	1.17	0.328	ND	-	-	-
		Diazepam	11	ND	0.61	0.032	1	ND	0.33	0.0047
		Sertraline	7	ND	0.15	0.01	ND	-	-	-
Anticonvulsants (2)		Carbamazepine	90	ND	34.6	6.10	51	ND	22.2	1.22
		Lamotrigine	76	ND	77.1	16.11	ND	-	-	-
Antifungal Agents (4)		Fluconazole	97	ND	42.1	8.77	94	ND	19.2	3.48
		Climbazole	60	ND	19.2	4.51	19	ND	8.11	0.58
		Flubendazole	49	ND	27.9	2.85	ND	-	-	-
		Thiabendazole	34	ND	1.19	0.12	3	ND	0.79	0.016
Antihypertensives (4)		Telmisartan	84	ND	596	131	54	ND	532	40.1
		Losartan	56	ND	5.50	1.26	14	ND	4.86	0.29
		Valsartan	40	ND	1.42	0.32	73	ND	44.4	6.36
		Diltiazem	ND	-	-	-	ND	-	-	-
Beta blockers (2)		Propranolol	27	ND	1.53	0.26	ND	-	-	-
		Metoprolol	3	ND	1.72	0.05	ND	-	-	-
Non-steroidal anti-inflammatory drugs (NSAIDs) (2)		Naproxen	16	ND	11.1	0.79	3	ND	1.65	0.05
		Ketoprofen	ND	-	-	-	ND	-	-	-
Metabolites (2)		Cotinine	80	ND	38.7	11.5	60	ND	21.9	3.73
		Fenbendazole-SO_2	3	ND	0.40	0.010	ND	-	-	-
Others (6)	Opioid Analgesic (1)	Tramadol	84	ND	92.2	15.9	6	ND	1.68	0.073
	Antihistamine (1)	Fexofenadine	70	ND	36.9	5.05	3	ND	0.80	0.022
	Antiarrhythmic (1)	Lidocaine	70	ND	34.2	8.21	ND	-	-	-
	Ectoparasite (1)	Crotamiton	59	ND	7.53	1.82	23	ND	3.12	0.27
	Contrasting Agent (1)	Iopromide	30	ND	12.5	1.63	9	ND	14.0	0.517
	Antibacterial Agent (1)	Triclocarban	ND	-	-	-	ND	-	-	-

* Non-detects (ND) were treated as zero for the calculation of mean and DF%

0.01 for sertraline to 131 ng/L for telmisartan. The most widely detected compounds included fluconazole (97 %), clarithromycin (81 %), carbamazepine (90 %), sulpiride (87 %), telmisartan (84 %), tramadol (84 %), and cotinine (80 %) with maximum concentrations of 42.1 ng/L, 57.4 ng/L, 34.6 ng/L, 234 ng/L, 596 ng/L, 92.2 ng/L, and 38.7 ng/L respectively. The antihypertensive drug, telmisartan and antidepressant, sulpiride were the highest contributors to the total PPCPs concentration (Table 1). The rise in usage of over the counter (OTC) drugs has resulted in the increased levels of pharmaceutical compounds in wastewater effluents (Choi et al., 2021). The high concentration and persistence of telmisartan could be attributed to its low metabolism in the human body and its relatively long half-life (Lee et al., 2023). From 2002 to 2018, the

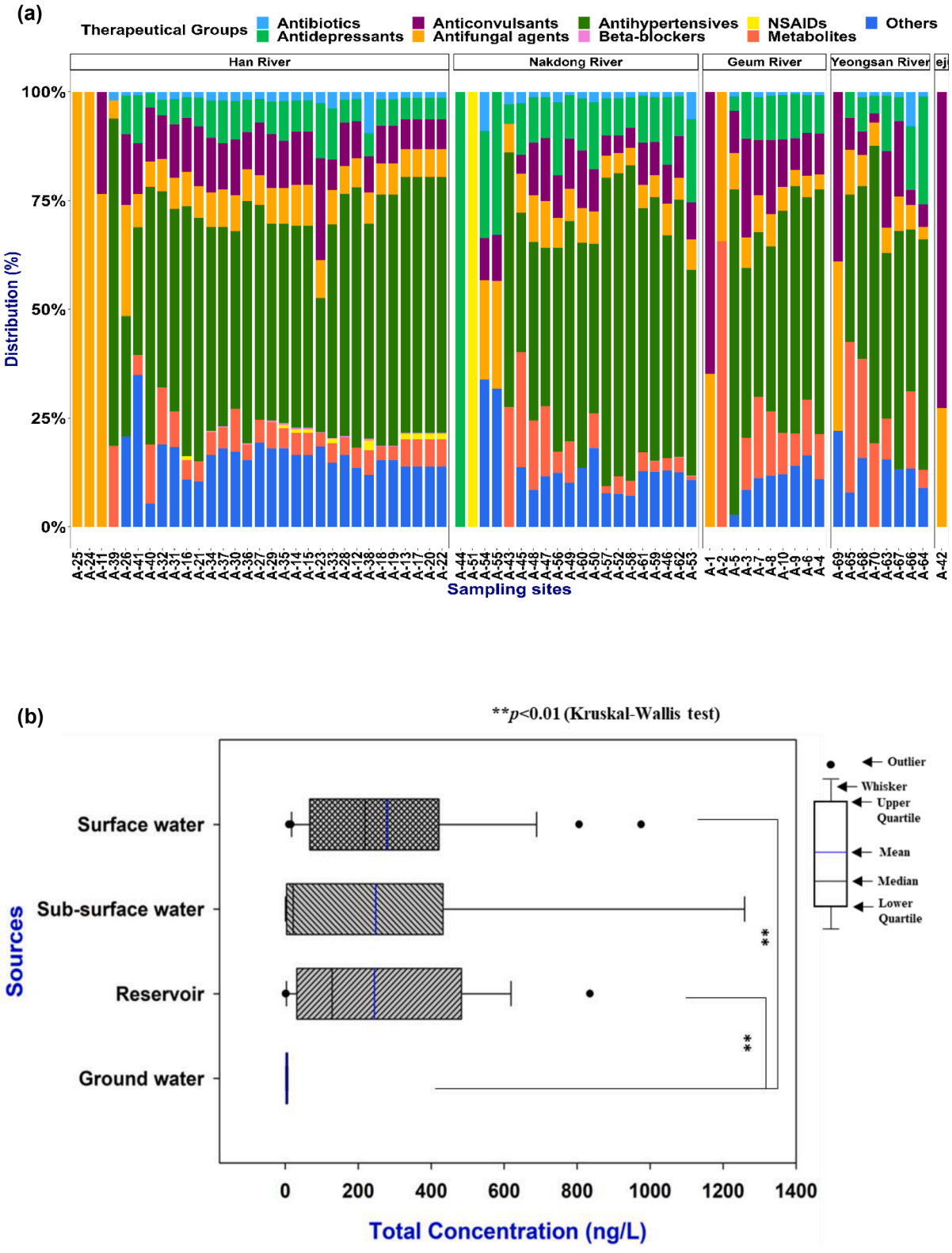

Fig. 1. (a) Distribution of pharmaceutical therapeutical groups in raw water, (b) Total PPCPs contamination (ng/L) in raw water according to their sources.

number of South Korean inhabitants using antihypertensive medication increased from 2.5 million to 9.0 million and amongst the antihypertensive medications, the angiotensin receptor blockers were the most commonly prescribed followed by channel blockers (Kim et al., 2021), which may further explain the high concentrations of the angiotensin II receptor blockers (telmisartan, valsartan, and losartan) in the raw water in this study. As reported by previous studies (Bayer et al., 2014; Jarari et al., 2016; Oliveros et al., 2020; Schwabe and Paffrath, 2013), in aging societies, more and more PPCPs, especially antihypertensives are being prescribed. The high concentrations of antihypertensives and antidepressants may also give insight into the aging population and the mental health of the population. Studies in several other countries also showed that the COVID-19 pandemic greatly affected the mental health of their populations (Diaz-Camal et al., 2022; Eichenberg et al., 2021; Ettman et al., 2020; Mazza et al., 2020; Perlis et al., 2021; Qiu et al., 2020).

Generally, the concentrations of target compounds in this study varied widely compared to other studies. The concentration of antibiotics (Table 1) (ND to 79.7 ng/L) in this study were much lower than concentrations in reports from Tama River in Japan (4 to 448 ng/L) (Anh et al., 2021), urban lakes in Vietnam (<MQL to 3508 ng/L) (Tran et al., 2019), and Leça River in Portugal (ND to 269 ng/L) (Fernandes et al., 2020), while the antidepressants concentrations (Table 1) in this study (ND to 241 ng/L) were found to be less than those detected at Leça River, Portugal (ND to 641 ng/L) (Fernandes et al., 2020), Tejo estuary (0.16 to 304 ng/L) (Gros et al., 2017), and higher than those reported in Huangpu River, China (Ma et al., 2018). The concentration of antihypertensives in this study (ND to 597 ng/L) were similar to the Emissary (site SCR) in Spain (457 to 534 ng/L), but higher than concentrations in Tejo estuary (1.52 to 64.70 ng/L) (Gros et al., 2017), and Ebro River (3.8 to 237.9 ng/L) (Čelić et al., 2021). For metabolites, cotinine, which is the major metabolite of nicotine and the main degradation byproduct of nicotine during oxidative processes in wastewater treatment plants (Zarrelli et al., 2012) was recently proposed as a possible indicator of domestic wastewater pollution in surface waters (Čelić et al., 2021). It had a detection frequency of 60 % with concentrations ranging from ND to 21.9 ng/L, implying the occurrence of metabolites in the hydrologic system. In other studies, cotinine has also been detected at similar detection frequencies (59.3 % to 61.1 %) with higher maximum concentrations (18.1 to 120 ng/L) (Bai et al., 2018). The distribution pattern of pharmaceuticals of this study was similar across all sites except for several sites which showed different patterns (Fig. 1a), mainly from ground water (A-1, A-2, A-11, and A-42) and subsurface water (A-25, A-24, A-54, A-55). Details of all site locations are shown in SI, table S1.

Considering the raw water samples in this study were obtained from different sources, further investigation of contamination status was conducted based on the source types. The raw water sources were organized based on their entry points into the treatment plants; as a result, there were 4 groundwater sources, 27 surface water sources, 9 subsurface water sources and 30 reservoir sources. Fig 1b shows that the mean concentration of surface water, sub-surface water and reservoir sites were higher than the groundwater sites. Statistically significant different results were observed between groundwater and surface water sites ($p<0.01$) and between groundwater and reservoir sites ($p<0.01$). However, there was no statistically significant difference between subsurface water and any of the other sources. We observed a much lower median value of 21.5 ng/L compared to the mean concentration of 248 ng/L for subsurface water sources (Fig 1b). This suggests that, although concentrations were generally low in this source type, the presence of a few samples with high concentrations may have led to an increase in the overall mean concentration value. Subsurface water refers to the water flowing in the hyporheic zones of the stream or riverbed. Water flowing in this region can be influenced by both surface water and the underlying groundwater (Binley et al., 2013). In this study, the high mean concentration of subsurface water sources may imply a higher influence of surface water compared to groundwater. The primary source of micropollutants in surface water is the discharge of wastewater treatment plant effluent (WWTP), while groundwater contamination has various sources such as landfill leachate, sewer leakage, livestock breeding, interaction between surface and groundwater, and the intrusion of contaminated agricultural lands (Fatta-Kassinos et al., 2011; Gupta and Bharagava, 2021). However, in this study due to the low concentrations of PPCPs observed in groundwater sources, we suggest that attenuation occurs by riverbank filtration. Therefore, it is likely that groundwater sources may be better sources for drinking water compared to surface water. In Korea, around 87 % of the water consumption is supplied from surface water (such as rivers and lakes), with the remaining 13 % obtained from groundwater sources. Additionally, most urban and agricultural areas are located along rivers, implying water discharged to upstream regions is inevitably reused further downstream (Cho et al., 2014). Hence, given this reliance on surface water, it is essential to rigorously assess the safety and quality of drinking water sources. Their contamination risks underline the need for more stringent regulations regarding the discharge of PPCPs into these drinking water sources, as well as an overall improvement on the cost and efficiency of wastewater treatment plant techniques.

2.2. Occurrence of pharmaceutical residues in treated water

In this study, 17 out of 37 pharmaceuticals were detected in treated drinking water as opposed to the 30 detected in source water, implying substantial reduction in pharmaceutical residues by DWTP treatment processes. High removal of pharmaceuticals such as NSAIDs, beta-blockers from DWTPs have also been previously reported (Cai et al., 2015; Maycock and Watts, 2011; Yang et al., 2017). The mean total concentrations of detected PPCPs ranged from 0.005 ng/L to 40.1 ng/L and detection frequencies ranged from 1.4 % to 94.3 %. The most predominant compounds with detection frequencies greater than 40 % included carbamazepine (51.4 %, ND – 22.2 ng/L), telmisartan (54.3 %, ND – 532 ng/L), cotinine (60 %, ND – 21.9 ng/L), clarithromycin (61.4 %, ND – 0.46 ng/L), valsartan (72.9 %, ND – 44.4 ng/L), and fluconazole (94.3 %, ND – 19.2 ng/L). In another extensive study in the US, carbamazepine and cotinine were among the most frequently detected compounds with maximum concentrations of 26.5 and 15.8 ng/L, respectively (Furlong et al., 2017; Glassmeyer et al., 2017). In tap water samples from Shanghai, valsartan was widely detected with maximum concentrations of 66.8 ng/L, which is higher than that in our study. Mean concentrations of fluconazole, valsartan and telmisartan in DWTPs from Europe and Asia ranged from ND to 13.8 ng/L, ND to 16.6 ng/L, and ND to 0.77 ng/L, respectively (Tröger et al., 2021).

The spatial distribution and relative contribution of the six predominant PPCPs at DWTPs sites are shown in Fig. 2, revealing the prevalence of telmisartan in most DWTPs. Nonetheless, the contribution of telmisartan was notably low in several DWTPs, indicating variations in the occurrence or removal patterns of the PPCPs across different locations. Generally, the distribution and occurrence of pharmaceutical residues in treated drinking water are known to be related to the water treatment techniques employed or source water characteristics (Furlong et al., 2017; Huerta-Fontela et al., 2011).

Considering the 6 most predominant compounds, when sites were grouped by the source water type, no clear distinction of distribution patterns between the source water types was observed. Hence, treatment plants were grouped into two based on the treatment techniques they utilized, namely, DWTPs utilizing advanced, and conventional treatment techniques. Conventional treatment techniques involve coagulation/flocculation, sedimentation, filtration, and disinfection steps while the advanced treatment techniques include the use of additional processes such as ozonation, granular activated carbon (GAC), or membrane filtration. The removal efficiencies of PPCPs from these two groups were calculated (Table S4) and generally, advanced treatment techniques exhibited better removal of contaminants (except for cotinine) compared to conventional treatment techniques. For DWTPs using advanced treatment, average removal efficiencies ranged from negative

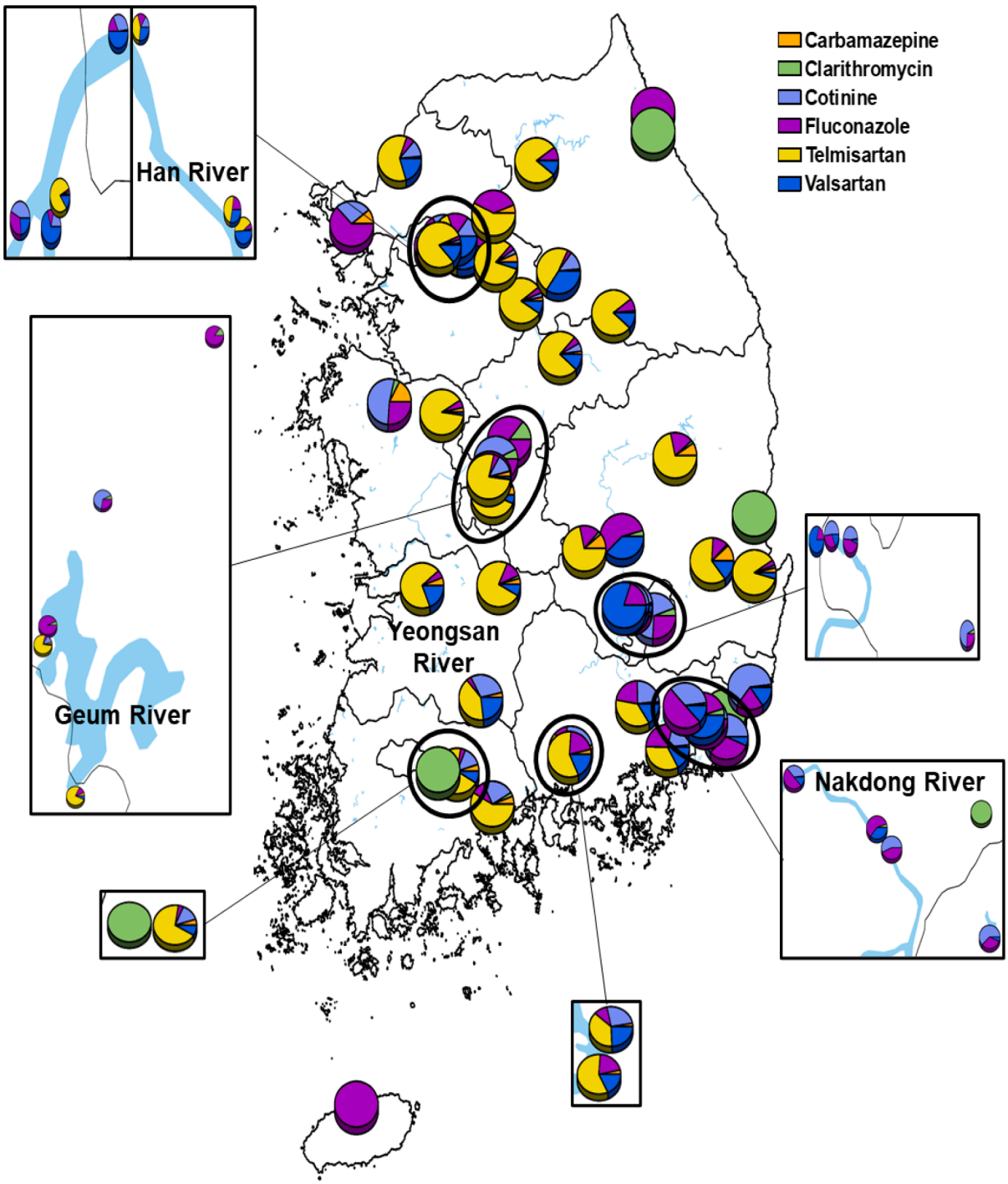

Fig. 2. Nationwide distribution of PPCPs with detection frequencies > 40 % in treated drinking water (HR = Han River, GR = Geum River, NR = Nakdong River, YR = Yeongsan River).

values to 95.9 % (for carbamazepine), while for DWTPs using conventional treatment, average removal efficiencies ranged from negative values to 46.7 % (for carbamazepine). Specifically, all six predominant compounds showed poor removals (< 50 %) for conventional treatment techniques. For advanced treatment techniques, carbamazepine and telmisartan showed high removals (> 90 %), clarithromycin and fluconazole showed moderate removals (70–90 %), while cotinine and valsartan showed poor removals. The relationship between DWTPs and these 6 compounds were further evaluated and confirmed by PCA (Fig S1a). There was a distinction between DWTPs based on their treatment types (Fig 3a). In addition, the PCA biplot (Fig S1b), showing the distribution of the 6 main contributing compounds on the principal components, further revealed a clear separation of telmisartan from the rest of the compounds with its concentration being mostly affected by the conventional DWTPs.

Comparing our results with previous studies, we could confirm that a wide range of removal efficiencies from DWTPs and pilot scale plants had been reported. Nevertheless, the incomplete removal of these 6 compounds was equally evident (Cai et al., 2015; Furlong et al., 2017; Nakada et al., 2007; Padhye et al., 2014; Tröger et al., 2021; Zhang et al., 2016). Such variations between removal efficiencies from different studies could be related to the source water characteristics as earlier

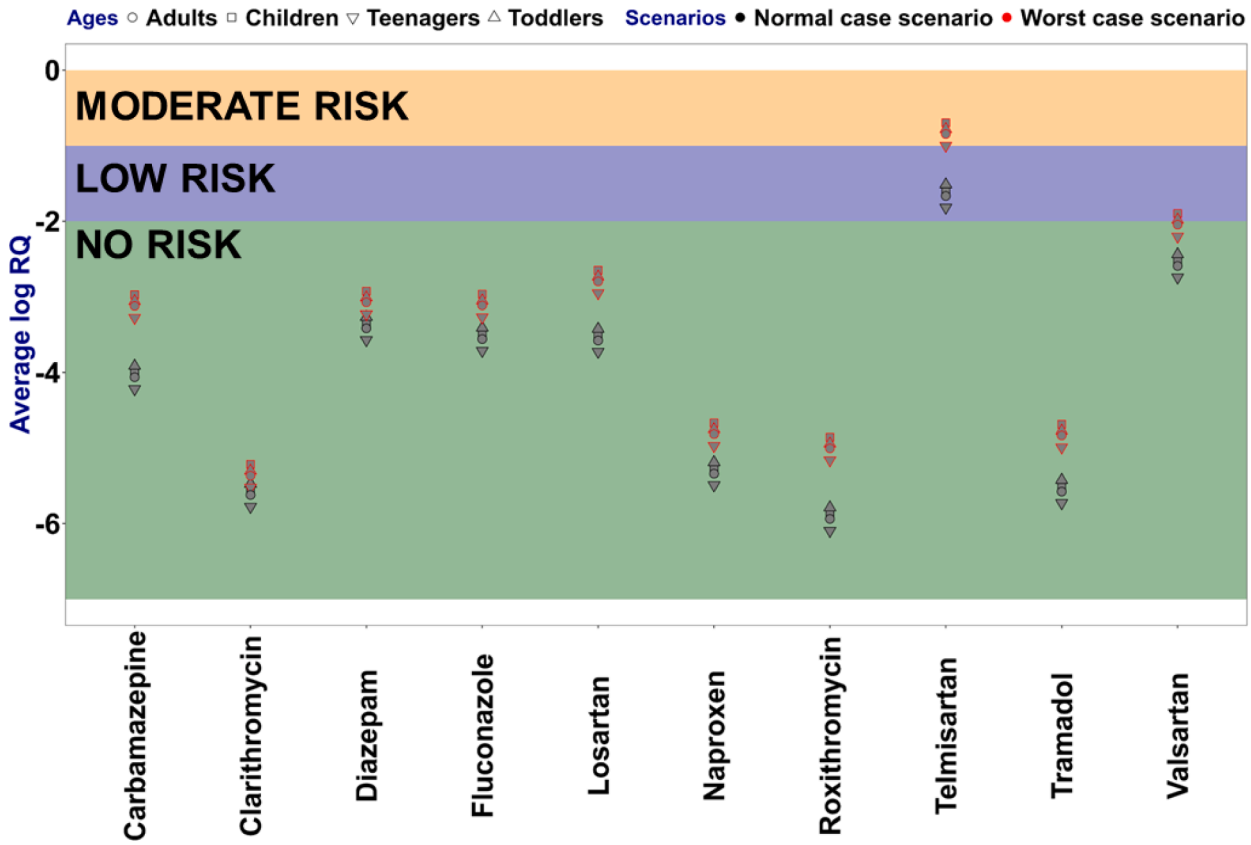

Fig. 3. Average risk quotients for human health risk assessment (based on log scale).

mentioned, meanwhile (Wu et al., 2012), showed that as the raw water matrix became more complex, removal of pharmaceuticals decreased. The presence of telmisartan in DWTPs has been rarely studied, with only one study by (Tröger et al., 2021) reporting its concentrations in full scale DWTPs, to the best of our knowledge. This study reported removal efficiencies of 13.5 to 89 % for advanced DWTPs and 86.5 % for one conventional DWTP, although it had low concentrations of telmisartan in the raw water. In our study we observed high removal efficiency by advanced treatment (93.6 %) and poor removal efficiency by conventional treatment (0 %) (Table S4). The behavior of these compounds through unit processes of the DWTPs in our study is not well known since only raw and treated water samples were collected. However, some studies have shown a critical interplay between molecular structure, physicochemical properties, and the removal of compounds from DWTPs (Kang et al., 2023; Kim et al., 2021; Nakada et al., 2007). As removal efficiencies are related to various factors such as physicochemical properties and treatment technologies utilized, further research using controlled pilot – or laboratory- scale studies is warranted. Furthermore, the persistence of these compounds in treated water raises concerns about their potential human health effects following long-term exposure.

2.3. Identification of PPCPs with the highest risks to humans and the aquatic ecosystems

2.3.1. Human health risk assessment based on PPCPs in treated drinking water

Mean and maximum concentrations were used to estimate the human health risk through consumption of drinking water to provide a "normal exposure scenario" and "worst-case exposure scenario", respectively. Acceptable daily intake (ADI) values used in this study were obtained from a previous study by (Khan and Nicell, 2015) and used to calculate the drinking water equivalent level (DWEL) for each age group. Due to the absence of ADI values for most pharmaceuticals, the risk quotient (RQ) was only estimated for 10 out of the 17 compounds detected, for which ADI values could be applied. For telmisartan, the ADI value for irbesartan was used to estimate the risk, since they have the closest properties such as mode of action (non-competitive antagonists), longer acting compared to the other sartans (Ladhari et al., 2021) and similar biodegradation half-lives, 34.7 days for irbesartan and 37.2 days for telmisartan, (Williams et al., 2017). Average RQs in normal exposure scenarios for toddlers, children, teenagers, and adults were in the range of 10^{-2}–10^{-7}, with valsartan, fluconazole, losartan, and telmisartan being at the lower end (Table S5). Telmisartan, particularly showed low risk for all age groups, while the risk for other PPCPs was negligible ($> 10^{-4}$). In the worst-case exposure scenario, toddlers and children had the highest exposures to telmisartan and valsartan (10^{-1} – 10^{-2}). Overall, toddlers and children may be more sensitive, and this is closely related to their smaller body weight and drinking water intake (DWI). In a Canadian study, (Khan and Nicell, 2015) identified candesartan and irbesartan (which are in the same pharmaceutical group as valsartan and telmisartan) amongst other PPCPs, as compounds that are relevant to human health to be prioritized for future monitoring studies in drinking water. Fig 3 shows the average risk quotients on a logarithmic scale.

2.3.2. Ecological risk assessment

To present an overview of the ecological risks associated with the occurrence of PPCPs, the RQ for 25 compounds was calculated, the PPCPs were prioritized, and the site dependent RQs were evaluated. The concentration of PPCPs in the 95th percentile was used to calculate the risk quotients (Fig 4). Accordingly, compounds with average high risk were telmisartan (RQ > 1), while cotinine, clarithromycin, and lamotrigine showed an average moderate risk (0.1 < RQ < 1), and compounds with average low risk were fexofenadine, iopromide, lidocaine, roxithromycin, sertraline, sulfamethazine, tramadol, and venlafaxine

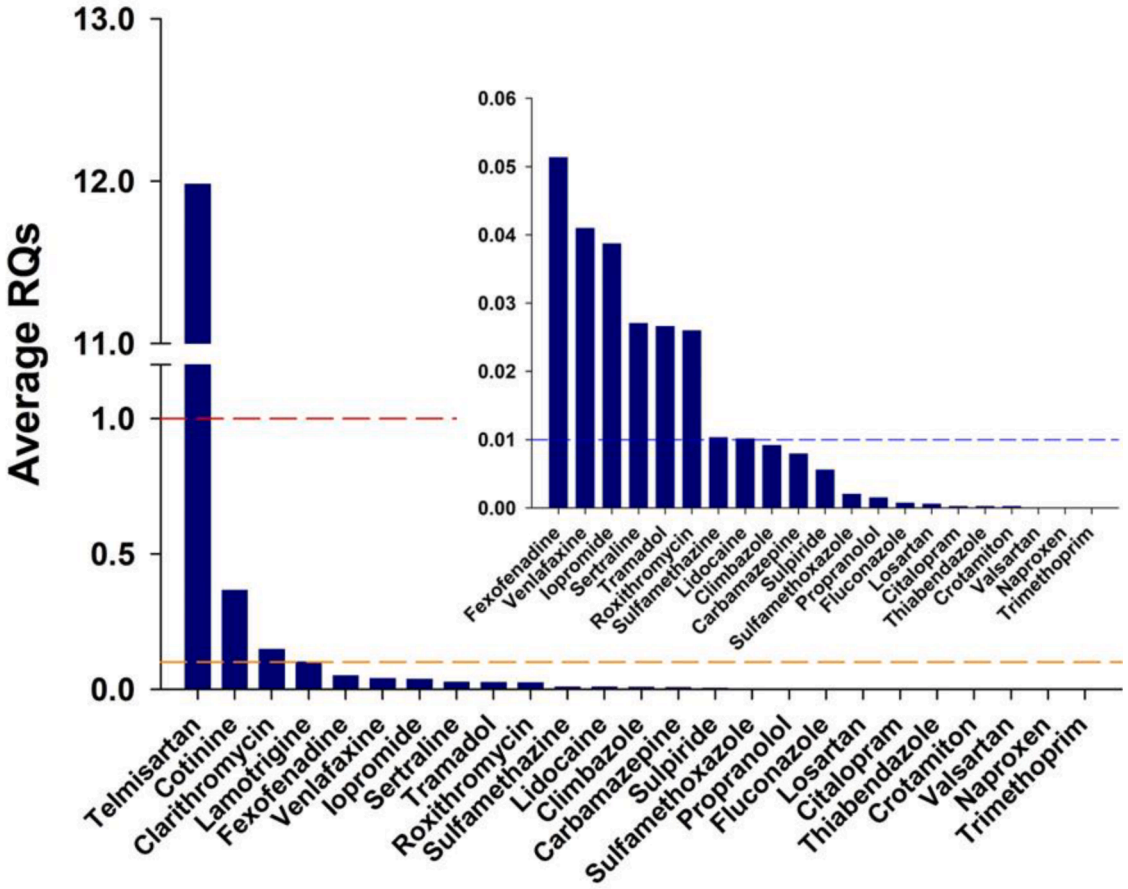

Fig. 4. Graph showing average risk quotients for PPCPs (RQ values are based on MECs in the 95th percentile) (Red line represents RQ = 1, orange line represents RQ = 0.1, blue line represents RQ = 0.01).

(0.01 < RQ < 0.1) as can been seen in Fig. 4. According to (Čelić et al., 2021), telmisartan, venlafaxine, and carbamazepine were found to be of high ecological concern in Spanish aquatic environment. Telmisartan, specifically, had RQ values ranging from 28 to 972 showing its toxic potential at environmentally relevant concentrations. In the Nakdong river, (Lee et al., 2024) also classified telmisartan as a very high-risk compound. It has the longest half-life among all the ARBs and is known to be problematic with low removal efficiencies in both surface water and sewage samples (Giebułtowicz et al., 2016; Mijangos et al., 2018). Some previous studies have shown that telmisartan, at environmentally relevant concentrations, also shows toxicity to aquatic life by reproductive toxicity and gene alteration (Meng et al., 2020; Muambo et al., 2024; Zuo et al., 2022).

In our study, although roxithromycin and venlafaxine showed low risk at the 95th percentile concentrations, they showed site-specific moderate risks at 2 sites (A-38 and A-53) and 1 site (A-53), respectively. Similarly, clarithromycin which showed an overall moderate risk, showed high risk at 1 site (A-53). Therefore, at these specific sites, the use of these PPCPs may require further investigation in a bid to decrease the potential risk they represent.

Furthermore, prioritization was done based on a strategy published by (Gros et al., 2017) with some modification. The factors that were considered include (a) detection frequency of compounds in samples, (b) maximum concentrations, (c) ecotoxicity data, based on RQ ratios, and (d) bioconcentration factors (SI, Table S6). Log of bioconcentration factors (Log BCF) were obtained from the US EPA, EPI suite™ v4.11. According to table S6, each PPCP was given a score ranging from 1 to 4 in each category (a) to (d) and the PPCPs with higher overall scores were suggested as the most environmentally relevant PPCPs. Details of the parameters used for scoring are included in the SI, Table S7. Consequently, based on nationwide data, 14 PPCPs, telmisartan, clarithromycin, lamotrigine, cotinine, tramadol, lidocaine, carbamazepine, climbazole, roxithromycin, fexofenadine, fluconazole, losartan,

Table 2
Priority PPCPs based on scoring system (see Table S6).

Compounds	Therapeutic Group	Score
Telmisartan	Antihypertensive	14
Clarithromycin	Antibiotic	13
Lamotrigine	Anticonvulsant	13
Cotinine	Metabolite	12
Tramadol	Opioid Analgesic	12
Lidocaine	Antiarrhythmic	12
Carbamazepine	Anticonvulsant	11
Climbazole	Antifungal agent	11
Roxithromycin	Antibiotic	11
Fexofenadine	Antihistamine	10
Fluconazole	Antifungal agent	10
Losartan	Antihypertensive	10
Sulpiride	Antidepressant	10
Venlafaxine	Antidepressant	10
Crotamiton	Ectoparasite	9
Iopromide	Contrasting agent	9
Citalopram	Antidepressant	8
Naproxen	Non-steroidal anti-inflammatory drug	8
Sertraline	Antidepressant	8
Propranolol	Beta-blocker	7
Thiabendazole	Antifungal agent	7
Sulfamethazine	Antibiotic	7
Sulfamethoxazole	Antibiotic	6
Trimethoprim	Antibiotic	6
Valsartan	Antihypertensive	6
Metoprolol	Beta-blocker	5

sulpiride, and venlafaxine were prioritized (Table 2). Previously, the study by (Choi et al., 2021) had classified fexofenadine, lamotrigine, lidocaine, telmisartan, tramadol as rarely reported (RRS) and unreported substances (URS) in the Korean aquatic environment. Therefore, in this study, more emphasis is put on these compounds as substances that need to be routinely monitored.

3. Conclusion

This comprehensive nationwide study examined the prevalence and risks of pharmaceutical compounds in 70 full-scale DWTPs focusing on pharmaceuticals that are rarely studied but are increasingly found in drinking water sources. Antihypertensives and antidepressants were specifically ubiquitous in drinking water sources, while six PPCPs (fluconazole, telmisartan, valsartan, cotinine, clarithromycin, and carbamazepine) were predominant in treated water across all DWTPs. In addition, antihypertensives (specifically, telmisartan) showed a higher potential for posing risk to human health through drinking water consumption compared to the other pharmaceuticals. However, due to the lack of ADI values for a majority of PPCPs, risk assessment studies were limited to only a few PPCPs. This urges the need for more data of ADI values for other PPCPs to be made available. Furthermore, the findings of this study call for lab- and pilot scale studies to ascertain the fate and behaviour of telmisartan during water treatment, as it has not been given much attention. Given that most of these compounds (except the antihypertensives) posed negligible risk to human health but moderate to high ecological risk, our prioritization study also underscores the necessity for further and continuous monitoring of these compounds in drinking water sources and treated water.

4. Materials and methods

4.1. Standards and Reagents

The PPCPs were divided into 8 groups according to their properties and uses. The groups are antibiotics (n=10), antidepressants (5), antifungal agents (4), antihypertensives (4), anticonvulsants (2), beta-blockers (2), non-steroidal anti-inflammatory drugs (NSAIDs) (2), metabolites of nicotine and fenbendazole (2), and others (6). The details of the pharmaceuticals and the groups they were placed in are presented in Table 1. All analytical standards were purchased from Sigma-Aldrich (St. Louis, MO, USA). The isotope-labeled pharmaceuticals, trimethoprim-d_9, sulfathiazole-$^{13}C_6$, sulfamethazine-$^{13}C_6$, sulfamethoxazole-$^{13}C_6$, clarithromycin-d_3, roxithromycin-d_7, sertraline-d_3, ketoprofen-d_3, and atrazine-d_5, were purchased from Sigma-Aldrich and were used as internal standards, while atrazine-d_5 was used as the recovery standard. HPLC-grade water and methanol were purchased from B&J Honeywell (Morristown, NJ, USA). Formic acid was purchased from Wako (Osaka, Japan).

4.2. Sample collection

In June 2022, raw water samples (n=70) and treated water samples (70) were collected from 70 drinking water treatment plants (DWTPs) located along four major rivers (Han (HR), Geum (GR), Nakdong (NR), and Yeongsan rivers (YR)) and in Jeju Island in South Korea. Surface river water is the major source water of drinking water in South Korea and the origin of source water in each DWTPs is summarized in the supporting information (SI), Table S1. Water samples were collected before entry into the treatment plant for processing and after treatment, hence two samples were collected from each treatment plant during the sampling campaign. Field blank and duplicate samples were also collected. All samples were collected in 1 L amber glass bottles by the grab sampling method and shipped in dry ice to the laboratory within 24 h. All samples were stored at 4 °C before analysis.

4.3. Sample pretreatment

Prior to sample pretreatment, the pH of all water samples was adjusted to 2.5–3 with 2N HCl and afterwards 5 ng of internal standards were added to the samples. Briefly, 500 mL of raw water samples were passed through a glass fiber filter (GF/F) and extracted using a solid phase extraction manifold purchased from Merck (Darmstadt, Germany). An Oasis HLB cartridge was preconditioned twice with 6 mL of methanol (MeOH) and 6 mL of HPLC water (H_2O). Samples were loaded at a rate of 6–8 mL/min, rinsed with H_2O and then dried for about 30 min. Following drying, 12 mL of MeOH was used for sample elution, after which the eluent was concentrated to about 1 mL under a gentle stream of nitrogen gas. Right before instrumental analysis, 5 ng of the recovery standard was added.

4.4. Instrumental analysis

Target analytes were analysed using a ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) using an Agilent 1290/6470 QQQ/MSD system (Agilent Technologies, Santa Clara, CA, USA). Chromatographic separation was carried out using a ZORBAX XDB-C18 HPLC column (4.6 × 150 mm, 3.5 μm; Agilent Technologies). The mobile phase solvents were 0.1 % formic acid in water and in methanol with a flow rate of 350 uL/min and a sample injection volume of 10 μL. The detailed instrument conditions are shown in SI, Table S2.

4.5. Quality assurance and quality control

Calibration curves consisted of 12 points (0.2 ng/L–800 ng/L) and the correlation coefficient (r^2) of each curve was over 0.998. The procedural blanks and method blanks were analyzed every 12 samples. All concentrations of PPCPs in field and procedural blanks were confirmed to be less than the method detection limit (MDL). Calibration standards were injected at the beginning and end of each sequence, and one calibration standard was measured repeatedly throughout the sequence, every 20–25 injections. Accuracy, which was expressed as percent error (%) and precision, which was calculated as the relative standard deviation were evaluated using triplicate water samples spiked with 20 ng of each native standard. The MDL was defined as three times the standard deviation of the measured concentration in seven replicate water samples spiked with target PPCPs. Sample concentrations less than the limit of detection were defined as 'not detected' (ND) and the zero (0) value was used for the calculation of mean concentrations in samples. The details of the MDL, accuracy, and precision results are shown in the SI, Table S3.

4.6. Risk assessment

In the present study, the calculation of ecological RQs was used to assess the potential risks of the target compounds. Ecological and human health risk assessments were performed for different age groups using Monte Carlo simulations. Non-detects were replaced by MDL/2 values for the risk assessment to avoid underestimation of mean concentrations. The following equation was used for the ecological risk assessment:

$$RQ = \frac{MEC_{95}}{PNEC} \quad (1)$$

Where MEC_{95} (ng/L) is the measured environmental concentration (assumed to be the exposure concentration) at the 95th percentile of detected compounds, PNEC (ng/L) is the predicted no-effect concentration, the concentration below which an unacceptable effect will most likely occur (Union, 1996). It is derived from laboratory data from standardized tests, if available, on organisms from three major trophic

levels of aquatic ecosystems. In this study, PNEC values were obtained from literature as reported by (Čelić et al., 2021; Figuière et al., 2022; Park and Jeon, 2021; Wang et al., 2015). Details of the values used are shown in the SI, table S8. The criteria for the risk rating were determined as high risk to the environment if RQ > 1, moderate risk to the environment if 0.1 < RQ < 1, low risk to the environment if 0.01 < RQ < 0.1, and no risk to the environment if RQ < 0.01.

For human health risk assessment, the age groups for Koreans were categorized as toddlers (> 2 years), children (3 – 12 years), teenagers (13 – 18 years), and adults (19–74 years). The average water intake rates and reference body weights were 0.411 L/day and 12.2 kg for toddlers, 0.720 L/day and 26.0 kg for children, 0.974 L/day and 58.2 kg for teenagers, 1.502 L/day and 62.8 kg for adults. These data were obtained from the National Survey on Exposure Factor of Korean Adults and Children (Jang et al., 2014b,2014a). RQ values were estimated based on the mean values of concentrations in treated water, while maximum concentrations were used for estimating 'worst-case' scenario. RQ was estimated by dividing the average and maximum concentrations found in treated water samples by a respective Drinking Water Equivalent Level (DWEL) (Eqs. (2) and (3)) (Liu et al., 2019).

$$RQ = \frac{C_s}{DWEL} \quad (2)$$

$$DWEL = \frac{ADI \times BW \times HQ}{DWI \times AB \times FOE} * 1000 \quad (3)$$

Where, C_s is the concentration (mean or maximum) of the PPCPs in treated water samples, ADI is the acceptable daily intake (μg/kg day), BW represents the average body weight for different ages (kg), HQ is the Hazard Quotient, which was assumed to be 1, DWI is the drinking water intake (L/day), with specific values for different age groups according to the US EPA (Health and Group, 1989), AB is the gastrointestinal absorption rate, assumed to be 1, and FOE is related to the frequency of exposure (350 days/365 days = 0.96) (de Jesus Gaffney et al., 2015).

4.7. Statistical Analysis

Statistical analysis was performed with SPSS software, version 26.0 (SPSS Inc, Chicago, IL, USA). In the statistical analysis, all undetected compounds were treated as zero, as was previously done by (Kim et al., 2024; Sim et al., 2021). Non-parametric, Kruskal-Wallis test was performed to assess statistical differences between groups. All tests were performed at 95 % confidence level. R Studio version 2023.12.1+402, Sigma Plot 12.5 and ArcMap 10.8, and R (ggbreak) function (Xu et al., 2021) were used for drawing figures. Monte Carlo simulation was performed using Oracle Crystal Ball (11.1.2.3.000), and the computation simulation was conducted at 100,000 iterations to ensure the reliability of the outcomes.

4.8. Removal efficiency

The removal efficiency for each compound was determined by first calculating the ratio of the compound concentration in drinking water to that in raw water. This ratio was subtracted from 1 and then multiplied by 100 to express the efficiency as a percentage. In cases where the concentration of target PPCPs in the raw water was <MDL, half of the MDL (MDL/2) for the specific target compound was used to calculate the removal efficiencies.

CRediT authorship contribution statement

Kimberly Etombi Muambo: Writing – original draft, Methodology, Investigation, Conceptualization. **Min-Gyeong Kim:** Methodology, Investigation. **Da-Hye Kim:** Writing – review & editing. **Sangmin Park:** Project administration, Funding acquisition. **Jeong-Eun Oh:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.wroa.2024.100256.

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