Ecological Risk Assessment of Pharmaceuticals and Personal Care Products in the Water Environment of 15 Cities in Japan

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Abstract

To assess the ecological risk of pharmaceuticals and personal care products (PPCPs) to the water environment of several cities in Japan, major local environmental research institutes, a private company, and an academic institution launched a joint research project in 2019. Under this initiative, local environmental research institutes surveyed the concentrations of 46 types of PPCPs at 59 points distributed across 15 cities in Japan. IDEA Consultants, Inc. calculated the unknown values of predicted no-effect concentration (PNEC) of six chemicals (telmisartan, candesartan, fexofenadine, diphenhydramine, diphenyl sulfone, and ketotifen) through bioassay experiments on aquatic organisms. Among the researched chemicals, the concentrations of clarithromycin, 14-hydroxyclarithromycin, erythromycin, diclofenac, carbamazepine, and telmisartan exceeded the PNEC in at least one sampling point. However, ozone treatment removed most of these chemicals, except for certain phosphate ester flame retardants. The mass balance of chemicals in the Tamagawa River flowing through Tokyo Prefecture was calculated by multiplying the concentration of each chemical with the flow rate at each sampling point in the river. The measured load of most chemicals at each sampling point of the Tamagawa River coincided to a certain extent with the cumulative load accumulated from the tributaries and sewage treatment plants to the uppermost point (Nagata Bridge). However, the measured load of diclofenac was significantly smaller than the estimated values at each sampling point, suggesting that diclofenac photodegrades while flowing down the river.

1. Introduction

Chemicals such as drugs, cosmetics, pesticides, and fertilizers are essential to maintain the current lifestyle of most societies worldwide. However, several of these chemicals are potential environmental pollutants (such as dioxins, polychlorinated biphenyls, and dichlorodiphenyltrichloroethane) and adversely affect resources and living beings (Carson 1962; Eskenazi et al. 2018; Yoshimura 2003). Various laws, including the Water Pollution Control Law, Air Pollution Control Law, and Act on the Regulation of Manufacture and Evaluation of Chemical Substances, have been passed in Japan to control environmental pollution derived from such chemicals. Accordingly, responsible management of chemicals is steadily progressing, and the concentrations of several chemicals in the environment have decreased (Government of Japan 2012; United Nations Environment Programme 2016). However, pharmaceuticals and personal care products (PPCPs), commonly used in our daily lives, have not been subjected to regulation despite being detected in many water bodies throughout Japan. Many studies on PPCPs in water environments, including ecological risk assessments, have been conducted both domestically and internationally; e.g., in Asia (Kim et al. 2007; Harada et al. 2008; Kim et al. 2009; Komori et al. 2013; Zhou and Broodbank 2014; Xie et al. 2015; Ma et al. 2016; Mano and Okamoto 2016; Ma et al. 2017; Miyawaki et al. 2021), Europe (Loos et al. 2007; Kasprzyk-Hordern et al. 2008; Kasprzyk-Hordern et al. 2009; Houtman 2010; Carmona et al. 2014), Australia (Birch et al. 2015; Roberts et al. 2016), North America (Blair et al. 2013; García et al. 2014; Cizmas et al. 2015), and Africa (Agunbiade and Moodley 2014; Archer et al. 2017). In Japan, the Ministry of the Environment is leading efforts to clarify the actual state of PPCP pollution. A joint research project named “Contamination of the Aquatic Environment by Pharmaceutical and Personal Care Products: Environmental Risk Assessment and Removal from Wastewater” backed by “The Environment Research and Technology Development Fund” of the Environmental Restoration and Conservation Agency of Japan was launched in the 2019 fiscal year. In this research project, four regional environmental research institutes located in main cities of Japan (Tokyo Metropolitan Research Institute for Environmental Protection, Osaka City Research Center of Environmental Sciences, Hyogo Prefectural Institute of Environmental Sciences in Kobe, and Nagoya City Environmental Science Research Institute), a company (IDEA Consultants, Inc.), and an academic institution worked in collaboration to assess the actual pollution and ecological risk of a wide range of these chemicals in the country. The local environmental research institutes investigated the PPCP contamination values, and the private company performed the toxicity assessment to provide information for the ecological risk assessment. Additionally, 11 regional environmental research institutes also cooperated in water sampling. This was the first time in Japan that a wide-ranging survey and risk assessment of PPCPs in the water environment across 15 areas were conducted.

Sewage treatment plants (STPs), known to be one of the main sources of PPCPs in aquatic environments (Kasprzyk-Hordern et al. 2008; Kasprzyk-Hordern et al. 2009; Kim et al. 2009; Zhou et al. 2009; Roberts et al. 2016; Archer et al. 2017), were also analyzed in this study. The effluent and influent samples of six STPs were used to evaluate the PPCP emissions and investigate the removal efficiencies of the STPs. In addition, the daily mass of PPCPs was calculated based on the flow rate and their respective concentrations in the Tamagawa River flowing through Tokyo, and it was determined whether chemicals were stable when flowing down the river. This paper aimed to report the most important results obtained from this joint research project.

2. Materials And Methods

2.1 Reagents

Table 1 shows the chemicals analyzed in this study, which include pharmaceuticals such as antibiotics, antihypertensives, and antihistamines, and phosphate ester flame retardants (PFRs); these were selected based on the comprehensive analysis of former research (Environmental Restoration and Conservation Agency of Japan 2020) while considering their high consumption and frequent detection in aquatic environments. Information on the primary use or origin of each chemical was collected from several sources (DrugBank, ChemIDplus Advanced, and PubChem). Deuterium or ^{13}C labeled analytes were used in surrogates to maintain the highest quantitative accuracy for the analysis.

Table 1
Chemicals analyzed in this study.

Pharmaceuticals			
Chemical	CAS RN	Main use or origin	Surrogate
clarthromycin	81103-11-9	Antibiotic[a]	clarithromycin-$^{13}C,d_3$
14-hydroxyclarithromycin	110671-78-8	Metabolite of clarithromycin	clarithromycin-$^{13}C,d_3$
erythromycin	114-07-8	Antibiotic[a]	erythromycin-$^{13}Cd_3$
trimethoprim	738-70-5	Antibiotic[a]	diphenhydramine-d_6
diclofenac	15307-86-5	Anti-inflammatory drug[a]	diclofenac-d_4
5-hydroxydiclofenac	69002-84-2	Metabolite of diclofenac	diclofenac-d_4
sulpiride	15676-16-1	Antipsychotic agent[b]	sulpiride-d_3
carbamazepine	298-46-4	Anticonvulsant[a)]	carbamazepine-d_8
2-hydroxycarbamazepine	68011-66-5	Metabolite of clabamazepine	carbamazepine-d_8
3-hydroxycarbamazepine	68011-67-6	Metabolite of clabamazepine	carbamazepine-d_8
carbamazepine-10,11-epoxide	36507-30-9	Metabolite of clabamazepine	carbamazepine-d_8
fexofenadine	83799-24-0	Antihistamine[a]	fexofenadine-d_6
epinastine	80012-43-7	Antihistamine[a]	diphenhydramine-d_6
ketotifen	34580-13-7	Antihistamine[a]	diphenhydramine-d_6
diphenhydramine	58-73-1	Antihistamine[a]	diphenhydramine-d_6
diphenylsulfone	127-63-9	Pesticide, dyes[c]	losartan-d_4
telmisartan	144701-48-4	Antihypertensive agent[b]	telmisartan-d_7
irbesartan	138402-11-6	Antihypertensive agent[b]	irbesartan-d_7
olmesartan	144689-24-7	Antihypertensive agent[b]	olmesartan-d_6
valsartan	137862-53-4	Antihypertensive agent[b]	valsartan-d_9
losartan	114798-26-4	Antihypertensive agent[b]	losartan-d_4
candesartan	139481-59-7	Antihypertensive agent[b]	valsartan-d_9
crotamiton	483-63-6	Anti-parasite medicine[a]	crotamiton-d_5
N,N-diethyl-m-toluamide (DEET)	134-62-3	Insect repellent[b]	DEET-d_6
Phosphate ester flame retardants (PFRs)			
Chemical	CAS RN	Main use or origin	Surrogate
triethyl phosphate (TEP)	78-40-0	Flame retardant, Adhesive[c]	TEP-d_{15}
tris(2-chloroethyl) phosphate (TCEP)	115-96-8	Flame retardant, Adhesive[c]	TCEP-d_{12}
tris(2-choroisopropyl) phosphate (TCPP)	13674-84-5	Flame retardant, Adhesive[c]	TCPP-d_{18}
tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	13674-87-8	Flame retardant, Plasticizer[c]	TDCPP-d_{15}
tributyl phosphate (TBP)	126-73-8	Flame retardant, Solvent[c]	TBP-d_{27}
triphenyl phosphate (TPhP)	115-86-6	Adhesive, Antifouling[c]	TPhP-d_{15}
tris(2-butoxyethyl) phosphate (TBOEP)	78-51-3	Flame retardant, Plasticizer[c]	TBOEP-d_{12}
tricresyl phosphate (TCP)	1330-78-5	Flame retardant, Plasticizer[c]	TCP-d_{21}
[a]Source: DrugBank			

Pharmaceuticals
[b]Source: ChemIDplus Advanced
[c]Source: Pubchem

Pharmaceutical-grade chemicals were purchased from several suppliers, including Fujifilm Wako Pure Chemical (Osaka, Japan), Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), Cambridge Isotope Laboratories, Inc. (Tewksbury, MA, USA), and Hayashi Pure Chemicals (Osaka, Japan). The solvents used for the chemical extraction were residual pesticides of analytical grade (Kanto Chemicals, Tokyo Japan), and the ones used for the Liquid chromatograph-Mass spectrometer (LC-MS/MS) analysis were of LC/MS grade or high-performance liquid chromatographic grade (Kanto Chemicals; Fujifilm Wako Pure Chemical).

For the analysis of pharmaceuticals, standard chemicals were individually dissolved with methanol at 100–1000 ng mL^{-1} as the first solution, which was then mixed and diluted to 1.0 ng mL^{-1} with methanol. The surrogate mixture solution was prepared by a similar method. To prepare the standard PFRs and their surrogates, mixture solutions (Hayashi Pure Chemicals) were purchased and prepared using the same method as that employed for the pharmaceutical samples.

2.2 Solid-phase extraction

2.2.1 Pharmaceuticals

Oasis-HLB plus (225 mg; Waters Associates, Milford, MA, USA) was used in the solid-phase cartridge to extract pharmaceuticals. The cartridge was preconditioned with 5 mL of acetone followed by 10 mL of ultrapure water. After adding 10 µL of the surrogate mixture solution (1.0 mg L^{-1} for each chemical) to 200 mL of river water samples (50 and 100 mL for STP influents and effluents, respectively), the samples were loaded to the solid-phase cartridges at a flow rate of 10 mL min^{-1}. The cartridge was then washed with 30 mL of ultrapure water and dried using centrifugation (2000 rpm, 5 min) and a nitrogen gas flush.

The chemicals were eluted from the dried cartridge using 3 mL of methanol, followed by the addition of 3 mL of acetone and 2 mL of dichloromethane; these three solvents were mixed in a 10-mL glass tube. The mixed solvent was concentrated with nitrogen gas to approximately 0.1 mL and adjusted to 1 mL with 80% methanol aqueous solution. The solution was filtered with a syringe filter (Millex®-LG, pore size: 0.2 µm, diameter: 4 mm; Merck Millipore Corporation, Burlington, MA, USA) and analyzed with LC-MS/MS (Xevo-TQS: Waters Associates). Fig. S1 (Online Resource 1) shows the analysis procedure for the pharmaceuticals.

2.2.2 PFRs

Plastic materials were avoided in the extraction of PFRs since certain PFRs exhibit plasticizer properties. InertSep Glass PLS-3 (200 mg/6 mL) was used for PFR extraction after being preconditioned with 8 mL of methanol followed by 10 mL of ultrapure water. To analyze the water samples, 10 µL of surrogate mixture solution (1.0 mg L^{-1} for each chemical) was added to 200 mL of river water samples (50 mL for STP influents, and 100 mL for STP effluents); the subsequent mixture was poured into a polypropylene container connected to a concentrator. Although plastic materials were avoided in the PFRs analysis, glass containers were excessively heavy and unstable to be connected to a concentrator.

Before the extraction, the containers were thoroughly washed with ultrapure water and methanol. The samples were loaded to the solid-phase cartridges at 10 mL min^{-1}. The cartridge was then washed with 10 mL of ultrapure water and dried with a flush of nitrogen gas. The chemicals were eluted from the dried cartridge with 8 mL of acetone. The solvent was concentrated with nitrogen gas to approximately 0.1 mL and adjusted with 1 mL of methanol. The solution was filtered with a syringe filter (Millex®-LG, pore size: 0.2 µm, diameter: 4 mm; Merck Millipore Corporation) and analyzed with LC-MS/MS (Xevo-TQS: Waters Associates). Fig. S2 (Online Resource 1) shows the analysis procedure for PFRs, and Table S1 (Online Resource 1) shows the LC-MS/MS analysis conditions for pharmaceuticals and PFRs.

2.3 Quality control

Recovery tests were conducted as quality tests using STP effluent and ultrapure water. The method detection limits (MDLs) and method quantification limits (MQLs) were estimated based on data from eight different analyses of the standard PPCP mixture added to ultrapure water at 0.5 and 5.0 ng L^{-1}.

2.4 PNECs of PPCPs

For the risk assessment, the measured value of each analyte was compared with the respective predicted no-effect concentration (PNEC) obtained from the literature (Harada et al. 2008; Environment Agency of UK 2009; The National Research and Development Agency Public Works Research Institute 2010; Verlicchi et al. 2012; Deo et al. 2013; Komori et al. 2013; Furberg 2014; Baumann et al. 2015; Mano et al. 2016) and from the official websites of the European Chemical Agency and Ministry of Environment, Japan. A summary of PNEC information is shown in Table 2. The PNEC values for the same chemical varied significantly among different references. For example, the PNEC of diclofenac varied from 1000 (Furberg 2014) to 10000 (Komori et al. 2013). In this study, the smallest values were adopted for the risk assessment to ensure a higher safety standard. The PNECs of six chemicals (telmisartan, candesartan, fexofenadine, diphenhydramine, diphenyl sulfone, and ketotifen) have not been widely investigated. Therefore, IDEA Consultants, Inc., calculated them through experiments on aquatic organisms under the test guidelines TG-212 for fishes and TG-201 for algae (Organization for Economic Cooperation and Development 1998, 2011) while using the biological test method for crustaceans (*Ceriodaphnia dubia*) (Environment Canada 2007). The No Observed Effect Concentration (NOEC) of the investigated species was elucidated based on the bioassay data. The PNEC of each chemical was then calculated based on the lowest NOEC among the three species by using an assessment factor.

Table 2
Predicted no effect concentrations of chemicals analyzed in this study.

Chemical	Reference										
	Furberg 2014	Deo et al. 2013	Komori et al. 2013	Harada et al.2008	Verlicchi et al. 2012	Baumann et al. 2015	Mano et al. 2016	European Chemical Agency	Initial risk assessment by the Ministry of Environment, Japan	Aquatic toxicity tests of chemicals conducted by the Ministry of Environment, Japan	National Research and Developr Agency Public W Research Institute, Japan, 2
clarithromycin			52	50	70		**20**		69		**20**
14-hydroxyclarithromycin						**270**					
erythromycin		**20**			**20**				360		100
trimethoprim		**1000**			2600						60000
diclofenac	**66.3**		10000	460	9700				1100		5000
carbamazepine	**29.7**	420	250		13800						5200
fexofenadine											
ketotifen											
diphenhydramine											
diphenyl sulfone								50000			
telmisartan											
candesartan											
crotamiton			21000	20830			**3500**				**3500**
N,N-diethyl-m-toluamide (DEET)			**5200**	5210							**5200**
triethylphosphate (TEP)								**632000**			
tris(2-chloroethyl)phosphate (TCEP)									**100000**		
tris(2-choroisopropyl) phosphate (TCPP)								**420000–640000**			
tris(1,3-dichloro-2-propyl) phosphate (TDCPP)								**200**			
tributyl phosphate (TBP)								35000–82000	**11000**		
triphenyl phosphate (TPhP)								3700	**3000**		
tris(2-butoxyethyl) phosphate (TBOEP)								24000		**21000**	
tricresyl phosphate (TCP)								1000	1500		

Among the predicted no-effect concentrations (PNECs) of TBOEP, 21000 ng L^{-1} was calculated by dividing the acute toxicity data for fish (*Oryzias latipes*) of factor of 1000, following the guidelines of the Initial Environment Risk Assessment of Chemicals.

The PNEC of 14-hydroxyclarithromycin, 270 ng L^{-1} was calculated by dividing the chronic toxicity data for algae (*Anabena flos-aquae*) of 2.7 μg L^{-1} (NOEC) the guidelines of the Initial Environmental Risk Assessment of Chemicals in Japan.

For each chemical, the PNEC used for the risk assessment in this study is highlighted and written in bold.

2.5 River water samples

The total number of sampling points was 59. The water samples were collected by hanging a stainless-steel bucket from either the bridge or shore for each sampling point from July to September 2019. If the sampling point was influenced by the ebb and flow of the tide, sampling was conducted during the low tide. The collected samples were sent to the Tokyo Metropolitan Research Institute for Environmental Protection under refrigeration. The received samples

were immediately processed by a solid-phase extraction method and then analyzed using LC-MS/MS. The sampling points of this study (considering the four institutes participating in this joint research) are shown in Table S2 (Online Resource 1) and Fig. S3 (Online Resource 1).

2.6 PPCPs in STPs

As STPs are known sources of PPCPs (Archer et al. 2017; Balakrishna et al. 2017), influent and effluent water samples from six STPs were collected, and their PPCP removal efficiencies were evaluated by comparing the concentration of pollutants in the influent and effluent samples. The researched STPs use an anaerobic–anoxic–oxic process for wastewater treatment. All effluent and influent STP samples analyzed in this study were composite samples prepared by mixing sample fractions collected every 2 h over a 24 h period. This approach considers the variability of pollution load throughout the day.

2.7 Mass balance of chemicals in the Tamagawa River in Tokyo

The mass balance of six chemicals, whose concentrations exceeded PNEC in at least one sampling point, was calculated for the Tamagawa River flowing through Tokyo.

The Tamagawa River has a simple channel because its flow is not influenced by the tide from the Chofu water intake, and it does not branch out until its estuary (Fig. 1). Furthermore, its shallowness allows the flow velocity entering the river channel to be measured more conveniently. The width of the Tamagawa River was first measured, then divided into 10–12 sections, and finally, the flow velocity of each section was measured using a current meter. When the depth of each sampling point was ≥ 40 cm, the flow velocity was measured at two depth points: 20% and 80% of the depth from the surface to the bottom; when the depth was < 40 cm, it was measured at 60% of the depth. The flow rates from the STPs were obtained from the Tokyo Bureau of Sewerage.

3. Results And Discussion

3.1 Quality control

Recovery rates, calculated by subtracting the concentration of the sample without the chemical from that of the sample with the chemicals added, was within the ranges of 71–143% (average: 98%) and 61–147% (average: 99%) for ultrapure water and the STP effluent, respectively.

3.2 Calculation of MDLs and MQLs

The MDLs and MQLs of the analyzed chemicals were calculated based on the results of the recovery tests conducted by adding the chemicals to ultrapure water and adjusting the concentration at the lowest calibration curve level. Eight extracted samples were analyzed with LC-MS/MS, and the respective t-values were calculated based on the standard deviation for each chemical. The MDLs and MQLs were calculated using the following formulas (Currie 1997): $MDL = 2 \times t\,(n\text{-}1, 0.05) \times \sigma_{n-1} \times 2$, and $MQL = 10 \times \sigma_{n-1}$; where $t\,(n\text{-}1, 0.05)$ indicates the *t*-value (one-sided) for the risk factor of 5% and the degree of freedom of $n\text{-}1$.

3.3 PNECs of PPCPs

The assessment factors were obtained from the “Guidelines for the Initial Environmental Risk Assessment of Chemicals,” published by the Ministry of Environment, Japan (2019). Following these guidelines, when chronic toxicity data were obtained for the three species (fish, algae, and crustacean), the assessment factor was 10; however, when chronic data were obtained for one or two species, the assessment factor was 100. Among the three methods used to calculate PNECs, TG-212 is considered an acute toxicity test, while the others are chronic toxicity tests. Therefore, the assessment factor for the six analyzed chemicals was set at 100.

Algae are highly susceptible to 14-hydroxyclarithromycin, compared to other species, with half (50%) maximal effective concentrations (EC50) > 2000 μg L^{-1} for fish and EC50 > 2000 μg L^{-1} for crustaceans; the concentration that results in 50% inhibition of growth rate (ErC50) of algae is 27.2 μg L^{-1} (Baumann et al. 2015). In this case, according to the guideline published by the Ministry of Environment, Japan (2019), the assessment factor can be assumed to be 10. Therefore, the PNEC of 14-hydroxyclarithromycin was set at 270 ng L^{-1}, calculated by dividing the lowest NOEC (2.7 μg L^{-1}) by the assessment factor of 10. Similarly, for tris(2-butoxyethyl) phosphate (TBOEP), the minimum PNEC was calculated by dividing 21 mg L^{-1} (96 h-lethal concentration for 50% of animals (LC50)) (obtained from the toxicity tests conducted by the Ministry of the Environment, Japan) by the assessment factor of 1000.

3.4 River water samples

Analyzed data for PPCP detected at a concentration more than the PNEC of each chemical or 1000 ng L^{-1}, in at least one sampling point, are shown in Table 3, and the details of the data are shown in Tables S3 and S4. The names of the municipalities were indicated with letters (A to K), and the sampling points in each municipality were assigned identification numbers (e.g., "A-1" or "C-5”) based on the data obtained from the 11 institutes collaborating in this joint research.

Table 3
Concentrations of pharmaceuticals and personal care products (PPCPs) in water environment samples (ng L− 1)

Four institutes participating in this joint research project												
City or Prefecture	River name	Chemical Sampling point	clarithromycin	14-hydroxy clarithromycin	erythromycin	diclofenac	carbamazepine	sulpiride	fexofenadine	diphenyl sulfone	telmisartan	va
Osaka C[a].	Daini Neyagawa R[c].	Shigino-ohashi Bridge	600	580	100	45	42	890	2500	1200	860	44
		Shimoshiromi Bridge	570	510	370	45	36	760	2200	970	810	42
Hyogo P[b].	Inagawa R.	Inagawa Bridge	N.D.[e]	N.D.	57	N.D.	4.8	4.1	N.D.	(2.5)	(2.2)	N.
		Tokura Bridge	470	470	57	70	51	1000	3500	76	1300	18
Nagoya C.	Hori kawa R.	Johoku Bridge	340	330	23	17	22	400	2400	83	600	11
		Nakatsuchito Bridge	400	390	25	27	26	470	2900	83	730	11
Tokyo P.	Tama gawa R.	Nagata Bridge	N.D.	N.D.	N.D.	N.D.	(0.11)	N.D.	N.D.	N.D.	N.D.	N.
		Hino Bridge	180	220	30	29	39	360	1700	47	620	13
11 institutes cooperating in this joint research project												
Institute		Chemical Sampling point	clarithromycin	14-hydroxy clarithromycin	erythromycin	diclofenac	carbamazepine	sulpiride	fexofenadine	diphenyl sulfone	telmisartan	va
A		A-1	35	39	40	(1.9)	5.1	56	180	14	61	98
		A-2	160	230	39	19	13	220	1600	63	270	78
B		B-1	21	24	57	(1.7)	3.7	42	82	19	69	66
		B-3	200	240	N.D.	21	21	480	1100	62	670	37
C		C-3	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	(3.2)	N.D.	N.
		C-4	750	910	370	140	72	1200	3600	120	2300	33
D		D-2	15	20	(3.4)	4.4	5.5	43	67	19	50	77
		D-3	360	390	57	69	38	480	1300	56	820	26
E		E-1	510	540	57	120	60	970	2100	74	1300	24
		E-2	58	59	9.8	(2.8)	10	100	230	26	200	10
F		F-1	79	88	N.D.	25	37	220	550	23	290	53
		F-2	96	120	15	14	27	220	650	20	290	49
G		G-1	9.5	10	N.D.	5.6	5.7	19	44	N.D.	49	37
H		H-1	72	75	(3.8)	12	6.2	81	320	14	130	11
		H-2	310	290	11	43	39	300	1200	41	490	18
I		I-1	9.1	12	N.D.	4.5	6.2	59	99	6.7	87	(7.
		I-2	28	34	(5.1)	25	22	230	520	17	400	59
J		J-1	3.0	3.0	N.D.	4.9	5.0	43	48	N.D.	39	18
		J-2	860	900	80	220	75	1400	3200	160	2200	30
K		K-1	2.4	2.3	N.D.	N.D.	4.4	6.2	23	(4.1)	(4.3)	22
		K-2	430	430	53	79	62	750	2300	57	810	28

a: City, b: Prefecture, c: River, d: tris(2-butoxyethyl) phosphate, e: not detected

Four institutes participating in this joint research project										
Method Detection Limit (MDL)	0.8	0.2	3.3	1.2	0.1	1.2	1.7	1.9	2.1	3.1
Method Quantification Limit (MQL)	2.2	0.7	8.7	3.3	0.2	3.3	4.6	5.0	5.6	8.1
Predicted no-effect concentration (PNEC)	20	270	20	66	30	> 100000	300000	3500	1600	—
a: City, b: Prefecture, c: River, d: tris(2-butoxyethyl) phosphate, e: not detected										

The blank test value was subtracted from the raw measured values for *N,N*-diethyl-*m*-toluamide (DEET) and diphenyl sulfone because the blank test values were above the MDL for both chemicals. The gray cells shown in Table 3 indicate that the measured values exceeded the respective PNECs. The concentrations of clarithromycin, 14-hydroxyclarithromycin, erythromycin, carbamazepine, diclofenac, and telmisartan exceeded their respective PNECs at several sampling points, and almost all these points were in the downstream areas.

For risk assessment, the concentrations of these chemicals were compared with their respective PNECs. Among the chemicals studied, carbamazepine and diclofenac are the most frequently researched in previous studies (Bendz et al. 2005; Kim et al. 2007; Kim et al. 2009; Agunbiade and Moodley 2014; Olaitan et al. 2014; Zhou and Broodbank 2014; Xie et al. 2015; Ma et al. 2016; Ma et al. 2017). The concentrations of these chemicals were nearly the same as or lower than those reported in previously published studies.

3.5 Removal efficiency of STPs

Table 4 shows the PPCP concentrations at each process step in the six investigated STPs. The removal rates of the macrolide antibiotics, i.e., clarithromycin, 14-hydroxyclarithromycin, and erythromycin, were approximately 24–53% (35% on average), 18–57% (36% on average), and − 59–84% (− 10% on average), respectively. The concentration of erythromycin in the effluent of F STP was below the MQL. As mentioned above, all effluent and influent STP samples analyzed in this study were composite samples used to determine the average variability of pollution load throughout the day. However, when preparing composite samples, sampling of both influent and effluent fractions starts simultaneously. In typical STPs, there is a time lag of 6–8 h even only for a reactor in which conventional activated-sludge treatment is conducted (Japan Sewage Works Association 2013). Therefore, even for composite samples, the gap due to time lag cannot be compensated totally.

Table 4
Concentrations of the pharmaceuticals and personal care products (PPCPs) at each process in the six sewage treatmer

Chemical STPs	clarithromycin	14-hydroxy clarithromycin	erythromycin	trimethoprim	diclofenac	5-hydroxy diclofenac	sulpiride	carbamazepine	2-hydroxy carbamazepine	3-hydroxy carbamazepine	carbamazepine 10,11 epoxide
A ozonized water	5.4	8.2	N.D.[a]	N.D.	N.D.	39	140	(0.23)	N.D.	4.9	28
A effluent	540	540	59	120	180	110	1300	91	61	63	57
A influent	730	850	40	210	250	220	1600	81	48	50	33
Removal rate by ozone (%)	99%	98%	100%	100%	100%	64%	89%	100%	100%	92%	50%
Removal rate (%)	26%	36%	-49%	43%	28%	50%	19%	-12%	-26%	-26%	-73%
B effluent	740	840	31	150	210	190	1400	120	86	85	76
B influent	980	1100	31	240	230	230	1600	97	67	62	50
Removal rate (%)	24%	24%	-1%	38%	9%	17%	13%	-24%	-28%	-38%	-51%
C effluent	620	770	67	120	160	160	1400	85	72	73	64
C influent	840	940	42	150	200	230	1400	84	66	64	51
Removal rate (%)	26%	18%	-59%	20%	20%	30%	0%	-1%	-10%	-14%	-25%
D effluent	390	420	23	75	180	140	1200	89	66	77	64
D influent	750	970	23	210	210	220	1200	69	64	62	54
Removal rate (%)	48%	57%	-1%	64%	14%	37%	0%	-30%	-3%	-24%	-18%
E effluent	510	630	76	110	150	140	1100	78	53	55	47
E influent	790	910	58	170	170	180	1200	77	53	44	33
Removal rate (%)	35%	31%	-31%	35%	12%	22%	8%	-2%	0%	-25%	-45%
F effluent	520	670	(7.6)	100	84	180	1100	71	57	60	47
F influent	1100	1300	46	170	200	230	1100	56	47	47	32
Removal rate (%)	53%	48%	84%	41%	58%	22%	0%	-27%	-20%	-28%	-49%
Method Detection Limit (MDL)	0.8	0.2	3.3	3.1	1.2	2.0	1.2	0.1	0.4	0.2	1.1
Method Quantification Limit (MQL)	2.2	0.7	8.7	8.2	3.3	5.2	3.3	0.2	0.9	0.6	3.0
Average removal rate (%)	35%	36%	-10%	40%	24%	30%	7%	-16%	-15%	-26%	-43%
LogKow	3.18	1.64	2.48	0.73	4.51	3.18	0.65	2.25	1.42	1.42	0.95
Max removal rate (%)	53%	57%	84%	64%	58%	50%	19%	-1%	0%	-14%	-18%
Min removal rate (%)	24%	18%	-59%	20%	9%	17%	0%	-30%	-28%	-38%	-73%
Chemical STPs	telmisartan	irbesartan	olmesartan	valsartan	losartan	candesartan	crotamiton	DEET[b]	TEP[c]	TCEP[d]	TCPP[e]
A ozonized water	530	210	(1.8)	130	N.D.	110	(4.0)	44	21	230	630
A effluent	1800	470	670	330	76	380	2000	63	23	230	590

a: not detected, b: *N,N*-diethyl-*m*-toluamide, c: triethyl phosphate, d: tris(2-chloroethyl) phosphate, e: tris(2-chloroisopropyl) phosphate, f: tris(1,3-dichloro-2-pro

Chemical STPs	clarithromycin	14-hydroxy clarithromycin	erythromycin	trimethoprim	diclofenac	5-hydroxy diclofenac	sulpiride	carbamazepine	2-hydroxy carbamazepine	3-hydroxy carbamazepine	carbamazepine 10,11 epoxide
A influent	2100	580	780	2600	230	340	1600	300	28	180	870
Removal rate by ozone (%)	71%	55%	100%	61%	100%	71%	100%	30%	5%	0%	-7%
Removal rate (%)	14%	19%	14%	87%	67%	-12%	-25%	79%	21%	-27%	32%
B effluent	1900	680	780	870	170	350	1800	51	22	160	620
B influent	2600	700	740	3300	260	300	1600	670	24	150	680
Removal rate (%)	27%	3%	-5%	74%	35%	-17%	-13%	92%	6%	-7%	9%
C effluent	2000	600	530	180	160	410	2000	50	23	140	690
C influent	1700	490	530	3000	250	360	2100	410	34	330	650
Removal rate (%)	-18%	-22%	0%	94%	36%	-14%	5%	88%	33%	58%	-6%
D effluent	1800	700	600	140	35	370	1800	48	27	150	570
D influent	1900	710	590	4700	180	310	1400	400	22	120	410
Removal rate (%)	5%	1%	-2%	97%	81%	-19%	-29%	88%	-22%	-25%	-39%
E effluent	1400	410	560	210	130	300	1400	36	18	140	420
E influent	1600	450	530	2300	220	250	1500	430	23	110	430
Removal rate (%)	13%	9%	-6%	91%	41%	-20%	7%	92%	23%	-27%	2%
F effluent	1400	600	730	73	71	220	1900	25	22	230	500
F influent	1800	590	730	2100	250	220	2000	240	27	120	570
Removal rate (%)	22%	-2%	0%	97%	71%	0%	5%	90%	19%	-92%	12%
Method Detection Limit (MDL)	2.1	0.19	1.4	3.1	0.15	2.5	2.5	2.2	0.42	5.4	4.1
Method Quantification Limit (MQL)	5.6	0.51	3.7	8.1	0.40	6.6	6.7	5.9	1.1	14	11
Average removal rate (%)	11%	1%	0%	90%	55%	-14%	-8%	88%	13%	-20%	2%
LogKow	8.42	5.31	3.63	3.65	4.01	4.79	2.73	2.26	0.87	1.63	2.89
Max removal rate (%)	27%	19%	14%	97%	81%	0%	7%	92%	33%	58%	32%
Min removal rate (%)	-18%	-22%	-6%	74%	35%	-20%	-29%	79%	-22%	-92%	-39%

a: not detected, b: *N,N*-diethyl-*m*-toluamide, c: triethyl phosphate, d: tris(2-chloroethyl) phosphate, e: tris(2-chloroisopropyl) phosphate, f: tris(1,3-dichloro-2-pro

Anti-hypertensive agents (telmisartan, irbesartan, olmesartan, valsartan, losartan, and candesartan) presented a wide range of average removal rates (from −14% for candesartan to 90% for valsartan). High removal rates for valsartan have been reported in multiple studies; for example, the removal rate was reported to be 90% by Archer et al. (2017) and approximately 75% by Kasprzyk-Hordern et al. (2009). Carbamazepine and its metabolites (2-hydroxycarbamazepine, 3-hydroxycarbamazepine, and carbamazepine-10,11-epoxide) were scarcely removed, and this trend was also reported by Jelić et al. (2011). The overall concentrations of chemicals were greatly reduced by ozone treatment in STP A. In terms of PFRs, triphenyl phosphate (TPhP), TBOEP, and tricresyl phosphate (TCP) were relatively well removed (average removal rates of 61%, 73%, and 75%, respectively). In addition, the ratio of PFRs subjected to biodegradation removal by sewage treatment was almost negligible. For example, the removal rate of triethyl phosphate (TEP) calculated by the EPI suite and attributed to biodegradation was 0.09%, while the total removal rate was 1.87%. Similarly, a TPhP removal rate of 0.56% was attributed to biodegradation, while the total removal rate was 60.71%. The correlation factor between removal rates and octanol-water partition coefficient (log K_{ow}) of PFRs was 0.6989. In contrast, the removal rates obtained by ozonation ranged from − 23% for tributyl phosphate (TBP) to 38% for TBOEP, with an overall low value for PFRs. The removal of

hydrophobic chemicals, such as TBOEP and TBP, was nearly negligible, including that by ozonation. Among PFRs, tris(2-chloroethyl) phosphate (TCEP), tris(1,3-dichloro-2-propyl) phosphate (TDCPP), and tris(2-chloroisopropyl) phosphate (TCPP) were particularly unsusceptible to ozonation (removal rates < 5%); however, their concentrations were found to be reduced by advanced oxidation processes (AOPs; UV/H_2O_2 treatment) (Yuan et al. 2015). Watts and Linden (2009) determined the second-order rates of reactions of four PFRs (TBOEP, TBP, TCEP, and TCPP) with ultraviolet and ozone-generated •OH in water. Among them, TBOEP was the fastest to react with •OH (kOH = 1.03×10^{10} M^{-1} s^{-1}), followed by TCPP, TCEP, and TBP (6.40×10^9, 5.60×10^8, and 1.98×10^8 M^{-1} s^{-1}, respectively). Yuan et al. (2015) reported the energy consumption for the degradation of PFRs from municipal secondary effluents by ozone and UV/H_2O_2 treatment. They estimated the total cost of the ozone and UV/H_2O_2 treatments (reaction time: 10 min) to be 0.344 and 0.279 € m^{-3}, respectively. Therefore, the AOP method can be used to regulate PFR emissions effectively.

3.6 Mass balance of chemicals in the Tamagawa River in Tokyo

Figure 2 shows the PPCP loads measured at each sampling point along the Tamagawa River. Six PPCPs exceeded their PNEC at one sampling point at least, and their respective loads were calculated. The load of each sampling point was calculated by multiplying the concentration and the flow rate at that point, whereas the cumulative load indicates the accumulated load of the tributary streams and STPs, starting from Nagata Bridge, which is the most upstream point in this study. When the load of a chemical at a point on the Tamagawa River (Hino, Sekido, or Tamagawara bridges) coincided with the cumulative one, the chemical was considered to flow downstream without degrading, volatilizing, or getting adsorbed on the riverbed. For all chemicals, except diclofenac, the measured load at each point on the Tamagawa River coincided with the cumulative one to a certain extent. The measured loads of diclofenac at Hino, Sekido, and Tamagawara bridges were significantly lower than its cumulative load at each point; the ratios of the measured and cumulative loads at Hino, Sekido, and Tamagawara bridges were 0.33, 0.48, and 0.42, respectively. Since diclofenac is reported to photodegrade in water environments (Buser et al. 1998; Bartels and Tümpling Jr. 2007), we assumed that it photodegraded while flowing down the river.

4. Conclusions

In this study, we conducted a nationwide survey and ecological risk assessment of PPCPs in water environments in Japan. For risk assessment, PNEC values were collected from the reported literature, such as studies on ecotoxicological aspects. For pharmaceuticals whose PNEC values have not been clarified, their PNECs were calculated by conducting bioassay experiments on aquatic organisms. In the risk assessment study, 59 water samples were collected from sampling points throughout Japan and analyzed for chemicals using LC-MS/MS. The PNEC concentration was exceeded at one point, at least, for clarithromycin, 14-hydroxyclarithromycin, erythromycin, diclofenac, carbamazepine, and telmisartan. The removal rates for these chemicals at STPs were investigated by comparing their concentrations in the influent and effluent.

Although many pharmaceuticals and PFRs were not effectively removed by the activated-sludge treatment, almost all of them were decomposed by ozonation, except for certain PFRs. The mass balance of six chemicals, whose concentrations exceeded PNEC at one sampling point at least, was calculated by multiplying the concentration of each chemical and the flow rate through the Tamagawa River. The results indicated that diclofenac is likely photodegraded while flowing down the river. Through this joint research project, many institutes and different industries were able to work together to contribute to a deeper understanding of the ecological risks posed by PPCPs in Japan. The study demonstrated that environmental surveys could be efficiently conducted over a wide area through joint research. However, the study was conducted in winter, and it is known that the discharge of PPCPs into the environment varies with the season (Golovko et al. 2014; Marques dos Santos et al. 2019). Therefore, we plan to conduct a survey in summer to better understand the concentrations, and therefore risks, of PPCPs. In addition, we plan to conduct a survey of wastewater discharged from sites other than STPs, especially commercial sites, to better understand the various sources of PPCP emissions.

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and materials

All data generated or analyses during this study are included in this published article and its supplementary information files.

Competing interests

None

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Authors' contributions

Conceptualization of the research project, writing the original draft, and funding acquisition were performed by TN. Methodology was performed by MK and YM (PPCP analysis) and TO and AS (bioassay experiments with aquatic organisms). Project administration was performed by MK and YM (Tokyo prefecture), TT (Osaka city), CM (Hyogo prefecture), and HH (Nagoya city). Investigation was performed by DA and MO (Osaka city), YH and TK (Hyogo prefecture), HH (Nagoya city). Review and editing of the manuscript were performed by DA, YH, and HH. AS advised on toxicity information. All authors read and approved the final manuscript.

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Figures

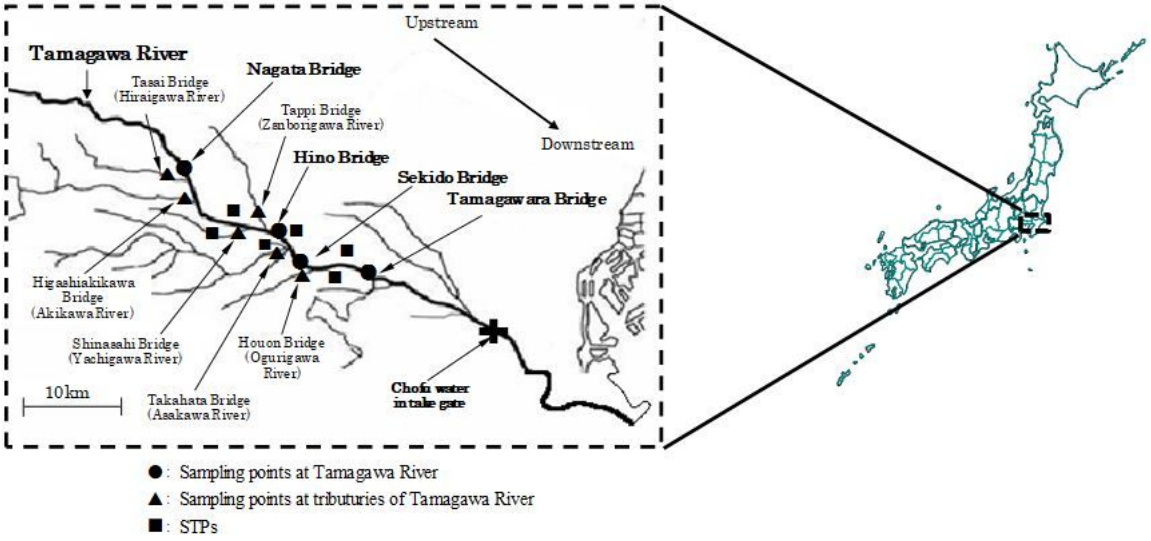

Figure 1

Sampling points in the Tamagawa River Basin

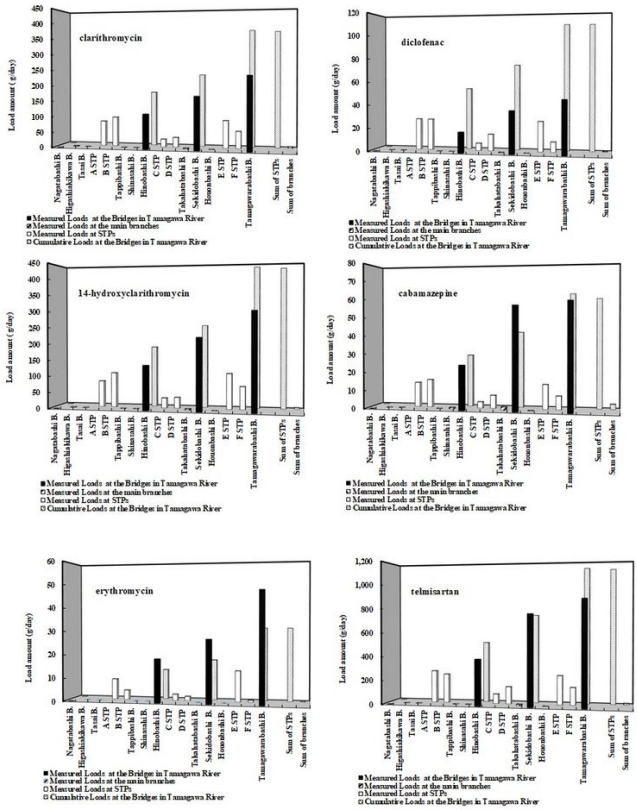

Figure 2

Cumulative and measured mass loads of PPCPs in water samples obtained at sampling points between the Nagata Bridge and the Tamagawara Bridge

Supplementary Files

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