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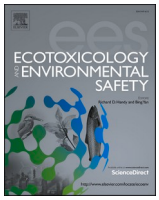

# Prioritization of pharmaceuticals and personal care products in the surface waters of Korea: Application of an optimized risk-based methods

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ABSTRACT

The occurrence of PPCPs in aquatic environments and their potential adverse effects on aquatic organisms have raised worldwide concerns. To address this issue, a study was conducted to analyze 137 selected PPCPs in Korean surface waters, and an optimized risk-based prioritization was performed. The results revealed that 120 PPCPs were detected, with 98 quantified at concentrations ranging from few ng/L to 42,733 ng/L for metformin. The 95% upper confidence limit (UCL95) of the mean value of the measured environmental concentration (MEC) for Metformin was about eight times higher than the second highest compound, dimethyl phthalate, indicating that antidiabetic groups had the highest concentration among the therapeutic groups. An optimized risk-based prioritization was then assessed based on the multiplication of two indicators, the *Frequency of Exceedance* and the *Extent of Exceedance* of Predicted No-Effect Concentrations (PNECs), which can be calculated using the traditional risk quotient (RQ) approach. The study found that clotrimazole had the highest risk quotient value of 17.4, indicating a high risk to aquatic organisms, with seven and 13 compounds showing RQ values above 1 and 0.1, respectively. After considering the frequency of exceedance, clotrimazole still had the highest novel risk quotient ($RQ_f$) value of 17.4, with 99.6% of its MECs exceeding PNECs. However, the number of compounds with $RQ_f$ values above 1 decreased from seven to five, with cetirizine and flubendazole being excluded. Furthermore, only 10 compounds exhibited $RQ_f$ values above 0.1. The study also observed significant differences in the results between risk-based and exposure-based prioritization methods, with only five compounds, cetirizine, olmesartan, climbazole, sulfapyridine, and imidacloprid, identified in both methods. This finding highlights the importance of considering multiple methods for prioritizing chemicals, as different approaches may yield different results.

## 1. Introduction

Pharmaceuticals and personal care products (PPCPs) are a significant group of emerging contaminants that have raised worldwide concerns due to their occurrence in aquatic environments and potential adverse effects on aquatic organisms (Ebele et al., 2017a). PPCPs comprise prescription and non-prescription drugs, veterinary drugs, and consumer chemicals found in cosmetics, personal hygiene products, sunscreen agents, fragrances, domestic insect repellents, and food additives (Liu and Wong, 2013). The global production of PPCPs exceeds 50,000 tons, and their consumption is estimated to be 30 million tons (Liu et al., 2020), leading to their continuous introduction into the environment through various routes, such as municipal sewage treatment plants, wastewater treatment plants, and leachate from landfill sites. They are typically considered "pseudo-persistent" due to their continuous use and release into the environment (Osuoha et al., 2023; Ebele et al., 2017b; Santos et al., 2009; Daughton and Ternes, 1999). Despite efforts to remove PPCPs through conventional water treatment methods, their complex structure and wide range of physico-chemical properties make them significantly difficult to remove, leading to their detection in various water systems, including surface water and groundwater (Salah et al., 2023; Tijani et al., 2016; Stuart et al., 2012).

PPCPs are designed for specific physiological effects on humans and animals; however, information on the environmental risk for non-target organisms and their chronic toxic effects is insufficient. Most studies have focused on the acute toxic effects of PPCP exposure; however, it is predicted that PPCP exposures may have more chronic effects (Chaves et al., 2022). Some PPCPs, such as dextropropoxyphene, sertraline,

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thioridazine, and diphenhydramine, have been found to have the potential to cause acute toxicity to algae, invertebrate, and fish populations (Prasad et al., 2019). On the other hand, some PPCPs, including antiarrhythmic, antidepressant, antidiabetic, antiandrogenic, and synthetic estrogen compounds, have been reported not to pose an acute risk to aquatic organisms at expected environmental concentrations (Cizmas et al., 2015). However, these PPCPs tend to have chronic adverse effects on aquatic organisms, such as reproductive failure due to the presence of diclofenac in fish organs (Brausch et al., 2012; Mehinto et al., 2010). Most toxicity information for PPCPs has been derived from the effects observed for regulatory assessment purposes. However, these methods mostly neglect responses for nonstandard endpoints that can occur at concentrations much lower than those observed in regulatory endpoints (Boxall et al., 2012). Traditional methods for toxicity identification evaluation mainly focus on endpoints directly related to mortality and population group for acute exposure, which typically occurs at relatively high concentrations (Boxall et al., 2012). Therefore, these traditional methods are unsuitable and insufficient for assessing the environmental risk of PPCPs. The toxicity of PPCPs can also vary by species. For example, analgesic drugs were found to be acutely toxic to phytoplankton and invertebrates, while bacteria, fish, and amphibians were less vulnerable to these compounds (Cizmas et al., 2015). Another major concern related to the presence of PPCPs is the exposure of aquatic organisms to hormones, which can cause endocrine disruption. The development of antibiotic-resistant bacteria due to the presence of antibiotic residues is also a major concern of PPCP contamination, which can alter microbial community structure (Kraemer et al., 2019).

Given the vast number of PPCPs in use and the limited resources available for monitoring and management, prioritization is essential for efficiently identifying and addressing the most significant risks posed by these compounds (Mo et al., 2022). There are three general categories in prioritization approaches employed worldwide including exposure-based, hazard-based, and risk-based methods. Each method aims to achieve a specific objective: exposure-based methods focus on selecting PPCPs for environmental monitoring, hazard-based methods prioritize PPCPs for toxicity testing, and risk-based methods concentrate on assessing the ecological risk associated with PPCPs. While various adaptations of the three prioritization approaches have been implemented, a universally accepted method has yet to be established (Burns et al., 2018b). Nonetheless, the majority of prioritization methods and exercises described in the scientific literature are risk-based, and previous assessments of these methods have concluded that a risk-based approach is the most appropriate to prioritize PPCPs (Burns et al., 2018b; Caldwell et al., 2014; Roos et al., 2012). A widely used method for risk-based prioritization is the simple deterministic approach known as the risk quotient (RQ). This method involves dividing the exposure concentration by the effect concentration, which is utilized for screening pollutants for potential environmental risks (Desbiolles et al., 2018; Thomaidi et al., 2017; Wang et al., 2017; Donnachie et al., 2016; Mendoza et al., 2015; Houtman et al., 2014; Palma et al., 2014; Thomatou et al., 2013; Vazquez-Roig et al., 2012; Vryzas et al., 2011; Sanderson et al., 2004). The RQ approach relies on either measured environmental concentrations (MECs) or predicted environmental concentrations (PECs) (Li et al., 2014; Morais et al., 2014; Perazzolo et al., 2010). Reported concentrations for MECs are frequently based on maximum or median values and often fail to account for seasonal and spatial variations. In contrast, PECs are commonly estimated using mathematical models that incorporate limited environmental factors, potentially deviating from real-world conditions (Burns et al., 2018b; Donnachie et al., 2016; EMA, 2006) Furthermore, due to the scarcity of chronic toxicity information, acute toxicity data were predominantly employed in determining Predicted No-Effect Concentrations (PNECs). This limitation of the RQ approach could potentially lead to bias or misinterpretation of risks (Liu et al., 2020; Godoy et al., 2015; Carlsson et al., 2006). To overcome this issue, an additional indicator that accounts for the frequency of sites with observations exceeding a certain effect threshold has been proposed and utilized in many studies (Liu et al., 2020; Zhou et al., 2019; Desbiolles et al., 2018; Tousova et al., 2017; Dulio and von der Ohe, 2013; von der Ohe et al., 2012, 2011). Therefore, the main objectives of this study were to: 1) measure MECs by quantifying the exposure of PPCPs in Korean surface water through a spatiotemporal assessment using LC-HRMS multiresidue screening methods with year-long monitoring campaigns, 2) conduct an optimized risk-based prioritization that considers the *Frequency of Exceedance* and the *Extent of Exceedance* of the lowest PNEC to account for both the spatial aspect of exposure and the intensity of potential impacts and 3) propose a priority list of PPCPs in Korean surface water utilizing optimized risk-based methods. Finally, the study aims to propose a priority list of PPCPs in Korean surface waters and suggests subsequent risk management measures.

## 2. Materials and methods

### 2.1. Measured environmental concentration

#### 2.1.1. Targeted PPCPs

The 137 PPCPs were selected based on the results obtained from the quantitative target screening, which included initial target substances, as well as identified PPCPs from the suspect and non-target analysis approach using LC-HRMS analysis, and that are frequently detected in the surface waters of Korea (Choi et al., 2021; Park and Jeon, 2021; Park et al., 2018).

#### 2.1.2. Sampling and pretreatment

The sampling was conducted in four major Korean rivers including the five sites at Han River, four sites at Geum River, seven sites at Yeongsan River and six sites at Nakdong River, to provide spatial distribution of PPCPs. The four rivers represent differing levels of urbanization and size. Sampling sites were selected based on the location of branches to the river from densely populated and less populated areas and position in relation to WWTP outfalls. Water samples were collected monthly in the same order and on approximately the same day from April 2020 to March 2021. Grab sampling was performed according to EPA Method 5035 A using 1 L amber round glass bottles, with duplicates taken from the centroid of the flow. Samples were then kept in storage until pretreatment, which occurred within two days.

The samples were treated prior to their analysis using LC-HRMS by following the method developed by Kern et al. and modified by Park et al. The collected water samples were filtered through a glass fiber filter (GF/F, 0.7 μm, Whatman, Bentfort, UK). Then, 80 μL of 0.5 M citrate buffer and 100 μL of a mixture of calibration solution for mass spectrometry were added. A multi-layer SPE cartridge was used to detect a broad substance spectrum, consisting of HLB (200 mg, Oasis, Waters, USA), ENV+ (150 mg, International Sorbent Technology, UK), Strata X-AW, and X-CW (each 100 mg, Phenomenex, UK). The cartridge was conditioned with 5 mL of methanol and 10 mL of deionized water (D.I) prior to loading water samples at 15 mL/min using a vacuum pump. Then, wet cartridges were dried with nitrogen gas for 1 h. The dried cartridge was eluted with 6 mL of ethyl acetate and methanol in a 50:50 v/v mixture with 0.5% ammonia and 3 mL of ethyl acetate and methanol with a 50:50 v/v mixture with 1.7% formic acid. The combined extracts were evaporated using a nitrogen concentrator at 35 °C and reconstituted to a final volume of 1 mL with D.I water and methanol in a ratio of 90:10 (Park et al., 2018; Kern et al., 2009).

#### 2.1.3. Instrumental analysis

Extracts from water samples were measured by LC-HRMS using an X bridge C18 Column for chromatographic separation (the ultimate 3000 UPLC System, Thermo Fisher Scientific, San Jose, CA, USA) and a heated electrospray interface (HESI) in both positive and negative modes on a QExactive plus Orbitrap mass spectrometer (Thermo Fisher Scientific, San Jose, CA, USA) for detection. The mobile phase consisted of DI water

**Table 1**
a) The mean summed concentration of the detected PPCPs in four major rivers in Korea, and b) the mean summed concentration for each therapeutic group including veterinary drugs and personal care products.

| | Nationawide (ng/L) | Four major rivers (ng/L) | | | |
|---|---|---|---|---|---|
| | | Han | Geum | Yeongsan | Nakdong |
| **a) Mean summed concentration (number of detected PPCPs)** | $3.61 \times 10^6$ (120) | $6.82 \times 10^5$ (117) | $4.81 \times 10^5$ (119) | $1.73 \times 10^6$ (117) | $7.11 \times 10^5$ (118) |
| **b) Class (number of PPCPs)** | | | | | |
| Analgesic/anti-inflammatory (18) | 32.50 | 26.10 | 25.20 | 45.90 | 26.40 |
| Anesthetic (4) | 38.30 | 46.80 | 28.90 | 40.60 | 34.30 |
| Anthelmintic (4) | 6.54 | 5.27 | 6.82 | 7.72 | 5.98 |
| Antibiotic (18) | 23.30 | 16.80 | 22.90 | 25.60 | 26.70 |
| Anticonvulsant (5) | 174.00 | 109.00 | 135.00 | 255.00 | 159.00 |
| Antidepressant (9) | 41.90 | 36.30 | 38.50 | 45.40 | 44.90 |
| Antidiabetic (7) | 1050.00 | 861.00 | 655.00 | 1680.00 | 697.00 |
| Antiemetic (1) | 30.70 | 10.00 | 41.70 | 29.90 | 42.90 |
| Antifungal (3) | 114.00 | 93.00 | 87.00 | 137.00 | 124.00 |
| Antihistamine (4) | 242.00 | 193.00 | 198.00 | 285.00 | 264.00 |
| Antihypertensive (13) | 126.00 | 112.00 | 103.00 | 152.00 | 120.00 |
| Antineoplastic (3) | 29.80 | 25.20 | 19.20 | 34.00 | 36.40 |
| Antipsoriatic (1) | 4.40 | 4.27 | 4.77 | 4.61 | 3.98 |
| Antithrombotic (1) | 3.62 | 2.67 | 3.50 | 3.73 | 4.45 |
| Antiulcer (2) | 77.60 | 33.60 | 20.10 | 151.00 | 65.80 |
| Antiviral (6) | 2.40 | 2.77 | 2.28 | 2.50 | 2.02 |
| CNS stimulant (4) | 229.00 | 111.00 | 121.00 | 353.00 | 260.00 |
| PCP (11) | 126.00 | 124.00 | 115.00 | 196.00 | 46.10 |
| Veterinarian (4) | 4.05 | 2.65 | 4.09 | 5.60 | 3.31 |

(solvent A) and methanol (solvent B), both with 0.1% formic acid. The gradient was as follows with B: 0–4 min, 10%; 4–17 min, 50%; 17–25 min, 95%; 25–25.1 min, 10%, 25.1–29 min, 10%. The heated electrospray ionization (HESI) interface was used for compound ionization, operating in positive and negative mode with the following parameters: sheath gas flow (45 L/min), capillary temperature (320 °C), spray voltage (3800 V/3000 V), auxiliary gas pressure (10 arbitrary units), and ion sweep gas (2 arbitrary units) (Park et al., 2018).

Quantitative data from targeted screening were processed using TraceFinder 5.1. To confirm the targeted screening, the isotope pattern and MS/MS fragment were evaluated using Xcalibur 4.5 software with the mzCloud database. The MEC was estimated using ProUCL 5.2 to compute upper confidence limits (UCLs) for actual measured concentrations, which included non-detect observations with multiple detection limits, with a UCL of the 95th percentile ($UCL_{95}$) to avoid skewing with a bias to a few lower or higher concentrations (Singh et al., 2006). For concentrations greater than or equal to the method detection limits (MDLs) and less than or equal to the limit of quantification (LOQ), the reported LOQ value was used to consider the worst case (Barnett et al., 2021; US EPA, 2019; Senn et al., 2012; Data Quality Assessment: Statistical Methods for Practitioners, 2006).

### 2.2. Predicted no-effect concentration

The PNEC values were derived in the following order: 1) retrieval of PNEC values from the REACH Registered Substances database maintained by the European Chemical Agency (ECHA) and proposed environmental quality standards (EQS) from international, regional, and national legislation. If no registered PNEC is available, 2) calculation using a combination of available experimental acute and chronic toxicity data for representative species for three different trophic levels (algae, invertebrates, and fish) with the assignment of application factors (AF) based on the logic flow of EU TGD based PNEC derivations (Belanger et al., 2021). Chronic toxicity data were selected in order of preference: 1) no-observed effect concentration (NOEC) and 10% effective concentration (EC10) for the most sensitive effect measurement, or in the absence of NOEC or EC10, 2) the lowest-observed effect concentration (LOEC) divided by 2 or maximal acceptable toxicant concentration (MATC) divided by 2 or maximal acceptable toxicant concentration (MATC) divided by $\sqrt{2}$ was used. The experimental data was compiled from the ECOTOX knowledgebase (US EPA, 2022a) and EnviroTox Database version 2.0.0 (HESI, 2021).

Thirdly, in case experimental data were unavailable, quantitative structure-activity relationship (QSAR) based in silico tools, VEGA QSAR (Benfenati et al., 2013) was used to predict toxicity values for the three standard species. In brief, the VEGA platform consists of several QSAR models, and in this study, the Aquatic Chronic (NOEC) Toxicity Model (IRFMN) version 1.01 for fish, *Daphnia magna*, and algae were employed. SMILES, as input data, were obtained from PubChem and ECOSAR version 2.2 (US EPA, 2022b). Subsequently, the lowest chronic value was selected, and an application factor of 100 was applied to derive PNEC (Amiard and Amiard-Triquet, 2015).

### 2.3. Optimized risk-based prioritization

The traditional RQ approach calculates the ratio of MEC to PNEC. This approach often relies on mean or maximum concentration as MEC, which may not accurately reflect the real-world exposure scenario or could potentially overestimate the potential risk respectively. For this reason, a new RQ approach for prioritization is proposed, modified from previous studies (Liu et al., 2020; Zhou et al., 2019; Desbiolles et al., 2018; Tousova et al., 2017; Dulio and von der Ohe, 2013; von der Ohe et al., 2012, 2011). In brief, an optimized risk-based method or a novel risk quotient ($RQ_f$) considers the frequency of MEC exceeding PNECs to address the significant spatial and seasonal variation observed in the detected concentrations used to calculate. The $RQ_f$ can be calculated in two different ways: the sum of resulting values from two indicators, the *frequency of exceedance* and the *extent of exceedance* of lowest PNEC, or their multiplication. In this study, the $RQ_f$ value was calculated as the result of the *extent of exceedance* of lowest PNEC multiplied by the *frequency of exceedance* according to the following equations:

$$RQ_f = Extent \quad of \quad Exceedance \times Frequncy \quad of \quad Exceedance$$

The *extent of exceedance* of lowest PNEC can be calculated in the same way as the traditional RQ approach, which can be calculated by dividing the MEC by the PNEC. The resulting indicator value can be then classified into risk severity or scored by risk, ranging from 0 to 1. In this study, the *extent of exceedance* of the lowest PNEC was classified as high risk if MEC/PNEC (or RQ) $\geq 10$; moderate risk if $1 \leq RQ < 10$; low risk if $0.1 \leq RQ < 1$, and negligible if $RQ < 0.1$ (Liu et al., 2020; Chen et al.,

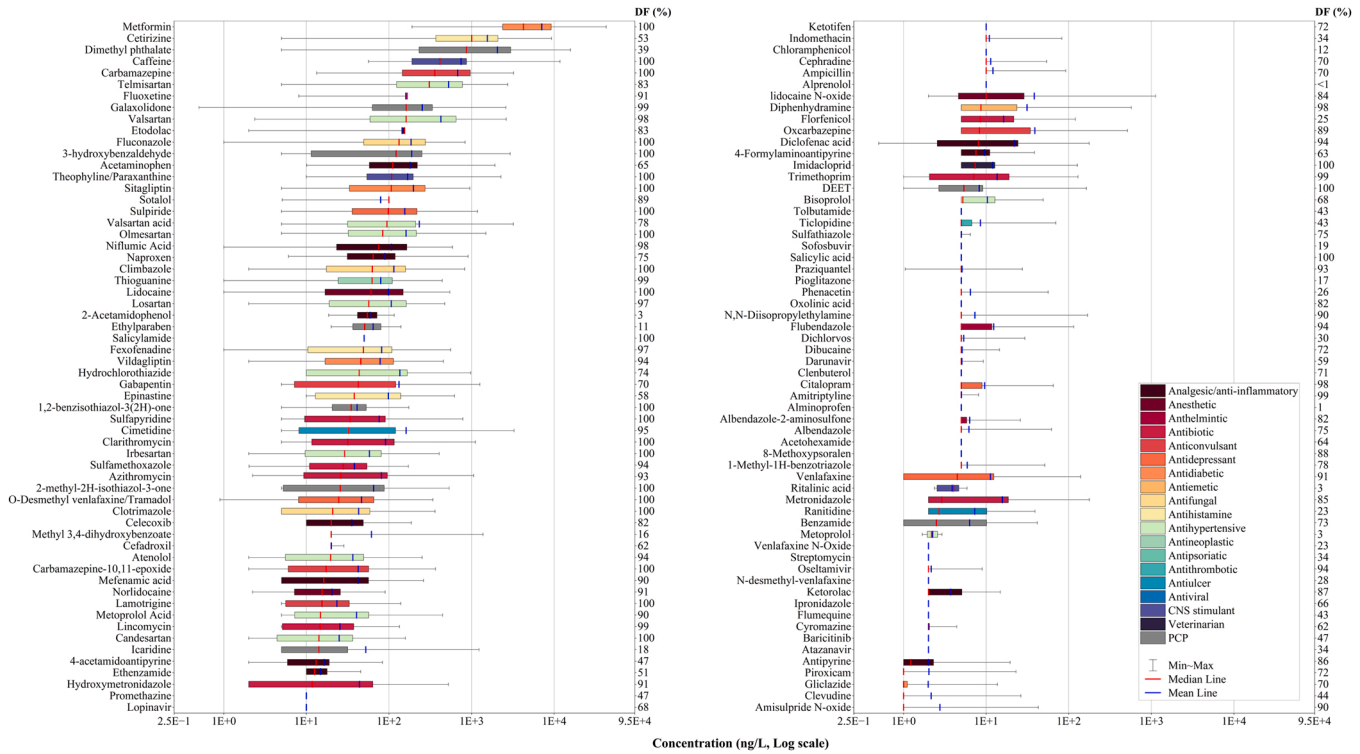


**Fig. 1.** Concentration ranges for the quantification of 120 PPCPs above the limit of detection (LOD) in the surface waters of Korea during the April 2020 to March 2021 monitoring campaign. DF represents the detection frequency of compounds as a percentage. The box represents the range between the 25th and 75th percentiles, while the whiskers represent the range from the minimum to maximum concentrations. The red line represents the median, and the blue line represents the mean. The color of the box indicates the therapeutic group or personal care product (PCP) to which the compound belongs.

2020). The *frequency of exceedance* was calculated by the number of sites with measured concentrations above PNECS divided by the total number of sampling sites (von der Ohe et al., 2012, 2011).

## 3. Results and discussion

### 3.1. PPCPs occurrence in Korean surface waters

During the April 2020 to March 2021 monitoring campaign, 120 out 137 monitored PPCPs were detected in four major rivers in Korea. Of these, 87 pharmaceuticals and 11 personal care products were quantified above the LOQ at least once. The limits of detection (LOD) ranged from 0.1 ng/L to 50 ng/L, and the LOQ ranged from 0.5 ng/L to 100 ng/L, with a relative standard deviation (RSD) of $\leq$ 25%. The calibration range exhibited good linearity, with values of $R^2$ of at least 0.990, and the recovery rate was within the range of 50–150% for 129 compounds and 75–125% for 105 compounds (Table S1).

Table 1 shows the mean summed concentration of the detected PPCPs in four major rivers in Korea, as well as the mean summed concentration for each therapeutic group, including personal care products and veterinary drugs. Among the four rivers, the Yeongsan River showed the highest mean summed concentration of PPCPs, followed by the Nakdong River, Han River, and Geum River. The Geum River detected the most PPCPs, with a total of 119, followed by the Nakdong River, Han River, and Yeongsan River. Of the detected PPCPs, 18 therapeutic groups, including veterinary drugs, and personal care products were identified. The therapeutic group with the highest mean summed concentration was antidiabetic compounds, with a concentration of 1050 ng/L, followed by antihistamines, personal care products, antihypertensives, central nervous system (CNS) stimulants, anticonvulsants, antifungals, anesthetics, antidepressants, antiulcers, analgesics and anti-inflammatories, antineoplastics, antibiotics, antiemetics, anthelmintics, antipsoriatics, antivirals, antithrombotics and veterinary drugs. Fig. 1 shows the MECs of the detected PPCPs and their detection frequencies in order of median concentration. Nationally, the top five annual median concentrations of PPCPs were metformin (4239 ng/L), cetirizine (1004 ng/L), dimethyl phthalate (865 ng/L), caffeine (414 ng/L), and carbamazepine (359 ng/L), respectively. A similar trend was observed in all four rivers, where these five compounds were ranked among the top 10 highest annual median concentrations (Tables S2 and S3). Metformin, caffeine, and carbamazepine are frequently detected in the environment worldwide, likely due to their widespread use as lifestyle medicines (Wilkinson et al., 2022). Other PPCPs showed similar trends across the watersheds, indicating that commonly used PPCPs exhibit comparable usage patterns, WWTP removal efficiencies, and environmental fate in all four rivers (Su et al., 2021).

Among the seven compounds detected in antidiabetic drugs, metformin, a type II diabetes drug, predominantly showed high concentrations in the range of 190–42,733 ng/L and a detection frequency of 100%. The concentration of metformin in this study is comparable to that detected worldwide due to its wide range of use and being one of the most commonly prescribed drugs worldwide. Metformin was detected in Korea with a concentration up to 1908 ng/L in Yeongsan River (Park et al., 2018) and up to 3600 ng/L in Nakdong River with 100% detection frequency (Park et al., 2018). Worldwide, the presence of metformin in the surface of China was up to 121.4 ng/L (He et al., 2022), ranging from 145 to 10,100 ng/L in Canada (Caldwell et al., 2019), maximum concentrations in the range of 8.7–9249 ng/L in Lake Michigan (Briones et al., 2016) and 933–9258 ng/L in the Delaware River of the USA (Vilimanovic et al., 2020), a highest concentration of 2592 ng/L in the UK (Burns et al., 2018a), and a concentration of 1800 to 3900 ng/L in the surface water of the Netherlands (Balakrishnan et al., 2022). Sitagliptin and vildagliptin were also frequently detected in 100% and over 94% of the 235 samples monitored in four rivers, with median concentrations of 107 ng/L and 46 ng/L, respectively.

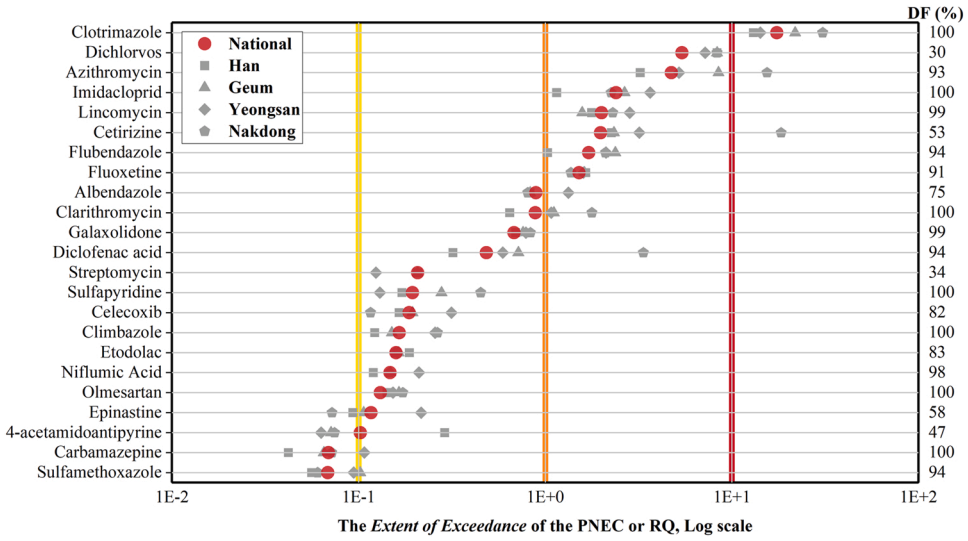


**Fig. 2.** The extent of exceedance of the predicted no-effect concentration (PNEC) or risk quotient (RQ) for the detected PPCPs in Korean surface waters, listed in descending order. The vertical line represents the RQ level, with yellow indicating low risk (RQ $\geq$ 0.1), orange indicating moderate risk (RQ $\geq$ 1), and red indicating high risk (RQ $\geq$ 10). The detection frequency (DF) is shown on the right axis. Each Symbol in the graph represented the national scale and each of four major rivers in Korea (Han River, Geum River, Yeongsan River, and Nakdong River).

Cetirizine, an antihistamine drug used to treat allergy symptoms, was overwhelmingly detected with higher concentrations than other compounds belonging to the antihistamine group in this study. Cetirizine concentrations varied widely between sampling sites and time from non-detect to 9297 ng/L with a detection frequency of 53%. Previously reported concentrations in surface water in Seoul and sewage treatment plants (STPs) in the Nakdong River basin ranged from 67 to 177 ng/L and 8.3–300 ng/L, respectively, with lower orders of magnitude but higher detection frequencies. However, this result is consistent with reported concentrations in Brussels in Belgium, North Liberty and Las Vegas in the USA, Lahore in Pakistan, and Delhi and Hyderabad in India (Wilkinson et al., 2022).

For other pharmaceuticals, caffeine, a psychoactive stimulant, was detected in 100% of samples, with concentrations ranging from 57 to 11,789 ng/L among CNS stimulants group. Metabolites of caffeine, paraxanthine/theophylline, were also detected as a substantial portion of the CNS stimulants, ranging from LOQ to 2271 ng/L with a 100% detection frequency. Carbamazepine and its metabolite carbamazepine-10,11-expoxide, anticonvulsants used to treat seizures and neuralgia, were found in the range of 13–3229 ng/L and LOQ to 366 ng/L, respectively, with both having a 100% detection frequency. In some previous studies, gabapentin was reported as the highest concentration among the detected anticonvulsant group (Rose and Kam, 2002), but in this study, it was followed by carbamazepine with concentrations ranging from LOQ to 1262 ng/L with a detection frequency of 70%. Some antihypertensive agents suggested and used for patients with COVID-19, such as telmisartan, valsartan and its metabolite, valsartan acid, olmesartan, and losartan (Rothlin et al., 2020), were found in surface water with high detection frequencies (74–100%) and concentrations (LOQ to 2739 ng/L, 2–2626 ng/L, LOQ to 3213 ng/L, LOQ to 1493 ng/L and LOQ to 473 ng/L, respectively).

Dimethyl phthalate, a type of plasticizer which is also used as a solvent for dyes, perfumes, and other organic compounds, and as a mosquito repellent, was detected in the highest concentration up to 15,799 ng/L. Among personal care products, the annual median concentration of dimethyl phthalate was about 5–6 times higher than the second and third highest concentrations of personal care products, galaxolidone (161 ng/L) and 3-hydroxybenzaldehyde (122 ng/L), respectively. However, the detection frequency of dimethyl phthalate was 39%, whereas galaxolidone and 3-hydroxybenzaldehyde were detected at 98% and 100%, respectively. This result is consistent with a previous study (Cho et al., 2014), where dimethyl phthalate was found in the range of 40–15,100 ng/L in four rivers in Korea.

### 3.2. Derivation of the PNEC

The derived PNECs were prioritized according to the reliability and accuracy of the data sources. Among the 137 PPCPs, PNECs for 42 pharmaceuticals and 10 personal care products were secured from REACH and other EQS established by organizations such as the US Environmental Protection Agency (EPA) or The Swiss Centre for Applied Ecotoxicology. At least one experimental toxicity data, excluding secured PNECs from the previous step, was available for 26 PPCPs. The data set contained a variety of data combinations from one trophic level of acute toxicity data to three trophic levels of both acute and chronic toxicity data, and application factors were assigned from 10 to 1000. The remaining 59 PPCPs NOECs for aquatic species belonging to three different trophic levels were predicted by using VEGA QSAR with an assignment of an application factor of 100 (Bouzas-Monroy et al., 2022; Topaz et al., 2020; Zhou et al., 2021). Dichlorvos, an organophosphate insecticide used in veterinary medicines to control parasites in animals, had the lowest PNEC ($6 \times 10^{-4}$ μg/L) (Papich, 2016), and saccharin, an artificial sweetener, had the highest PNEC (5000 μg/L) among the 137 PPCPs (Azeez et al., 2019). As a result of the prediction from the QSAR-based in silico tool, the PNEC for 96 pharmaceuticals and 9 personal care products was derived based on the NOEC for fish and its most sensitive taxonomic group among three trophic levels, followed by invertebrates (12 pharmaceuticals and 4 personal care products), i.e., *Daphnia manga*, and algae (14 pharmaceuticals and 2 personal care products) (Table S4). It has been reported that fishes are more sensitive to pharmaceuticals than invertebrates or algae (Liu et al., 2020). The species sensitivity distribution (SSD) approach was also considered to derive the PNEC, which is known to be more robust. However, only one PPCP, i.e., carbamazepine, was available to develop the SSDs, which correspond to the taxonomic groups considered standard for acceptance in regulatory frameworks such as ECHA, USEPA ambient water quality criteria, and CCME.

### 3.3. Optimized risk-based prioritization

The values of the *extent of exceedance* of the lowest PNEC, or simply RQ, for the PPCPs above 0.1 from at least one watershed are shown in Fig. 2, in descending order (more details about RQ values for all studied PPCPs are provided in Table S5). Overall, RQ ranged from 17.4 for antifungal clotrimazole to $9.98 \times 10^{-6}$ for anti-inflammatory antipyrine, and for 21 compounds, the obtained RQ values were higher than 0.1. Clotrimazole was the only compound exceeding RQ values of 10, indicating a high environmental risk in Korean surface waters. This result is

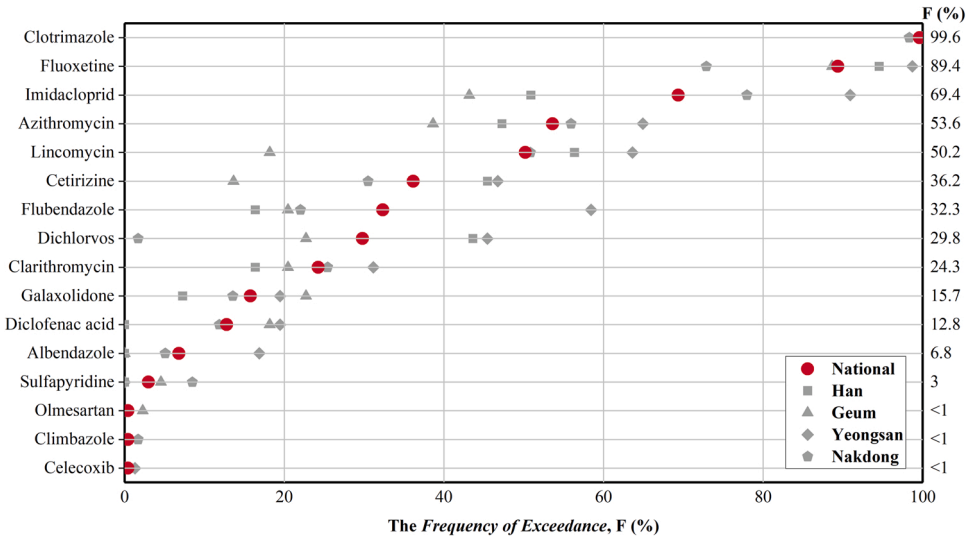


**Fig. 3.** The frequency of MECs exceeding PNECs (F) for 16 PPCPs in descending order. Each Symbol in the graph represented the national scale and each of four major rivers in Korea (Han River, Geum River, Yeongsan River, and Nakdong River).

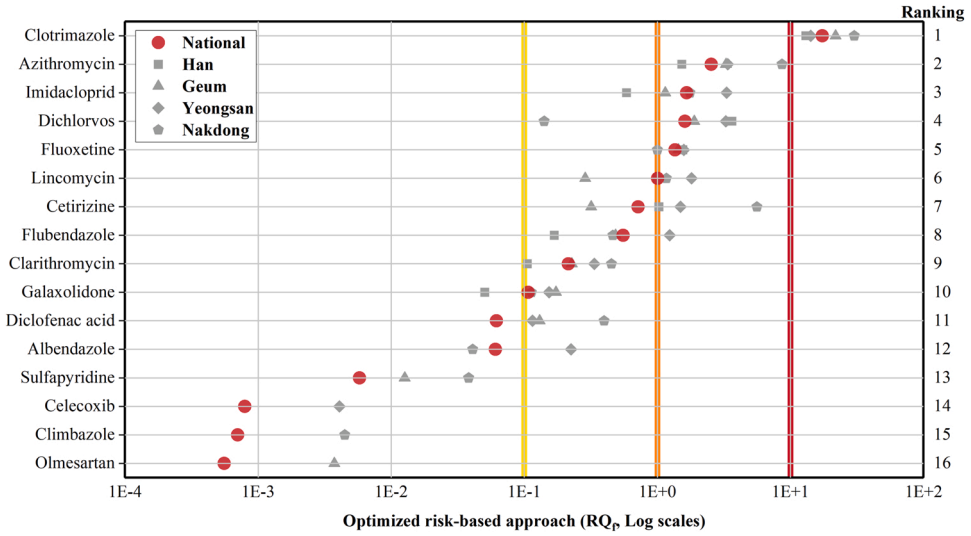


**Fig. 4.** An optimized risk-based approach or RQf values of 16 prioritized PPCPs ranked in order of their RQf value, from highest to lowest. The vertical line represents the RQf level, with yellow indicating low risk (RQf $\geq$ 0.1), orange indicating moderate risk (RQf $\geq$ 1), and red indicating high risk (RQf $\geq$ 10). Each Symbol in the graph represented the national scale and each of four major rivers in Korea (Han River, Geum River, Yeongsan River, and Nakdong River).

consistent with previous studies in China where clotrimazole was found to pose a medium to high risk to aquatic organisms (Chen and Ying, 2015; Liu et al., 2015; Zhang et al., 2015). The RQ values for seven compounds yielded results between 1 and 10, indicating a moderate environmental risk was likely. The remaining 13 compounds were classified as a low risk to aquatic organisms. Among these 21 compounds that posed a discernible or potential risk to aquatic organisms, pharmaceuticals made a major contribution (20 out of 21) and one personal care product, galaxolidone. Antibiotics and analgesics/anti-inflammatories accounted for the largest contribution to the risk for aquatic organisms (5 out of 21), followed by anthelmintics (2), antifungals (2), antihistamines (2), veterinary drugs (2), antidepressants (1), and antihypertensives (1). Additionally, site-specific ecological risk assessment was assessed in each river. The risk assessment in the Han River, Geum River, Yeongsan River, and Nakdong River found 20, 21, 21, and 19 PPCPs with RQ above 0.1, respectively. Nakdong River had the highest RQ of 30.7 for clotrimazole, and most RQs were above 10, including 18.4 for cetirizine and 15.4 for azithromycin.

Fig. 3 shows the frequency of MECs exceeding PNECs in descending order, represented as percentages. Only PPCPs with MEC/PNEC ratios above 1 were considered to derive the frequencies. Overall, 16 PPCPs in Korean surface waters were found to be likely to cause detrimental effects on certain vulnerable species. Clotrimazole had the highest likelihood of exceeding PNECs at 99.6%, followed by fluoxetine (89.4%), imidacloprid (69.4%), azithromycin (53.6%), lincomycin (50.2%), cetirizine (36.2%), flubendazole (32.3%), dichlorvos (30.0%), clarithromycin (24.3%), galaxolidone (15.7%), diclofenac acid (12.8%), albendazole (6.8%), sulfapyridine (3.0%), and less than 1% for the remaining three PPCPs.

The prioritized PPCPs according to $RQ_f$ values are shown in Fig. 4. The $RQ_f$ values for 17 PPCPs ranged from 17.3 for clotrimazole to $6 \times 10^{-4}$ for olmesartan, and 10 of them yielded values above 0.1. When compared to the original RQ values, the ranked substances remain the same but in a different order and with lower values. The frequency of PNEC exceedance cannot be greater than 1 or 100%. Hence, $RQ_f$ must be smaller or equal to the values used for calculating the RQ. The $RQ_f$

**Table 2**
Comparison of prioritized PPCPs based on multiple approaches, including the extent of exceedance of lowest PNEC or RQ, the frequency of exceedance in percentage, optimized risk-based approach or RQf values, and scores from an exposure-based approach derived from the Rhine monitoring program of 2013 that were above 100 (ICPR, 2013).

| Relative Ranking | Extent of Exceedances of lowest PNEC (RQ) | Frequency of Exceedance (F, %) | Novel Risk Quotient ($RQ_f$) | Exposure-based Scores (>100) |
|---|---|---|---|---|
| 1 | Clotrimazole (17.41) | Clotrimazole (99.57) | Clotrimazole (17.34) | Metformin (200) |
| 2 | Dichlorvos (5.40) | Fluoxetine (89.36) | Azithromycin (2.54) | Caffeine, Carbamazepine, |
| 3 | Azithromycin (4.74) | Imidacloprid (69.36) | Imidacloprid (1.66) | Valsartan acid (175) |
| 4 | Imidacloprid (2.39) | Azithromycin (53.62) | Dichlorvos (1.61) | |
| 5 | Lincomycin (2.00) | Lincomycin (50.21) | Fluoxetine (1.36) | Cetirizine (150) |
| 6 | Cetirizine (1.98) | Cetirizine (36.17) | Lincomycin (1.00) | Dimethyl phthalate (125) |
| 7 | Flubendazole (1.71) | Flubendazole (32.34) | Cetirizine (0.72) | Climbazole, Fluconazole, |
| 8 | Fluoxetine (1.52) | Dichlorvos (29.79) | Flubendazole (0.55) | Lidocaine, Olmesartan, |
| 9 | Albendazole (0.89) | Clarithromycin (24.26) | Clarithromycin (0.21) | Sulpiride, Theophyline/Paraxanthine (110) |
| 10 | Clarithromycin (0.88) | Galaxolidone (15.74) | Galaxolidone (0.11) | |
| 11 | Galaxolidone (0.68) | Diclofenac acid (12.77) | Diclofenac acid (0.06) | |
| 12 | Diclofenac acid (0.48) | Albendazole (6.81) | Albendazole (0.06) | |
| 13 | Streptomycin (0.21) | Sulfapyridine (2.98) | Sulfapyridine (0.01) | 2-methyl-2 H-isothiazol-3-one, Irbesartan, |
| 14 | Sulfapyridine (0.19) | Celecoxib (0.43) | Celecoxib (8.00E-4) | O-Desmethyl venlafaxine/Tramadol, Salicylamide Sulfapyridine (104) |
| 15 | Celecoxib (0.19) | Climbazole (0.43) | Climbazole (7.00E-4) | |
| 16 | Climbazole (0.17) | Olmesartan (0.43) | Olmesartan (6.00E-4) | |
| 17 | Etodolac (0.16) | - | - | |
| 18 | Niflumic Acid (0.15) | - | - | Candesartan, Imidacloprid, |
| 19 | Olmesartan (0.13) | - | - | Lamotrigine (101), |
| 20 | Epinastine (0.12) | - | - | |
| 21 | 4-acetamidoantipyrine (0.10) | - | - | DEET, Salicylic acid (100) |

values for 6 PPCPs, clotrimazole (17.34), azithromycin (2.54), imidacloprid (1.66), dichlorvos (1.61), fluoxetine (1.36), and lincomycin (1.00), were higher than 1, indicating moderate to high risk posing in Korean surface waters. Four compounds had the new $RQ_f$ values ranging between 0.1 and 1, indicating a lower environmental risk. Among these, cetirizine and flubendazole initially exhibited RQ values exceeding 1. The $RQ_f$ values for the remaining six PPCPs yielded values below 0.1, indicating no expected environmental risk after considering the frequency of MECs exceeding PNEC. Out of the 10 PPCPs, seven were listed on the NORMAN Priority List, notably all of the five highest ranked compounds with an $RQ_f$ above 1 were included (Dulio and von der Ohe, 2013). Four compounds were added to the EU watch list 2020/1161/EU (clotrimazole) (European Commision, 2020) and 2013/39/EU (azithromycin, clarithromycin, and imidacloprid) (European Commision, 2013), and clotrimazole was also included in the chemicals for priority action list of OSPAR commission in 2002 (Kryczyk-Poprawa et al., 2019).

### 3.4. Overall priority

Table 2 shows a comparison of prioritized PPCPs based on the RQ, the frequency of MECs exceeding PNEC, $RQ_f$ values, and scores from an exposure-based method. The RQ assesses the potential risk of a chemical by comparing its MEC to the PNEC. Traditional RQ has been widely used in environmental risk assessments due to its simplicity and ease of interpretation. This deterministic approach can be applied in various scenarios when MEC data is insufficient, allowing for valuable insights into potential risks despite limited data availability. However, this deterministic approach does not consider statistical probabilities and can over or underestimate the risk due to outliers in MEC and PNEC. Therefore, when MEC is derived from the robust monitoring campaign, the $RQ_f$, which accounts for the frequency of PNEC exceedance and mimics natural scenarios, provides a more comprehensive assessment of potential risk by providing detailed perspectives on both spatial distribution and intensity of potential impacts.

Exposure-based prioritization is often used to compensate for insufficient ecotoxicological knowledge. In this study, the targeted PPCPs were prioritized using a scoring system based on the Rhine Monitoring Programme Chemistry. The evaluation of the scoring system is based on the sum of the maximum concentration of the substance and the frequency of occurrence (ICPR, 2013). However, in this study, the scoring system was modified by replacing the score based on maximum concentration with the UCL95 of the mean value of the MEC. In the exposure-based method, 24 chemicals received scores above 100,

indicating high exposure to the environment (ICPR, 2013). More details about the scoring system are provided in Table S8. In the exposure-based method, 24 chemicals received total scores above 100, indicating high exposure to the aquatic environment. The results of $RQ_f$ and exposure-based prioritization differed significantly. Only five compounds, cetirizine, olmesartan, climbazole, sulfapyridine, and imidacloprid, were identified by both methods, highlighting the importance of employing multiple approaches to prioritize chemicals.

Although this study comprehensively assessed the risk in aquatic environment, there are additional considerations that should be taken into account in the measurement of MEC and derivation of PNECs. The selection of PPCPs for this study was based on a literature review, including papers, domestic usage statistics, and substances of interest. However, it is important to note that the selected PPCPs may not be entirely representative of all the PPCPs present in the environment. Given the vast number of PPCPs, it is impractical to quantify each one. Therefore, it is essential to utilize appropriate techniques, such as calculating PEC and suspect screening, and assess whether quantitative analysis is necessary from an exposure or risk perspective (Park and Jeon, 2021; Park et al., 2018). Furthermore, it is important to consider the variations in concentrations and detection frequencies that may arise due to the temporal and spatial variability of sampling (Burns et al., 2018a). In addition, the toxicity values used to calculate PNECs are mostly based on endpoints that are a departure from those apical endpoints associated with traditional toxicology testing including immobilization, mortality, reproduction and growth. It should be noted that nonapical effects may occur at lower concentrations than traditional apical endpoints (Bouzas-Monroy et al., 2022). Additionally, PPCPs have been shown to have adverse effects on aquatic organisms through endocrine disruption, bioaccumulation, and the induction of bacterial antibiotic resistance. Given the potential ecological risks associated with PPCPs, a comprehensive risk assessment approach is necessary that considers both apical and nonapical endpoint types to ensure that potential risks are not overlooked and appropriate measures are taken to protect the environment (Kumar et al., 2023; Liu et al., 2020).

## 4. Conclusion

The 137 selected PPCPs were quantified for a year-long monitoring campaign with spatial variation. The results showed that the Yeongsan River had the highest average concentration of summed PPCP, followed by the Han River, Nakdong River, and Geum River. Metformin had the maximum concentration, with its value in $UCL_{95}$ being about eight times higher than that of the second highest PPCP, dimethyl phthalate. Thus, antidiabetics group also had the highest concentration among the therapeutic groups in this study. The highest RQ value for the PPCPs was observed for clotrimazole at 17.4, indicating a significant risk to aquatic organisms. Furthermore, seven and 13 compounds showed RQ values above 1 and 0.1, respectively. However, after considering the frequency of PNEC exceedance, the $RQ_f$ values for the compounds were relatively lower than their original values. Clotrimazole still exhibited the highest $RQ_f$ value of 17.4 with 99.6% of its MECs exceeding PNECs. Additionally, five compounds still exceeded the $RQ_f$ threshold of 1, while four others showed values above 0.1. Moreover, a comparison between risk-based and exposure-based prioritization revealed a significant difference in the priority lists. Therefore, adopting multiple prioritization approaches to evaluate the potential adverse effects of chemicals on aquatic organisms is an urgent and vital consideration. This approach enables comprehensive screening of environmental risks posed by chemicals and suggests further investigation for in-depth understanding of their potential effects, including mixture risks, to facilitate effective management.

## CRediT authorship contribution statement

**Jun Yub Kim**: Writing – original draft, Investigation. **Junho Jeon:** Methodology, Validation. **Sang Don Kim:** Conceptualization, Writing – review & editing, Supervision.

## 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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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2023.115024.

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