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# Prioritization of highly exposable pharmaceuticals via a suspect/non-target screening approach: A case study for Yeongsan River, Korea

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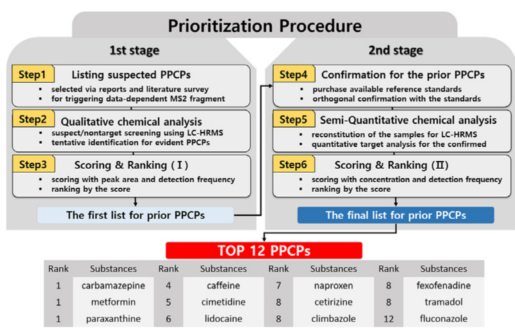
## HIGHLIGHTS

- Pharmaceuticals and personal care products (PPCPs) in the Yeongsan River, Korea were prioritized.
- Fifty one PPCPs were tentatively identified via suspect and non-target analysis using LC-HRMS.
- Twenty eight PPCPs were finally confirmed and prioritized by a scoring/ranking system.
- Top 12 PPCPs including carbamazepine, metformin, and paraxanthine are suggested for further monitoring plan.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Pharmaceuticals and personal care products (PPCPs) in the Yeongsan River, Korea were prioritized via suspect and non-target analysis using LC-HRMS (QExactive plus Orbitrap) followed by semi-quantitative analysis to confirm the priority of PPCPs. A scoring and ranking system for prioritization was suggested based on occurrence frequency and chromatographic peak area or concentration. Through suspect and non-target screening, more than 50 PPCPs were tentatively identified and ranked by the scoring system. Among them, 28 substances were finally confirmed using reference standards. For estimating concentration, 26 confirmed PPCPs and 12 additional substances not included in the first ranking were semi-quantitatively analyzed. We found that carbamazepine, metformin, paraxanthine, naproxen, and fluconazole occurred 100% of the time above the limit of quantification in 14 samples, whereas carbamazepine, metformin, paraxanthine, caffeine, and cimetidine showed maximum concentrations above 1000 ng/L. Thus, in the final prioritization list, carbamazepine, metformin, and paraxanthine shared first place, followed by caffeine, cimetidine, lidocaine, naproxen, cetirizine, climbazole, fexofenadine, tramadol, and fluconazole, with scores of 100 or above. We suggest that these 12 PPCPs are the most highly exposable substances, and thus must be considered in future water monitoring in the Yeongsan River.


## 1. Introduction

The number and types of chemicals used in everyday life are increasing and diversifying. These chemicals enter the environment, threaten ecosystems, and jeopardize the value of water resources. In Korea, the average sewerage service penetration rate reached about 93% in 2015,

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and, in particular, 97.4% or higher for seven metropolitan cities (Ministry of Environment, 2016). Various types of organic pollutants, defined as micropollutants, including pharmaceuticals and personal care products (PPCPs), originate in human daily life and activities; these pollutants are discharged into surface waters through sewage treatment plants. Most of them are biologically active, even at trace concentrations (Brausch and Rand, 2011; Tahar et al., 2017; Yang et al., 2017). Indeed, their numbers and types vary considerably, such that their risks should not be disregarded (Brausch and Rand, 2011; Leung et al., 2012). Information on their occurrence and concentration provides important clues for evaluating aquatic ecosystem risk and integrity. However, it is not technically easy to accurately analyze the numerous trace contaminants. Time, money, and skilled experts are needed for these chemical analyses. Fortunately, the recent rapid development of analytical technology for environmental pollutants using high-resolution mass spectrometry has made it possible to conduct research on trace pollutants. This advanced analytical tool enables new chemical screening approaches, namely suspect and non-target screening (SNTS), which allow for qualitative substance analysis even without reference standard materials. These emerging approaches go beyond the conventional target analysis, which relies on analytical information from existing reference standard materials (Bade et al., 2016; Bletsou et al., 2015; Gago-Ferrero et al., 2015; Hug et al., 2014; Krauss et al., 2010; Llorca et al., 2016; Muz et al., 2017; Singer et al., 2016). Target screening and comparable SNTS are well-documented in Bletsou et al. (2015).

SNTS have been suggested as novel approaches to prioritize environmental pollutants using information on occurrence frequency and concentration-relevant indices (e.g., peak area) provided by qualitative analysis (Hollender et al., 2017; Singer et al., 2016). These approaches can reduce the time required to acquire the reference materials and can save the expense of purchasing reference materials for non-existent pollutants.

For the purpose of evaluating environmental risk determined from effect and exposure assessment, conventional prioritization methods have often oriented to chemical effect (or toxicity) information (Caldwell et al., 2014; Roos et al., 2012; Sanderson et al., 2004; Singer et al., 2016). Additional information, such as the amount of chemicals used, the physico-chemical properties, environmental fate, and removal efficiency at the treatment site can also be considered in a comprehensive manner for prioritization, but not weighted higher than effect (toxicity) data. If such prior pollutants are selected mainly based on an effect assessment, those are examined further, and, when it is possible, analyzed. Thereafter, sample analysis, that is, exposure assessment, is performed. Thus, an effect-based prioritization might exclude low-toxicity pollutants from a monitoring plan, and consequently from a risk assessment, even if their occurrence frequency and concentrations overwhelm other chemicals. This results in an underestimation of the ecosystem risk posed. To overcome the limitations of the effect-based method, exposure information (e.g., occurrence and concentration) should be included in a prioritization. Chemical substance exposure information can be considerably extended using SNTS techniques via high-resolution mass analysis (Aalizadeh et al., 2016; Avagyan et al., 2016; Bade et al., 2016; Gago-Ferrero et al., 2015; Hollender et al., 2017).

Of the four major rivers in Korea, the Yeongsan River has the highest nutrient levels. It serves as the receiving body for effluent from the Gwangju metropolitan area, and also provides irrigation water for the large agricultural area in southern Jeolla Province. Unfortunately, around 14% of the 1.5 million residents in this metropolitan area lack sewerage (Ministry of Environment, 2016). As a result, a non-negligible loading of untreated contaminants into the river is expected, and downstream ecosystem protection is hardly guaranteed. In order to establish a long-term water quality monitoring plan to assess ecotoxicity, water-borne pollutant prioritization must be conducted. To date, there is little domestic information on micropollutants (i.e., PPCPs), but much more on major pesticides. Existing micropollutant information is limited to sporadic sampling and analysis. Some European countries, including Germany and Switzerland, have much more data on a greater number of investigated substances (Bonvin et al., 2011; Gago-Ferrero et al., 2015; Gracia-Lor et al., 2011; Loos et al., 2013; Mandaric et al., 2017; Murata et al., 2011; Ortiz de García et al., 2017; Ruff et al., 2015). Above all, most of the previously investigated micropollutants are those selected by the effect-based prioritization method, rather than on an exposure basis. Thus, information on exposure to a wider variety of substances is needed to conduct effect-exposure balanced risk assessments for aquatic ecosystems.

In this study, we applied SNTS using LC-HRMS, an approach suitable for measuring many PPCPs, to prioritize those chemicals in the Yeongsan River affected by the presence of a major city. We suggest a prioritizing technique consisting of four steps, including SNTS, which is designed to detect the presence of as many substances as possible. By applying this exposure-based ranking system that adopts SNTS data on occurrence frequency and chromatographic peak areas, the first prioritized list is extracted of PPCPs. The selected prior pollutants are then orthogonally confirmed using reference standards, then re-ranked after semi-quantitative target analysis. Then, the final prior PPCPs (top 12), which we define as the most highly exposable substances in the Yeongsan River, are suggested for inclusion in a long-term monitoring plan.

## 2. Materials and methods

### 2.1. Overall prioritization procedure

The suggested exposure-based prioritization for PPCPs is composed of two stages including six steps, as depicted in Fig. 1. At the first stage, the first prioritization list is suggested via steps 1–3. Step 1: A list of PPCPs suspected to be present in river was compiled via literature review and relevant database survey. The suspected PPCPs list was merged into the operating program of an analytical instrument (LC-HRMS) to trigger data-dependent MS2 fragmentation. Step 2: Instrumental analysis was performed to detect suspect or non-target PPCPs. The evident peaks for PPCPs were tentatively identified. Step 3: A score was given to the identified PPCPs according to exposure-relevant indices, namely, occurring frequency and chromatographic peak area. The scored PPCPs were then ranked.

The final list of prior PPCPs is extracted through the second stage with steps 4–6. Step 4: Chemical confirmation was conducted for the listed PPCPs whose reference standards were commercially available. Step 5: Quantitative target screening was conducted using LC-HRMS for the confirmed and other suspicious PPCPs after reconstituting the sample extracts with isotope-labeled internal standards. Step 6: The quantified PPCPs were scored and ranked for final prioritization according to occurring frequency and concentration. More detail for each step follows.

### 2.2. List of suspected PPCPs

The most common PPCPs were suspected and thus listed for MS2 spectra information acquisition via suspect screening. A commercial compound database by the name of Environmental Food Safety (EFS) (Thermo Fisher Scientific, San Jose, CA, USA) was used as the primary information source for the suspect list. Other information collected from the literature and a library survey was also used. In total, 189 compounds from 17 different classes were considered in suspect screening: analgesic/anti-inflammatory (49), anesthetic/anti-convulsant (9), anthelmintic (4), anti-biotic/anti-fungal (52), anti-coagulant (1), anti-depressant/anti-psychotic (17), ant-idiabetic (4), ant-ihistamine/anti-itching (3), anti-hypertensive agent (24), anti-migraine (2), anti-ulcer (4), artificial flavoring (1), CNS stimulant (5), contrast media (2), cosmetics (1), erectile dysfunction (4), hormone (5), and UV filter (2).