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Integrating data dependent and data independent non-target screening methods for monitoring emerging contaminants in the Pearl River of Guangdong Province, China

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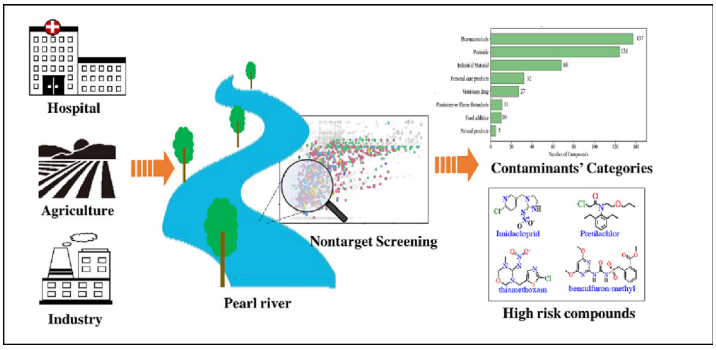
HIGHLIGHTS

- 620 compounds were identified in pearl river using Nontarget Screening method.
- Pharmaceuticals and pesticides are main Contaminants in Pearl river.
- Four pesticides are posing high health risks in Pearl river.
- Diagnostic fragment ion strategy was used to explore structurally-related compounds.

GRAPHICAL ABSTRACT



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ABSTRACT

The occurrence of Contaminants of Emerging Concern (CECs) in the Pearl River of Guandong province, China, was characterized using a nontarget screening (NTS) strategy combining both data dependent and data independent acquisition techniques. Our analysis identified 620 unique compounds, including pharmaceuticals (137), pesticides (124), industrial materials (68), personal care products (32), veterinary drugs (27), plasticizers or flame retardants (11), etc. Out of these compounds, 40 CECs were found with a detection frequency of over 60 %, including diazepam, a well-known drug to treat anxiety, insomnia, convulsion, etc., which had the highest detection rate at 98 %. Risk quotients (RQs) were calculated for CECs identified with high confidence (Level 1, confirmed with authentic standards), and it was found that 12 CECs had RQs > 1, with notable concern for pretilachlor (detection frequency: 48 %; 0.8–19.0 ng/L), bensulfuron-methyl (86 %, 3.1–56.2 ng/L), imidacloprid (80 %, 5.3–62.8 ng/L) and thiamethoxam (86 %, 9.1–99.9 ng/L), which exhibited RQs exceeding the threshold of concern (RQ > 1) at 46–80 % of sampling sites. Additionally, tentative identification of potential structurally related compounds provided valuable insight into the parent-product relationships in complex samples. This study highlights the importance and urgency of using NTS for CECs in the environment and presents a novel data sharing approach, which facilitates other scientists to assess, investigate further, and perform retrospective analyses.

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1. Introduction

Anthropogenic activities, such as fishing, the release of waste, shipping, and nutrient input, disturb both the ecological function and water quality of the environment (Zhao et al., 2022). Among these activities, pollution by contaminants of emerging concern (CECs) has recently caught the increasing attention of researchers and the public interest because many of them are frequently detected in surface water, and have been implicated in adverse biological effects even at very low concentrations (Noguera-Oviedo and Aga, 2016; Schwarzenbach et al., 2006). One example is *N*-(1,3-dimethylbutyl)-*N*′-phenyl-*p*-phenylenediamine-quinone (6PPD-quinone), a highly toxic quinone transformation product of a globally ubiquitous tire rubber antioxidant (i.e., 6PPD), which has caused acute mortality to Pacific Northwest coho salmon at LC_{50} value 95 ng/L (Tian et al., 2021b, 2022). This further increased the public concern about CECs because there might be other CECs in water with similar or even higher toxicity. However, previous target analysis is not able to find this novel and unexpected contaminant, leading to decreased confidence in water quality of the area being investigated. From an analytical point of view, tracking CECs and their transformation products in a complicated environment is one of the most greatest challenges in the 21st century (Escher et al., 2020).

Nontarget screening (NTS) techniques based on high-resolution mass spectrometry (HRMS) represent a state-of-the-art tool to meet this challenge and it can greatly enhance our understanding of the comprehensive characterization of CECs in our environmental systems (Krauss et al., 2010). Data Independent Acquisition (DIA) and Data Dependent Acquisition (DDA) are two most widely applied techniques in analytical chemistry for the identification of compounds in complex mixtures. The power of this technique is highly dependent on both instrumental capabilities and advanced data analyses method. Detected HRMS features can be prioritized by certain algorithms (usually including peak picking, peak alignment, blank comparison, etc.) (Hollender et al., 2017) and subsequently identified by database matching or authentic standard comparison. By using this technique, many CECs can be found in a variety of environmental matrices (e.g., water (Tian et al., 2020, 2021a), soil (Tian et al., 2017), sediment (Li et al., 2022), house dust (Wang et al., 2021a), and aerosols (Ouyang et al., 2017), etc.) with limited preexisting knowledge. These identified CECs (such as Caffeine, Metoprolol, Bisphenol S, etc.) were further quantified by target analysis and then the health risk was evaluated (Tian et al., 2020). Recent NTS studies have identified many CECs, which range from antibiotics, pesticides, pharmaceuticals, personal care products to food additives, surfactants, industrial chemicals, as well as their transformation products (Lara-Martín et al., 2020). Some of these CECs were first reported in the environment and their occurrences are important to better understand the impact of anthropogenic activities.

Pearl river, as the largest river in southern China, encompasses the watersheds of the West, North, and East rivers, as well as their tributaries and river networks. Flowing through numerous cities, the widespread wastewater discharge and urban runoff inevitably introduce CECs into the Pearl river. The river is of vital importance, providing water resources to over 150 million residents and serving as a drinking water source and a crucial habitat for local fisheries. The ecological health of the Pearl River has significant implications for the livelihoods and well-being of the local population. Researchers and regulators must be aware of the CECs present in the river, enabling the establishment of appropriate regulations, such as the US Clean Water Act and the European Water Framework Directive. Although many previous studies have investigated the occurrence of traditionally concerned contaminants (such as heavy metals (Ye et al., 2012; Zhang et al., 2018b), polybrominated diphenyl ethers (Huang, 2018; Mai et al., 2005; Zou et al., 2007), and antibiotics(Li et al., 2018; Liang et al., 2013), etc.) in Pearl river by target analytical methods, there is a lack of research employing non-targeted screening (NTS) methodologies to assess contaminants of emerging concern (CECs) in the river. One recent study utilized NTS to examine organic chemicals in the North River (a part of the Pearl River) (Zhao et al., 2022), but the scope was limited to only a section of the river, leaving the overall risks posed by CECs to the entire Pearl River ecosystem poorly understood. Consequently, there is an urgent need for the application of NTS approaches to characterize CECs in the Pearl River and evaluate their potential impacts on water quality.

Here, by using NTS approaches, we present a comprehensive characterization of CECs at 50 locations in Pearl river, including west, east, north rivers and river networks. The aims of this study were to (1) characterize potential CEC occurrence and identify their structures in the Pearl river; (2) quantify identified CECs by authentic standards and evaluate their ecological risks; (3) identifying potential transformation products of CECs. To the best of our knowledge, this study presents the first NTS analyses of surface water in a large representative basin in China, and it can provide valuable information for environmental monitoring and contamination control in the future.

2. Materials and methods

2.1. Chemicals and materials

Experimental chemicals and solution are available in Text S1.

2.2. Water sampling and extraction

A total of fifty sampling sites were selected along the Pearl River between August 15th and 22nd, 2022 (Fig. 1 and Table S1). The Pearl river comprises three primary tributaries: the West river (WR), East river (ER), and North river (NR), each originating from distinct locations before converging to create the Pearl river network (RN). The "river network" encompasses the interconnected system formed by these main tributaries and their subsidiary channels, resulting in a complex and extensive lattice of waterways that together constitute the vast Pearl river system. Pearl river supplies vital water resources, including drinking water, to local residents in the Pearl river delta before emptying into the South China Sea. Sampling included nine sites along the East River (ER-01 to ER-09), ten sites along the West river (WR-01 to WR-10), thirteen sites along the North river (NR-01 to NR-13), and eighteen sites within the river network (RN-01 to RN-18), providing comprehensive coverage of the entire Pearl river system in Guangdong province. Among these sampling sites, 23 locations (i.e., ER-03, ER-04, NR-03, NR-10, NR-12, WR-02, WR-04, WR-06, WR-07, WR-09, RN-01, RN-06, RN-07, RN-09 to RN-18) were chosen from major drinking water sources for cities. Samples were collected in pre-cleaned (i.e., rinsed with HPLC-grade hexane, acetone, and methanol) amber glass bottles (4 L) and refrigerated at 4 °C before being extracted using HLB cartridges within 24–72 h.

Before solid-phase extraction (SPE), all water samples were filtered through 0.45 μm glass fiber membranes to prevent clogging. From the initial 4 L of water, 3 L was divided into three 1 L bottles, serving as triplicates, and each was spiked with a set of 10 isotope-labeled internal standards. The remaining 1 L of water was not utilized in the analysis (ISTD, Table S2) to check the recoveries. The extraction and elution processes were performed on an automatic solid-phase extraction instrument (Fotector Plus, RayKol, China). The SPE cartridges (Oasis PRiME HLB, 6 cc, 500 mg) were preconditioned with 10 mL methanol and 10 mL DI water (3 mL/min). 1 L of water samples was loaded onto HLB cartridges at 12 mL/min. The cartridges were then rinsed with 10 mL of DI water (4 mL/min), dried with N_2 for 25 min, and eluted with 10 mL of methanol. Next, elutes were concentrated to 1 mL under N_2 by an Auto multiple sample concentrator-MPEva GS (Relabor Instruments, Guangzhou, China), and then spiked with a set of 5 internal standards. The final extracts were stored in 2 mL amber glass vials at −20 °C before instrumental analysis.

2.3. Instrumental analysis

The samples were analyzed by Waters high-performance liquid chromatography (UPLC) system coupled to a Xevo G2-XS quadrupole time-of-flight HRMS with electrospray ionization source (ESI) in positive and negative modes. For chromatographic separation, 1 μL of the extract was injected into an ACQUITY UPLC BEH C18 column (150 × 3.0 mm, 1.7 μm) with a guard column (2.1 × 5 mm, 1.7 μm). The column temperature was set at 40 °C. For ESI+, the mobile phase (0.35 mL/min) consisted of 5 mM

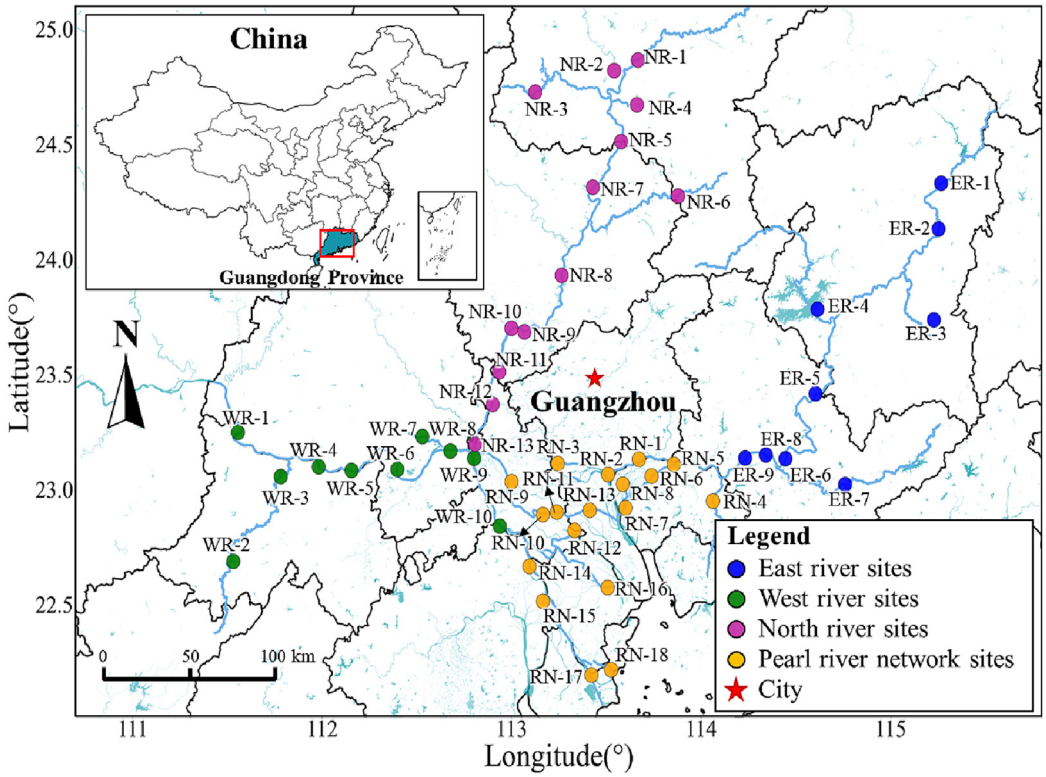

Fig. 1. Sampling site locations in Pearl River system.

ammonium acetate and 0.1 % formic acid in water (A) and pure methanol (B) using a gradient of 2 % B at 0–0.5 min, 98 % B at 18–24 min, 2 % B at 24.1 min; stop time at 27 min. For ESI−, the mobile phase consisted of 0.05 % formic acid in water (A) and methanol (B), respectively, using the same gradient. For mass spectrometric analysis, Data-dependent acquisition (DDA) and data-independent acquisition (DIA) were performed separately in the positive and negative ionization modes. For DIA analysis, we used Waters MS^E analysis to record both MS^1 and MS^2 data in the range of m/z 50–1000. The collision energy was set at a dynamic range of 15–45 V. The scan rate was 0.2 s/spectrum (i.e., 5 Hz) to ensure enough data points for chromatogram peaks of MS^1 (2.5 Hz) and MS^2 data (2.5 Hz). For DDA analysis, MS/MS data were acquired for the first 7 highest abundant masses, the m/z range, collision energy, and scan rate were the same as that in DIA analysis.

For quality assurance and quality control (QA/QC), mass calibrated before each analytical run, and mass accuracy was corrected by injection of calibration solution (Leucine Enkephalin) every 15 s. ISTD control solution (including 10 extracted and 5 instrumental isotope-labeled internal standards, as above-mentioned and listed in Table S2) and two methanol blanks were analyzed after every 12 samples. A triplicate of laboratory blanks and field blanks, which were extracted in the same manner as samples, were analyzed alongside samples for data comparison. The retention time (RT) deviation and mass error of ISTDs in all samples were < 0.1 min and < 5 ppm, respectively.

2.4. Data prioritization and identification

The workflow for data analysis is presented in Fig. 2. Specifically, raw data from HPLC-HRMS (Waters Technologies, USA) were converted into

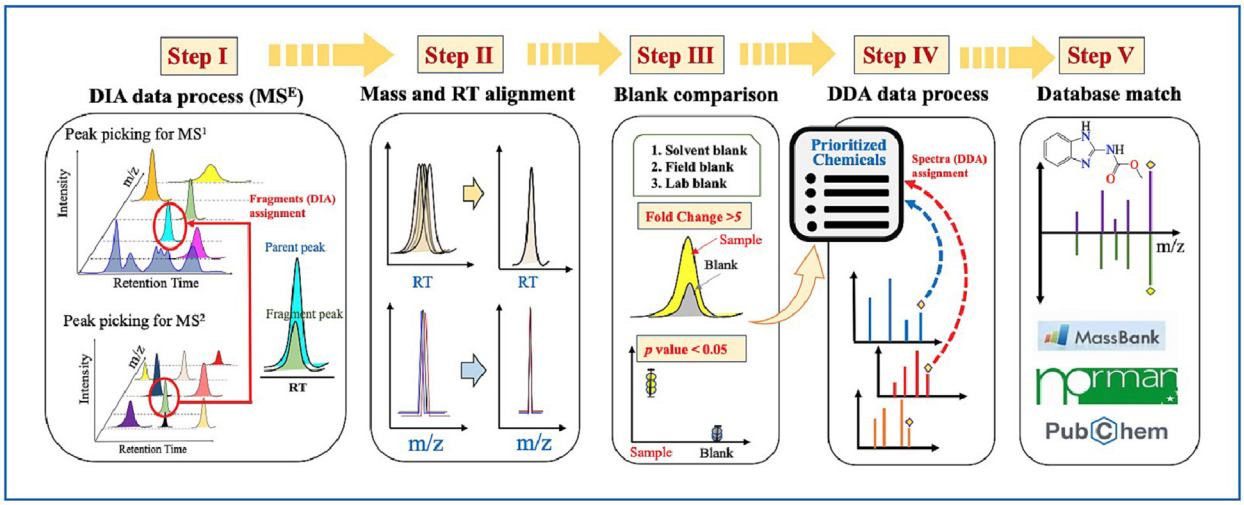

Fig. 2. Workflow of NTS by PyHRMS for environmental samples based on Data-dependent acquisition (DDA) and Data-independent acquisition (DIA) data.

mzML format by MSconvert. Then these data were processed by PyHRMS (https://pypi.org/project/pyhrms/) for non-target feature extraction and alignment across samples. The features were prioritized by blank subtraction and significance test analysis. Features with mass intensity > 500, having significant difference ($p < 0.05$) with each control set (i.e., solvent blank, method blank, and field blank), and present at an average peak area 5-fold greater than each of control set, were retained. The retained features were then matched by three major databases: (1) an in-house database that includes ~2000 CECs (including pharmaceuticals, pesticides, veterinary drugs, personal care products, etc.) with compound's information such as RT, *m/z*, and MS^2 fragments, etc.; (2) Massbank of North American (MoNA) that include >145, 000 MS/MS spectra (https://massbank.us/downloads); (3) NORMAN Suspect List Exchange (NORMAN-SLE). Details about this workflow are explained in Text S2 and Fig. S1. We assessed the performance of our NTS workflow using PyHRMS by analyzing a dilution curve of 118 CEC standards ranging from 0 to 1000 ng/mL with UPLC-HRMS. The results demonstrated good identification efficiency, as shown in Fig. S2.

The confidence level of CEC identification was based on previous studies. Confidence level 1 was achieved by matching the accurate mass (<10 ppm), RT (<0.1 min), and MS/MS fragment (≥1) with available reference standards, ensuring a high level of certainty in the identification process. In contrast, confidence level 2 was achieved by matching accurate mass (<10 ppm) and at least 2 fragment ions with MS/MS libraries, without the use of reference standards. For compounds that matched with only RT and MS^1 but failed to obtain their MS^2 information, we classified these compounds to level 3. For transformation product identification, the MS/MS spectra of prioritized features were compared with each other. Compounds with more than three identical fragments were considered to have a similar structural skeleton, and thus might have a parent-product relationship.

Level 1 CECs were quantified by the relative response factor (RRF) method. 5-point internal standard calibration curves with extraction ISTD (i.e., Atrazine-D5 or Propylparaben-D4) were used to calculate the RRF for quantification, which account for instrumental response, matrix effects, and extraction recovery.

2.5. Risk assessment

Risk quotients (RQ) were employed for risk assessment. RQ calculations for certain CEC in the Pearl river were achieved by comparing maximum measured environmental concentrations to the lowest predicted no-effect concentrations (PNECs) for aquatic organisms (Eq. (1)), such as fish and algae. The PNECs of CECs were obtained from the NORMAN ecotoxicology database (www.normannetwork.com). RQ > 1 implies a potential risk to aquatic organisms based on single compound exposure.

$$RQ = \max \text{ concentration}/\text{lowest PNEC} \quad (1)$$

3. Result and discussion

3.1. Prioritized characteristic features in Pearl river

HRMS analysis of the whole Pearl river revealed >15,000 characteristic features. Each of these features includes (if any) its C/Cl/S/Br isotopes and $Na^+/K^+/NH_4^+$ adducts, which were recognized by the peak-picking algorithm in PyHRMS. The features span from dissolved polar to the semipolar substance within an *m/z* range of 50–1000 Da under ESI. The number of characterized compounds in each sampling site were shown in Fig. S3a, and the average numbers of the north river (NR), west river (WR), east river (ER), and river network (RN) are 1687, 2359, 1355, and 2592, respectively (Fig. S3b). The average relative total signal intensities of these areas (normalized by considering matrix effects using internal standards) were shown in Fig. S3c. These results indicate that the number and signal intensities of organic compounds in the river network are higher than those in the north river, west river, and east river. The specific number of organic compounds at each sampling location in a certain area were shown in Figs. S4–S7. In these sampling sites, RN-4 and RN-16 featured the highest numbers of compounds (i.e., 5644 and 4687, respectively), and principal component analysis (Fig. S8) revealed that they differed substantially from the rest. It is worth noting that the number of characterized compounds doesn't represent the contamination level of the water because part of these characterized compounds might be natural products or organic matters. To explore the CECs in water samples, further structural elucidation and quantification processes are needed.

3.2. Identification and occurrence of CECs in Pearl River

One of the main goals of this study was to characterize CECs occurring in Pearl river, structural identification was performed for those characteristic compounds. Examples to illustrate the identification aspect (i.e., level 1 and level 2) are shown in Fig. S9. Specifically, the peak at 16.48 min was identified as metolachlor by using an authentic standard, the RT difference was 0.04 min, and the observed and optimized mass error were 7.4 and 4.9 ppm, respectively. 3 of its fragments (i.e., *m/z* 134.0963, 160.1095 and 252.1161) from DDA and DIA mode were matched with metolachlor recorded in massbank (Fig. S9a), and thus its identification confidence was level 1. For peak at 8.55 min, no authentic standards were available to confirm its RT, but its observed mass is very close (0.3 ppm difference) to the theoretic mass of 2-hydroxyatrazine, and 3 of its fragments (i.e., *m/z* 86.0356, 114.0665, 156.0904) from DDA and DIA mode were matched with 2-hydroxyatrazine recorded in massbank (Fig. S9b), and thus this identification confidence was level 2. For compounds that matched with only RT and MS^1 but failed to obtain their MS^2 information, we classify these compounds to level 3. For other compounds, we did not focus on them because of high uncertainties.

In general, a total of 620 different CECs were identified with confidence level 1 (107), level 2 (473), or level 3 (43) by using a combination of in-house (~2000) and online database (i.e., Massbank and Norman), which only account for <3.7 % of total prioritized compounds in Pearl river. The major detected contaminant classes are pharmaceuticals, pesticides, veterinary drugs, personal care products, industrial materials, etc. (Fig. 3). The detailed information on identified CECs was shown in Table S3. Among these compounds, 17 of them have detection frequencies > 80 %, 40 of them >60 %, and 66 of them >40 % (Fig. S10), indicating the ubiquity of these compounds in Pearl river.

3.2.1. Pharmaceuticals

Pharmaceuticals are the most frequently detected compounds in the Pearl river, with 137 pharmaceuticals structurally identified. Diazepam was detected in 98 % of samples (Fig. S11) at a concentration range of 0.9–93.6 ng/L. This concentration was much higher than the reported concentrations in rivers flowing through Beijing (0.9–7.1 ng/L) (Wang et al., 2017), but was lower than the concentration in the river of Shanghai (19–230 ng/L) (Liang et al., 2021). The diazepam concentration may reflect the mental and health status of local people because it is a well-known drug to treat a range of symptoms including anxiety, insomnia, and convulsion. Nicotine is also a ubiquitous compound in the Pearl river, with a detection frequency of 84 % and a detection concentration range of 13.1–648.5 ng/L. Nicotine is the main tobacco alkaloid and is also used to treat addiction to smoking cigarettes. It was also reported that the concentration of nicotine in wastewater treatment plant effluents and surface water can reach 32,000 and 9340 ng/L, respectively (Verovšek et al., 2022). Cotinine is a potential transformation product from nicotine, and can also be used as an antidepressant (Vlasceanu et al., 2019). The detection frequency of cotinine is 86 % and it co-occurred with nicotine.

Sulfamethoxazole is a common pharmaceutical and is widely used to treat various infections such as pneumonia and urinary tract infections (Di Cocco et al., 2009; Guneysel et al., 2009). Its detection frequency in the Pearl river is 72 %, and the detected concentration range is 5.3–118.1 ng/L. This antibiotic compound was frequently detected in rivers (Chen and Zhou, 2014; Deng et al., 2016; Luo et al., 2011; Ngumba et al.,

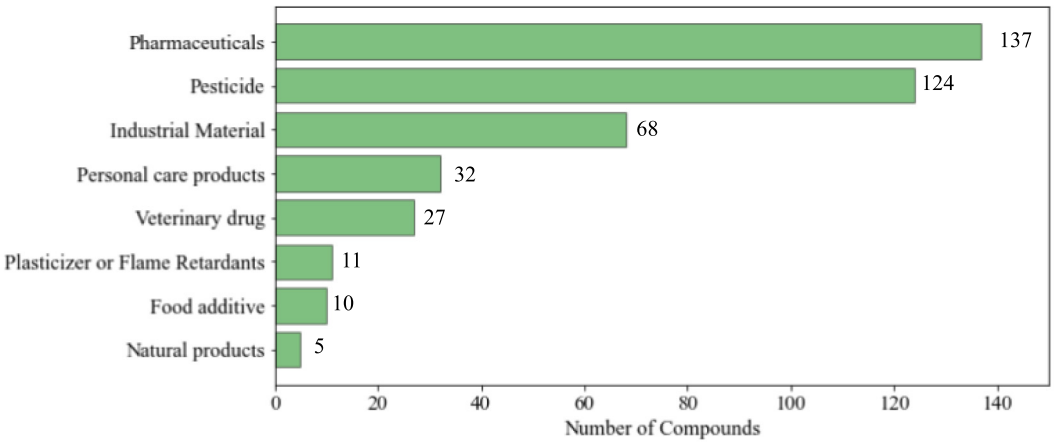

Fig. 3. Categories of organic compounds identified in Pearl river.

2016), lakes (Ding et al., 2017), estuaries (Yan et al., 2013) and marine waters (Du et al., 2017), with detected concentrations ranging from nanogram per liter to micro-gram per liter (Wang and Wang, 2018). Trimethoprim was frequently used in association with sulfamethoxazole in a 5:1 ratio (sulfamethoxazole: trimethoprim) for medication purposes, and thus these two compounds usually co-occurred (Thiebault, 2020). In Pearl river, trimethoprim was detected in 18 % of samples at 0.6–7.3 ng/L, and the ratios of sulfamethoxazole: trimethoprim were all >5, indicating the use of sulfamethoxazole alone in this industry. Irbesartan was detected in 62 % of samples of Pearl river, and it has been detected in the surface water of Africa and Europe up to 760 ng/L and 650 ng/L, respectively (Fekadu et al., 2019). Amantadine, telmisartan, artemisinin, and griseofulvin were detected in Pearl river at confidence level 2, with detection frequencies from 30 to 64 %. These pharmaceuticals were used to treat symptoms like dyskinetic syndrome, hypertension and skin infections, etc., and were also previously reported in surface water worldwide (Eysseric et al., 2021; K'oreje et al., 2020; Ngo et al., 2021; Peng et al., 2018). Other pharmaceuticals with detection frequency < 30 % or confidence level < 1 are available in Table S3.

3.2.2. Pesticides

A total of 124 pesticides were detected, including herbicides, fungicides, and insecticides. Azoxystrobin is used as a fungicide to protect crops from fungal disease. The detection frequency of azoxystrobin in Pearl river is 94 % (Fig. S11), with a concentration range of 0.5–10.9 ng/L, which is comparable to the detected concentration (4.9 ng/L) in Tengi river, Malaysia (Elfikrie et al., 2020). 4-Nitrophenol was also detected in 94 % of samples, and the observed concentration (6.2–101.4 ng/L) was lower than reported concentrations in Chinese estuaries (average concentration 276 ng/L) (Feng et al., 2021). Considering these measurements of 4-Nitrophenol were much lower than its PNEC (5000 ng/L), it can cause limited adverse effects to aquatic organisms. Isoprothiolane, used as a fungicide or insecticide, was detected in 90 % of the samples with concentrations ranging from 1.6 to 28.3 ng/L. This range is lower than the previously reported mean concentration of 58 ng/L in Taihu water, China (Wang et al., 2021b). Tricyclazole was detected in 88 % of the samples, with its highest detected concentration (87.1 ng/L) being much greater than the reported highest concentration (9.6 ng/L) in Baiyang Lake upstream, China (Sun et al., 2022). Carbendazim (level 2) was detected in 88 % of samples, and its occurrence in waste water and surface water has been reported all around the world with concentration range 10 ng/L to 6000 ng/L (Chen et al., 2014; Liu et al., 2015; Masiá et al., 2015; Merel et al., 2018).

Bensulfuron-methyl (BM) and 2-methyl-4-chlorophenoxyacetic acid (MCPA) are two of the most widely used herbicides to suppress weed in rice agroecosystems (López-Piñeiro et al., 2019). BM was detected in 86 % of samples with concentration 3.1–56.2 ng/L. Its ubiquity and relatively high concentration can be explained by its weak adsorption and long persistence (Battaglin et al., 2000; Sanchis et al., 2014), and it may have a negative impact on aquatic biota (Sabater et al., 2002) and soil's microbial communities (Saeki and Toyota, 2004). MCPA (in 10 % of samples) is one of the priority pollutants of the US and the European Community Environmental Protection Agencies (Sanchis et al., 2014). It is toxic for human and other animals and is classified as a possible mutagen and carcinogen by the International Agency for Research on Cancer (IARC) (López-Piñeiro et al., 2019).

Thiamethoxam, clothianidin and imidacloprid are three typical neonicotinoid insecticides and were consumed worldwide. Their detection frequencies in Pearl river are all above 80 %. Neonicotinoids have been implicated in a variety of adverse ecosystem effects (Christen et al., 2016; Goulson, 2013; Henry et al., 2012), and the chronic exposure to vertebrates remains a concern (Gibbons et al., 2015). It is reported the maximal concentrations of thiamethoxam, clothianidin and imidacloprid in Midwestern United States are 190, 260 and 43 ng/L, respectively (Hladik et al., 2014). In comparison, the detected concentration range for these three neonicotinoids in Pearl river are 0.24–57.3 ng/L, 2.7–91.7 ng/L, and 5.3–62.8 ng/L, respectively. In addition, these three compounds were ubiquitously present (i.e., detection frequency 100 %) in all investigated tap water samples in United States, with concentrations ranges 0.2–4.2 ng/L (thiamethoxam), 3.9–57.3 ng/L (clothianidin) and 1.2–39.5 ng/L (imidacloprid), respectively (Klarich et al., 2017). It is worth noting that the drinking water treatment indicate no apparent removal of clothianidin or imidacloprid, with modest removal of thiamethoxam (50 %) (Klarich et al., 2017), indicating a long-term threat to drinking water safety. Other pesticides with detection frequency ≥ 80 % are atrazine (0.5–57.2 ng/L), paclobutrazol (2.9–17.0 ng/L), metolachlor (1.6–246.1 ng/L), 2,4-Dinitrophenol (3.2–120.3 ng/L) and ametryn (0.7–57.6 ng/L), which were all reported in previous field studies (Acayaba et al., 2021; Byer et al., 2011; Rani and Rachna, 2020; Wang et al., 2021b).

3.2.3. Veterinary drugs

Veterinary drugs were widely used in animal husbandry and they can spread into water bodies via various ways. 4-Acetyl-aminoantipyrine (4-AAA) and 4-Formylaminoantipyrine (4-FAA) are mainly used as an analgesic and antipyretic for food-producing animals (Feldmann et al., 2008; Penney et al., 2005), they were detected in 88 % and 82 % of samples, respectively. These two compounds have also been found in surface water in Spain (Boix et al., 2014, 2016; Fonseca et al., 2020), with concentrations in municipal sewage effluents reaching up to μg/L levels (Feldmann et al., 2008). When compared to these studies, the concentration range for 4-AAA and 4-FAA in the Pearl River is lower, at 2.0–87.1 ng/L and 0.9–25.9 ng/L, respectively. Clopidol (0.3–19.6 ng/L) and zoalene (5.8–50.6 ng/L) were detected in 78 % and 22 % of samples, respectively. However, their occurrence in environmental samples were rarely reported

in previous literatures. Diclofenac is an anti-inflammatory drug used in livestock farming (Moreno-Opo et al., 2021). It was detected in 8 % of samples with concentration range 4.6–10.9 ng/L. In marine water, diclofenac concentration ranged from a few ng/L to ~100 ng/L (Bonnefille et al., 2018), while in estuaries, the detected diclofenac concentration can reach to 843 ng/L (Yang et al., 2011). Other veterinary drugs, such as erythromycin (also used as an antibiotic for humans), lidocaine (also used as a local anesthetic for humans), albendazole oxide, etc., were also previously reported in the environment (Chaves et al., 2020; Rúa-Gómez and Püttmann, 2012; Schafhauser et al., 2018), but their detection frequencies in Pearl river were all below 8 %.

3.2.4. Personal care products

Personal care products (PCPs) are a group of compounds used in soaps, fragrances, sunscreens and cosmetics. Thirty PCPs were identified in Pearl river, but none of these compounds have detection frequency > 40 %. Specifically, linoleic acid (32 %), 2,2'-Dihydroxy-4-methoxybenzophenone (26 %), ensulizole (18 %), sulisobenzone (8 %), piperine (8 %) and hydroxycinnamic acid are used as sunscreen. *N*,*N*-Diethyl-m-toluamide (DEET, 10 %) and dimethyl phthalate (6 %) are used as insect repellents. Diethyl phthalate (14 %) and hydrocinnamic acid (4 %) are ingredient cosmetics. Although previous studies have reported their occurrence in surface waters worldwide (Brausch and Rand, 2011; Domínguez-Morueco et al., 2014; Merel and Snyder, 2016; Nanusha et al., 2021; Scheurer et al., 2022), their concentration in Pearl river were not obtained because lack of standards. Methylparaben was identified at confidence level 1 and detected in 10 % of samples, its concentration range was 1.0–5.3 ng/L, which is much lower than the detected concentration (up to 15,200 ng/L) in the receiving water of Thailand (Juksu et al., 2019).

3.2.5. Industrial materials

A total of 68 industrial materials were detected in Pearl river, these compounds were used in the production of tire, dyes and detergent, etc. Benzothiazole-2-sulfonic acid (BTSA, 78 %), 1,2,3-Benzotriazole (54 %), 5-Methyl-1H-benzotriazole (54 %) and 4-Methyl-1,2,3-benzotriazole (38 %), which are anti-corrosives that can function as roadway tracers, were frequently detected in the Pearl River. Hexamethoxymethylmelamine (HMMM, 58 %) is a compound used to adhere steel belts to tire rubbers and within automotive plastics (Alhelou et al., 2019), which occurred in roadway runoff and surface water at concentration up to 6500 ng/L (Peter et al., 2018) and 46 ng/L (Rauert et al., 2020), respectively. Di-formylated HMMM (38 %) and Tetra(methoxymethyl)melamine (TMMM, 14 %) are potential transformation products of HMMM, and have also been detected with HMMM in highway runoff (Peter et al., 2018). In Pearl river, we found that TMMM and Di-formylated HMMM are co-occurred with HMMM, and they are simultaneously present in 14 % of samples (i.e., RN-01 to 04, RN-07, RN-08 and RN-13) (Fig. S12). Other tire related chemicals, such as 1,3-diphenylguanidine (40 %), dicyclohexylamine (40 %), and dicyclohexylurea (20 %), are used as accelerators, catalyst or endogenous inhibitor, etc., in the rubber industry, which are also ubiquitous in surface waters (Challis et al., 2021; Liu et al., 2019; Zahn et al., 2019). 6PPD-quinone, a transformation product of a common tire rubber antioxidant, has attracted considerable attention due to its acute toxicity for coho salmon (Tian et al., 2021b). In Pearl river, we have also found this compound but only at one sampling site (i.e., RN-04). The low detection frequency of 6PPD-quinone might be attributed to that it didn't rain during sampling, and it was mainly existed in the tire or road surface, and was expected to occur when stormwater transport it from road to the surface water (Tian et al., 2020). Tetraethylene glycol monododecyl ether (58 %) and 4-Isopropylbenzenesulfonic acid (14 %) were used as surfactants, and they were also detected in reusable plastic bottle waters (Tisler and Christensen, 2022). Naphthalene-2-sulfonic acid (74 %), *N*,*N*-Dimethyltetradecylamine (52 %), and 4-Methyl-1,2,3-benzotriazole (38 %) were used in the production of dyes, detergent, and corrosion inhibitor, respectively, which are usually detected in industrial effluent and landfill leachates (Been et al., 2021; Song et al., 2006; Wang et al., 2019).

3.2.6. Plasticizer and flame retardants

Bisphenol S (level 2) is used as plasticizer and is a major substitute for bisphenol A (Wu et al., 2018), with similar structure and potential of endocrine disruption for aquatic organisms (Ji et al., 2013). Bisphenol S was detected in 88 % of samples in Pearl river, which occurs more frequently than in the nearshore marine environment of Puget Sound (26 %) (Tian et al., 2020). Diisononyl cyclohexane-1,2-dicarboxylate (DINCH, 62 %) is used as a plasticizer for polyvinyl chloride (PVC) resins, and has been frequently detected in environmental matrices and human urine samples worldwide (Deng et al., 2021; Wu et al., 2020, pp. 2007–2010), while another plasticizer, isobutyl hydrogen phthalate (10 %), was rarely reported for its occurrence. Tris(2-chloroethyl) phosphate (TCEP) and triethyl phosphate (TEP) are two common organophosphates that were used in various industries as plasticizers/flame retardants, the reported concentration for TCEP and TEP in the river of New York state were 14.6–79.5 ng/L and 4.8–24.8 ng/L, respectively (Kim and Kannan, 2018). TCEP and TEP were detected in 28 % and 12 % of samples in Pearl river, which is much lower than the detection frequencies (51 % and 94 % for TCEP and TEP, respectively) in the river of New York state (Kim and Kannan, 2018).

The high occurrence of various contaminants in the Pearl River can be attributed to multiple anthropogenic influences within the watersheds. The Guangdong Province is an economically developed region with a large population (Zhang et al., 2018a, b), which contributes to the demand and consumption of pharmaceuticals and veterinary drugs. The presence of numerous pharmaceutical manufacturing facilities, hospitals, and veterinary clinics in the area leads to the discharge of these chemicals into the river system, either through wastewater treatment plants or direct discharge. Similarly, the widespread use of personal care products by the local population can result in the release of these compounds into the environment (Richardson et al., 2005). Intensive agricultural activities in the Guangdong Province (Guotong et al., 2022), known for its vast areas of farmland dedicated to rice, sugarcane, and various fruits and vegetables, contribute to the high occurrence of pesticides in the Pearl River. The use of pesticides is necessary to ensure high crop yields but can lead to their runoff into the river system. Moreover, land-use changes, such as urbanization and deforestation, could exacerbate pesticide contamination by altering the transport and fate of these chemicals in the environment. The detection of numerous industrial materials in the Pearl River can be associated with the thriving industrial sector in the region (Wei et al., 2019), which includes the production of tires, dyes, detergents, and other goods. Industrial effluents and landfill leachates, which often contain various chemicals used in these industries, can enter the river system and contribute to the contamination. The rapid economic development in Guangdong has led to an increase in industrial activities and, consequently, a greater potential for contamination of the Pearl River.

3.3. Prioritization list of CECs based on concentration and toxicity

A total of 92 compounds were semi-quantified by UPLC-HRMS, and we used the lowest PNEC and the concentration of CECs (Fig. 4) to calculate RQ (Eq. (1)). 12 compounds had RQ > 1: dichlorvos (RQ: 82.2), fipronil (24.0), pretilachlor (19.8), bensulfuron-methyl (5.6), imidacloprid (4.8), phorate sulfone (3.8), thiamethoxam (2.4), acetochlor (1.4), triazophos (1.3), metolachlor (1.2), caffeine (1.2) and diuron (1.1). The total RQ for these compounds in each site were shown in Fig. S13, and 86 % of sampling sites have a total RQ > 1, which make the detected concentrations of these compounds especially concerning.

Among these compounds, caffeine can be classified as a food additive or pharmaceutical. It was detected in 60 % of samples, and the highest concentration is 1389.3 ng/L in RN-04, and this is the only one site above its lowest PNEC (1200 ng/L). Despite caffeine showing excellent removal efficiency during the wastewater treatment process (Li et al., 2020), considering its significant consumption and multiple sources discharges, caffeine was still ubiquitous in surface waters at high concentrations (Korekar et al., 2020).

In addition to caffeine, other compounds with RQ > 1 are all pesticides. Pretilachlor is a pre-emergent herbicide (Wang et al., 2021a, b) and was

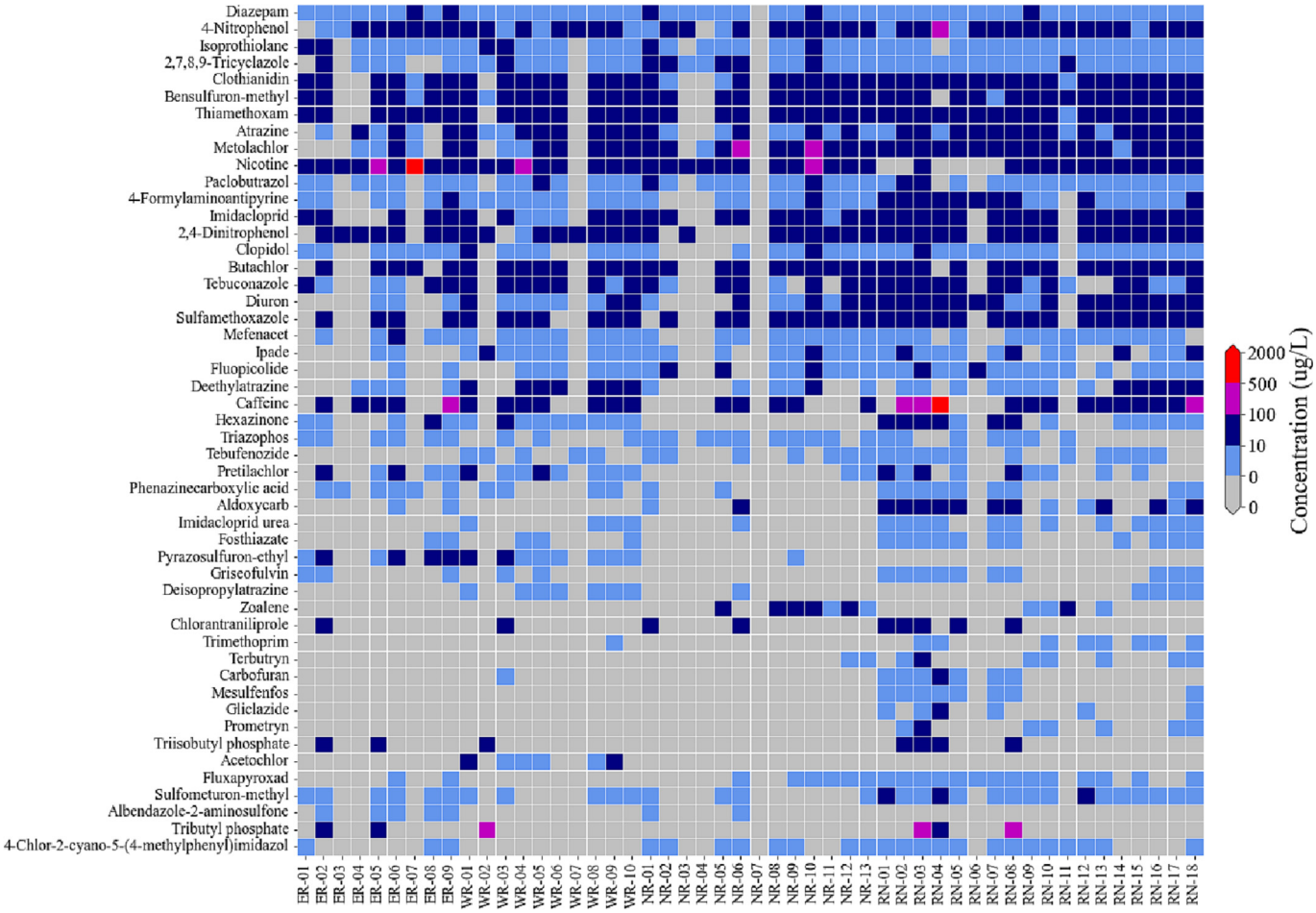

Fig. 4. Heatmap for the concentration of 50 CECs (frequency > 10 %) in Pearl river.

detected in 48 % of samples. We have found all detected concentrations of pretilachlor were above its lowest PNEC (0.96 ng/L), suggesting potential risk to fish and other aquatic life (Jiang et al., 2016). Likewise, the lowest PNEC for Bensulfuron-methyl, imidacloprid, and thiamethoxam are 10.0, 13.0, and 42.0 ng/L, respectively. The frequencies of sample sites for these compounds with RQ > 1 are 80 %, 70 %, and 46 %, respectively. In comparison, dichlorvos and fipronil have the highest RQ among these compounds (RQ: 82.2 and 24.0, respectively), but they were only detected in a few sample sites (i.e., RN-01 and RN-04). For other pesticides, such as phorate sulfone, acetochlor, triazophos, metolachlor, and diuron, the frequencies of high risk occurrences were only 2 % (i.e., only one sampling site), despite that some detection frequencies of these pesticides are above 60 %. The above result reveals that the presence of four particular pesticides in the Pearl River water—pretilachlor, bensulfuron-methyl, imidacloprid, and thiamethoxam—is a significant concern. The spatial distribution of these pesticides (Fig. S14) demonstrates that they were detected at most sampling sites with concentrations ranging from undetectable to approximately 100 ng/L. However, at sampling sites WR-2, WR-7, ER-3, ER-4, NR-3 and NR-4, none of these four pesticides were detected. This could be due to the fact that the surrounding areas have limited agricultural activity (resulting in minimal pesticide usage) or are well protected. In contrast, the remaining sites exhibit contamination by these four pesticides, indicating their widespread presence and potential high risk to the local environment. Other CECs with RQ > 1 might be site-specific, and their ecological risk might not be generalizable across the whole area. We suggest that future monitoring efforts should be focused on the occurrence of these compounds in wastewater effluent, surface water runoff, etc., to elucidate their source.

3.4. Structurally similar compounds identification

For many CECs, monitoring their parent compounds is not enough to evaluate the ecological risks, because many of them are transformed under environmental conditions, and their transformation products (TPs) may also be bioactive (Fenner et al., 2013), and can even revert to their parent compounds (Qu et al., 2013). Therefore, tracking the TPs of CECs in Pearl River is important to characterize the risk to water quality. However, identifying the TPs of CECs in a complicated sample is rather difficult, because the authentic standards of most TPs are not commercially available, and a large number of different compounds in the sample increase the difficulty for deconvolution and structure elucidation. Because the transformation usually may not drastically change the main skeleton of a compound, we can use the diagnostic fragment ion (DFI) strategy to find structurally related compounds and the potential parent-TP relationships (Xia et al., 2023).

As shown in Table S4, 107 level 1 compounds generate 1341 structural relationships with at least 3 fragments in common. Most of these compounds are level 2 and unidentified compounds. Take atrazine for instance, it is a frequently detected pesticide in Pearl river, with detection frequency of 86 %. We found three compounds, i.e., terbuthylazine, ametryn, and deethylatrazine, were structurally related to atrazine by using the DFI strategy (Fig. 5). In addition, although the MS^2 spectrum of 2-hydroxyatrazine (Fig. S9b) have no fragments in common with atrazine, a previous study has indicate it is a transformation product of atrazine, and they were usually co-occurred (Riedo et al., 2021). Fig. S15 shows the concentration/peak area for atrazine and its potential structurally related compounds in each sample site of the Pearl river, it indicates the profiles of these compounds in Pearl river are very similar, which is in agreement with the

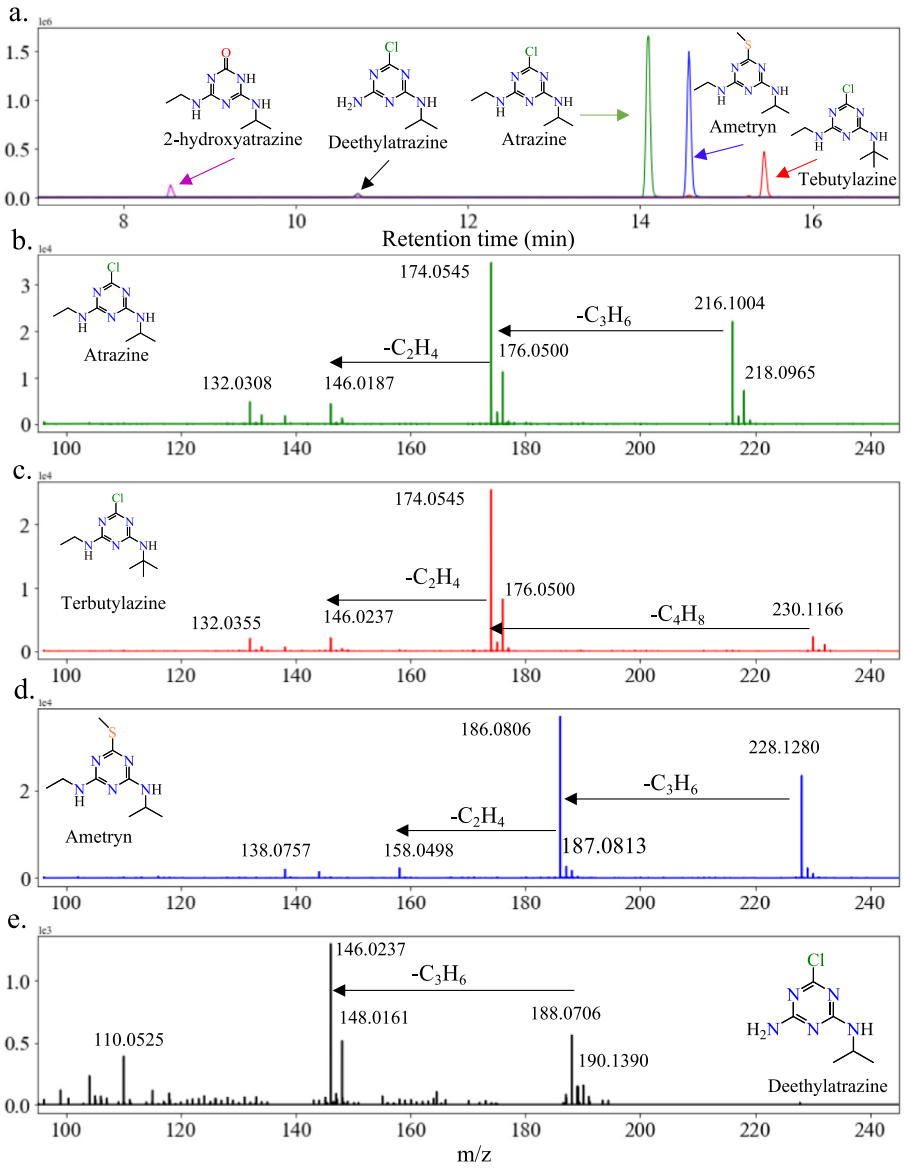

Fig. 5. Chromatograms of atrazine and its structurally related compounds and their MS^2 spectra.

reported occurrence in previous studies (Acayaba et al., 2021; Loos et al., 2010; Thurman et al., 1994).

It is worth noting that the compound pair with fragment ion (≥3) in common do not necessarily mean they are parent-TP relationship, because some compounds might be an insource fragment of the other, and some might just have the same functional group (e.g., atrazine and ametryn), thus the manual check is still needed to confirm the parent-product relationship. Nonetheless, the information of structural relationships based on the DFI strategy is still very useful to narrow the range of the compounds for searching potential parent-TP relationships.

4. Conclusions

Characterizing organic contaminants' occurrence and risks in the large river basin is critical to understanding the risk to and protecting ecological function. The NTS approach based on HRMS enables environmental scientists to identify organic contaminants more accurately and efficiently. In our study, we expanded upon previous research (Zhao et al., 2022) by applying an innovative combination of instrumental analysis methods (i.e., DDA and DIA modes) and a data processing tool (i.e., PyHRMS) to conduct a comprehensive case study on the Pearl River in Guangdong province. This method allowed us to uncover a large number of characteristic organic compounds (i.e., 15,912 in ESI positive mode and 13,807 in ESI negative mode) present in the Pearl River. Over 600 of these compounds were identified with confidence levels 1–3, and 92 CECs were semi-quantified by using authentic standards. Contrary to the previous study focused on a section of the Pearl River (North River) (Zhao et al., 2022), our research delved into the entire river basin and identified a broader range of CECs including pharmaceuticals, pesticides, veterinary drugs, industrial materials, and personal care products. We have also proposed a prioritized list of CECs with high detection frequencies and high ecological risks, which merit significant attention by scientist and policymakers.

Although this work has identified an unprecedented number of CECs for the large river basin, the identified CECs of this work only accounts for <3.7 % of total characteristic organic compounds. Therefore, the whole picture for CEC occurrence for the Pearl river might still be unclear to some extent. For example, some transformation products of CECs might be much more toxic than their parent compounds, but they can easily be overlooked by researchers because they are most likely not included in the database. Thus, the information on unidentified compounds is also significantly important for retrospective investigation when the database expands. Unfortunately, the raw data of LC-HRMS are usually large in size (e.g., 3.4 TB

for 150 samples in this study) and are very difficult to share or publish, which greatly inhibits other researchers to dig the remaining data. To improve data transparency and shareability, we have published the post-processed raw data. These data include all characteristic peaks with RT, accurate mass, intensity, area, signal-to-noise (S/N), peak area, isotope distribution, fold change and *p*-values (compared with blanks), MS^2 spectra, and database matching results. In the future, when new contaminants were confirmed or their MS^2 spectra/RT were available, we or other researchers can further analyze these data for the retrospective investigation to find the compounds of interest and conduct source apportionment analysis.

Pharmaceutical, pesticide, industrial material, personal care product, veterinary drug, food additive, natural products.

Please assist me in classifying the compounds into the following categories: Pharmaceutical, Pesticide, Industrial Material, Personal Care Product, Veterinary Drug, Food Additive, Natural Products. If a compound does not fit into any of these categories, please place it under 'Others'. Additionally, include a subcategory detailing the compound's use. If the use is not known, simply write "unknown". Kindly present the information in a table format to facilitate easy copying and pasting.

CRediT authorship contribution statement

Rui Wang: study design/execution, sampling, data analysis, PyHRMS development, manuscript writing. **Yanan Yan, He Liu, Yanxi Li, Meng Jin, Yuqing Li**: data analysis, compounds quantification. **RiZhu Tao, Qianghua Chen, Xuguang Wang**: Sampling sites selection and Sampling. **Bo Zhao, and Danping Xie**: study design and data analysis review and manuscript editing.

Data availability

I have shared the link to my data.

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.

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Appendix A. Supplementary data

The supporting information is available free of charge online.

The post-processed raw data are also available online at https://figshare.com/articles/dataset/Raw_data_for_nontarget_screening_of_Pearl_river/22093178 Supplementary data to this article can be found online at doi:https://doi.org/10.1016/j.scitotenv.2023.164445.

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