Environmental Pollution 363 (2024) 125128

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Review

Occurrence of contaminants of emerging concern in different water samples from the lower part of the Danube River Middle Basin – A review[☆]

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ARTICLE INFO

Keywords:
Contaminants of emerging concern
Middle danube basin
Wastewater
Surface water
Groundwaters
Drinking water

ABSTRACT

This study intends to assess the extent of the occurrence of CECs in different water types based on the literature data reported for the countries from a lower part of the Middle Danube Basin, including those belonging to the Western Balkan (WB) region and two upstream neighboring EU Member States, Croatia and Slovenia. These countries share main freshwater courses important for drinking water supply, agriculture, industry, navigation, tourism, etc, but in some of them there are low rate of wastewater treatment, impacting the chemical status of water resources in the region and probably beyond, if downstream countries are considered. The literature survey revealed 38 investigative studies reporting data on CECs in water matrices sampled in the region in the period 2008–2022. Surface water was the most frequently studied water type in WB countries, while wastewater was the dominant water type studied in Slovenia and Croatia. The most often analyzed compounds in the studies dealing with surface water and wastewater were the anti-epileptic drug carbamazepine, some non-steroidal anti-inflammatory drugs, and antibiotics; pharmaceutically active compounds were also the most analyzed CECs in groundwater and drinking water. Additionally, similarities/dissimilarities among the experimental approaches in these studies were discussed in relation to the state-of-the-art research directions for the CECs surveillance in the European Union, resulting in summarized strengths and gaps in capacities for the wide-range surveillance of CECs in the lower part of the Middle Danube Basin. This is the first integral overview of the studies on CECs in waters from the countries belonging to this part of the Danube Basin, representing a valuable baseline for further enhancement of the relevant monitoring efforts and chemical status of the regional water resources, especially in countries with poor wastewater management.

1. Introduction

Numerous substances from various anthropogenic sources reach the environment through accidental or unintentional emission during the production, use, and/or disposal of the products that contain them, which may result in undesirable and harmful side effects on both human health and the ecosystem (Köck-Schulmeyer et al., 2021). On the other hand, there is a rather small portion of the prioritized substances routinely monitored in the environment for which environmental quality standards (EQS) are set up (Köck-Schulmeyer et al., 2021). The disparity between the number of such priority substances and those suspected or known to be present in environmental resources (but not controlled/regulated) is enormous, so the occurrence and effects of many substances reaching the environment are still largely unknown. Moreover, the conventional analytical methods, often based on liquid or gas chromatography (LC or GC) coupled to single (MS) or tandem mass spectrometry (MS/MS), also impose a limitation on the number of substances that can be analyzed in one analytical run, as they are based on a set of pre-selected substances, which analytical standards are available at a laboratory for instrument calibration. The presence of all other substances in analyzed samples, which were not included in the calibration with the corresponding standards, is left unregistered (if not analyzed by high-resolution mass spectrometry, HRMS). Additionally, many investigative studies often cover different sets of limited numbers of unregulated substances in environmental resources, giving a fragmented insight into the chemical status of the environment;

[☆] This paper has been recommended for acceptance by Eddy Y. Zeng.

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https://doi.org/10.1016/j.envpol.2024.125128
Received 11 June 2024; Received in revised form 12 October 2024; Accepted 13 October 2024

nevertheless, they are important, ensuring inputs valuable for further investigation and stringent control of chemicals in the environment.

Contaminants of emerging concern (CECs) represent a large heterogeneous group of chemicals "which have been discovered or are suspected present in various environmental compartments and whose toxicity or persistence are likely to significantly alter the metabolism of a living being" (Sauvé and Desrosiers, 2014). The term CECs refers to a broad range of different chemical classes of substances such as pharmaceuticals, personal care products, polar pesticides, poly- and perfluoroalkyl substances (PFAS), microplastics, industrial chemicals, hormones, flame retardants, etc. The levels in which CECs have been detected in the environment ranged from a few ng/L or even pg/L (e.g., in groundwaters) to μg/L to even 100 mg/L (Liška et al., 2021; Yadav et al., 2021). Various sources are responsible for the emission of CECs into the environment, but wastewater discharge, regardless of the applied treatments, is of particular interest since the conventional wastewater treatment plants (WWTPs) are not designed to efficiently remove (all) organic micropollutants (Llamas-Dios et al., 2021; Yadav et al., 2021). Thus, many compounds survive the wastewater treatment processes (Munro et al., 2019), so WWTPs continuously discharge CECs into the environment (Tran et al., 2018). The effectiveness of eliminating organic contaminants from wastewater largely depended on their physical and chemical properties influencing processes of their biotransformation, sorption, and/or volatilization (Margot et al., 2015). Among numerous chemicals present in wastewater, there are those easily removed (e.g. typical removal rate of some anionic surfactants is above 97%) or removed with rates usually above 70% (e.g. paracetamol), but there are also those with removal rates between 30% and 70% (e.g. atenolol, ciprofloxacin, clarithromycin) (Margot et al., 2015). Remainings of those degradable CECs, still may enter the environment; if it is a compound with significant usage/consumption in everyday life, its traces may enter the environment continuously via WWTP effluents (Petrović et al., 2003; Wu et al., 2022; Li et al., 2020.) Additionally, landfill sites, agricultural and urban stormwater runoffs, industrial discharges, septic systems, and crop irrigation particularly if reclaimed wastewater is used, have been regarded as a significant source of CECs in water systems (Han et al., 2022; Khezami et al., 2024; Mutzner et al., 2023; Renau-Prunonosa et al., 2020).

Despite the known problems of often poor wastewater management practices and low investment rates in wastewater treatment facilities in developing countries (Brika, 2018), there are rather limited data or reports on the CECs contamination of their waters. This is also a major challenge for countries in the Western Balkan (WB) region, belonging to the lower part of the Middle Basin of the Danube River, known as the most water-rich countries in Europe with regards to the amount of water available per person (twice the European average (GRIDArendal, 2015)). Poor wastewater management practices in this region cause a considerable organic load with a very complex composition that is discharged into receiving watercourses (Terzić et al., 2008). Table SI1 shows the share of the population connected to at least secondary wastewater treatment in the countries from the lower part of the Middle Danube Basin in 2021. In the case of Serbia, the average age of WWTP is more than 20 years, while in the biggest cities such as Belgrade, Novi Sad, and Niš, wastewater is discharged directly to water recipients; by 2040 it was planned to significantly increase the number of WWTPs from about 40 currently operational to 140 with a help of foreign funds (Association for Water Technology and Sanitary Engineering, 2020). Such investments are expected to reduce the CECs burden on the recipient waters, so currently scarcely available data on CECs in this region might be also regarded as a baseline for assessment of the future improved wastewater management systems.

This paper aims to summarize the existing data on the CECs occurrence in wastewater, surface water, groundwater, and drinking water in countries belonging to the lower part of the Danube Middle Basin. Initially, the motivation for creating this regional review arose during the preparation of the proposal of the now already-funded TwiNSol-CECs project (no. 101059867, 2022–2025) under the HORIZON EUROPE program of the European Union (https://cordis.europa.eu/project/id/101059867). The focus of the project research activities is the monitoring of the CECs occurrence in the environmental resources of Serbia. To create a base for reliable comparison of the obtained project results, the need to compile the relevant data reported for Serbia and other countries of the WB region appeared. The database of results from reports publishing the data on the CECs presence in different water types from the WB countries was further widened with the data for Croatia and Slovenia as the nearest 'upstream' EU Member States from the same (lower) part of the Danube River Middle Basin. The starting point for compiling data set was taken to be 2008 as the year when the first study on CECs in water samples from WB region was published (Terzić et al., 2008). Nevertheless, there are very scarce papers published before 2008 in the lower part of the Middle Danube Basin and they primarily dealt with case studies in Croatia (water of the Krka river estuary (Kveštak et al., 1994); municipal wastewater of Croatian cities (Jeličić and Ahel, 2003; Terzić and Ahel, 2006); groundwater below a municipal solid waste landfill (Ahel and Jeličić, 2001); leachate of the main landfill of the Zagreb city (Ahel et al., 1998)). There are also some reports on organic micropollutants in surface waters coming from Serbia before 2008, but they were focused on "conventional" ("classical") pollutants such as atrazine (Gašić et al., 2002.) and petroleum hydrocarbons (Dalmacija et al., 2003.). A detailed description of the methodological approach in collecting and analyzing the literature data on the CECs surveillance in the region of interest for this study is given in Text SI1. In this way, up-to-date summaries of CEC profiles in different water types from the countries in this part of Europe, sharing major freshwater courses but differing in wastewater treatment rates, are revealed for the first time in the most comprehensive way. Special attention was paid to the analytical methodologies applied for the considered CECs surveillance studies, so gaps and inconsistencies among them, as well as in comparison to the most recent trends in developed EU countries, are highlighted. Hence, based on a set compiled of literature-based data, this review can be considered a source of valuable information for future research projects and efforts to fill the gaps in the monitoring capacities and schemes, and to improve the chemical status of water resources in the WB countries and other developing countries, lagging behind countries with stricter and more developed systems for wastewater management and control. It might be considered as going beyond the specific region of interest, knowing that many CECs are mobile and persistent and might impair the quality of downstream water, i.e. those in countries of Lower Danube Basin. Given the critical role of the Danube River and its tributaries in providing drinking water for millions, supporting agriculture, biodiversity, industry, navigation, and ultimately impacting the Black Sea's water quality, this study consolidates previously fragmented data and monitoring capabilities related to CECs throughout the lower Middle Danube Basin. It serves as a comprehensive reference for scientists, policymakers, decision-makers, utilities, media, and the public in the region and beyond, all of whom share a vested interest in establishing reliable management and control systems for ensuring safe water resources.

2. Overview of the collected data

Thirty-eight scientific papers have been found to report CECs occurrence in different water types from the countries belonging to the lower part of the Middle Danube Basin. These data were published in the period from 2008 to 2022. Tables SI2 and SI3 summarize the most important features of the studies reported for the countries currently considered as the Western Balkan countries and the EU States from this part of the Basin, respectively; the evaluation of similarities and differences among them is expected to enlighten if there are existing gaps that should be bridged by further efforts for the harmonization of the research capacities and activities in line with the latest trends in CECs research.

The total number of samples covered in 19 studies dealing with CECs in waters from the WB countries (Serbia, Bosnia and Herzegovina, North Macedonia) is 699: 374 of surface water, 70 of wastewater, 220 of groundwater, and 35 of drinking water (Table SI2, Fig. 1a). The total number of samples analyzed in 19 studies from Slovenia and Croatia (the EU Member States in the selected part of the Danube Basin) is 574: 318 wastewater, 137 surface water, and 119 groundwater (Table SI3, Fig. 1b). Most of the WB studies (Table SI2) were conducted in Serbia (16 of 19); 1 study was conducted in Bosnia and Herzegovina and North Macedonia, separately, and 1 reported summarized data from Bosnia and Herzegovina, Serbia, and Croatia, which was indicated as “WBC“ study in Fig. 1c. Regardless of the water type examined, pesticides were the most dominant class if the number of compounds targeted by the WB studies is taken into account, followed by pharmaceuticals (Fig. 1d), whereas in the studies from Slovenia and Croatia, this order was reversed (Fig. 1e). Generally, pharmaceuticals and current-use pesticides are often analyzed in environmental media worldwide: this is also confirmed by a 50-year bibliometric survey of Muir et al. (2022).

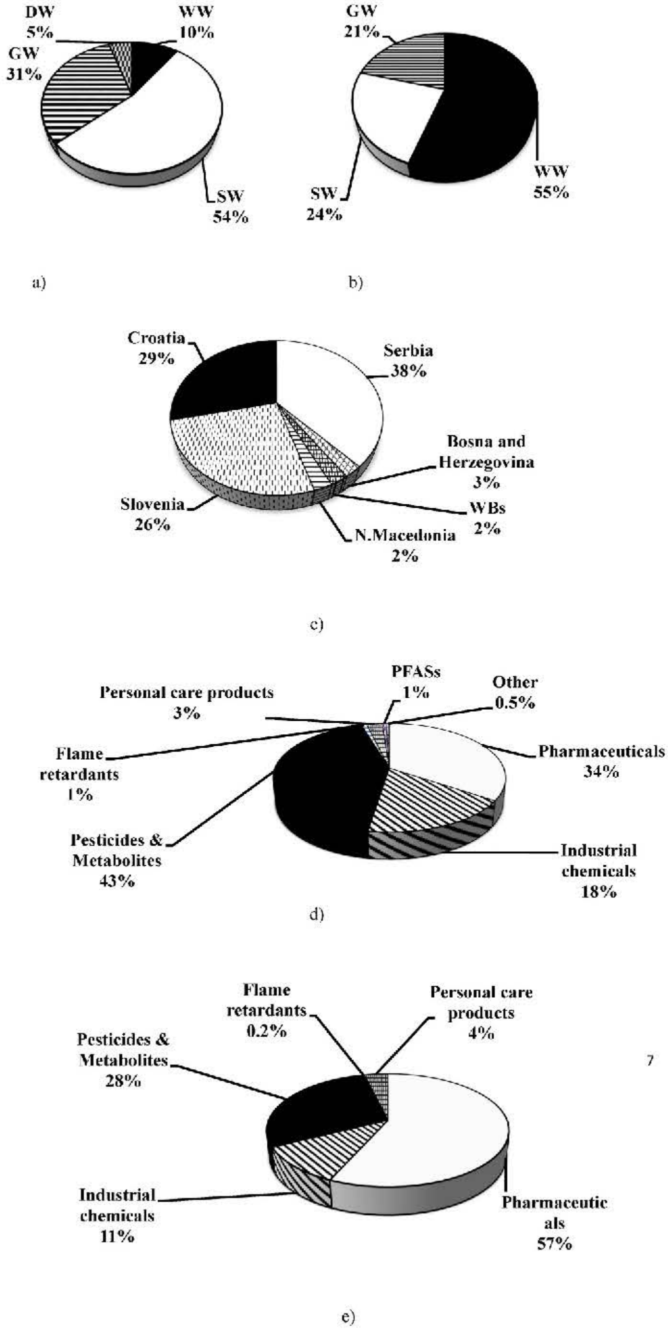

Fig. 1. Overview of literature-based data from the studies that reported levels of CECs in different water types (WW-wastewater; SW-surface water; GW-groundwater; DW-drinking water) from countries belonging to the lower part of the Danube River Middle Basin: a) the percentage of different water type samples relative to the total number of samples considered in WB region and in b) Slovenia and Croatia, c) the percentage of studies on CECs occurrence in water samples conducted in countries of the lower part of the Middle Danube Basin in relation to 38 relevant studies reviewed here in total, and d) the percentage of studied CECs classes in the analyzed studies based on the number of compounds belonging to a particular class in relation to the total number of compounds included in WB studies and e) in Slovenian and Croatian studies.

The research design in the WB studies was based primarily on the grab water sampling (Table SI2); in 4 studies some or all samples were taken as 24-h flow-proportional composite samples or average 7-day composite samples, while in one study water was sampled by use of a passive sampler. In the Croatian and Slovenian studies, grab-water sampling and 24-h flow-proportional composite sampling were almost equally represented (Table SI3). Analysis of water samples for the presence of CECs was conducted mainly by target methods, either LC-MS/MS or GC-MS (Tables SI2 and SI3); in 5 studies, HRMS detection was applied alone or in combination with an instrument equipped with MS/MS, but primarily it was used for target analysis. Only in one study based on GC-MS, screening analysis in conjunction with a mass spectral database was used, which makes this report very specific for the region, enabling insight into the presence of more than 700 semi-volatile organic compounds (Škrbić et al., 2018), even though most of these compounds have been uniquely targeted if compared to other studies considered here. This study of Škrbić et al. (2018) is based on the GC-MS method of Kadokami et al. (2005), who developed an automated identification and quantification system with a GC-MS database for the compound identification and quantification of micropollutants in environmental and food samples. However, this GC-MS method is based on single quadrupole MS (not high-accuracy and high-resolution MS), and it is not based on the 5-level classification scheme proposed by Schymanski et al., in 2014 for communicating the confidence of identification in non-target analysis (Schymanski et al., 2014; Hollender et al., 2023). Thirty-three out of 38 studies targeted a few to several dozen compounds (up to 81), while only 5 studies analyzed more than 100 compounds (Fig. SI1, Tables SI2 and SI3).

3. Occurrence of CECs in wastewaters

The widest concentration ranges of several orders of magnitude were determined for pharmaceutically active compounds in wastewaters, followed by pesticides and industrial chemicals. The highest value in wastewater samples of more than 2000 μg/L (Terzić et al., 2008) was detected for linear alkyl benzene sulfonates (grouped in industrial chemicals); Terzić et al. (2008) did not link the extremely high level of linear alkyl benzene sulfonates to any specific source, but they reported it was present at relatively uniform levels in all examined municipal wastewaters. There were numerous high-level extremes for pharmaceuticals in wastewater samples, implying their specific sources at respective sampling locations. The highest value of pharmaceuticals in wastewater (39.15 μg/L of carboxy-cyclophosphamide (Isidori et al., 2016) was found for sample from Slovenia, representing hospital effluents; without this extreme, the ranges of pharmaceuticals in the WB and the EU countries within the lower part of the Middle Danube Basin were similar, with maximum values about 20 μg/L. Levels of the reported PFAS levels in wastewaters span over a similar range of concentrations throughout the region, if the extreme value observed for PFOS in Slovenia (Alygizakis et al., 2019) is not considered (Fig. 2).

Fig. SI2 and SI4 depict the average levels of particular contaminants from each study on wastewater. In the framework of considered WB studies, out of a total of 401 compounds that were analyzed in wastewater samples, 170 have never been detected. In Slovenia and Croatia, a waters of Slovenia and Croatia, 523 compounds were detected in total. The average concentrations of different CECs detected in surface waters of the reviewed studies are shown in Fig. SI3 and SI5. Regarding determined concentrations, 99% of the analyzed compounds were found at levels below 1 μg/L throughout the region of lower Middle Danube Basin. As can be seen from Fig. SI3 and SI5, the concentrations of detected CECs were compared with the corresponding PNEC (Predicted No-Effect Concentration) values available in the NORMAN database (https://www.norman-network.com/nds/ecotox/lowestPnecsIndex.php). Only 6.2 and 7.7% of the analyzed compounds in the surface waters of the WB countries and in Croatia and Slovenia, respectively, were detected at levels above the respective PNEC. As expected, the concentrations of detected compounds in surface waters were notably lower compared to those found in wastewater, except for a few compounds from the group of antibiotics and their derived compounds. Fig. 3 shows ranges of average contents for different CEC classes in surface waters from the region. As in the case of wastewaters, the range of pharmaceutically active compounds was the widest with numerous extreme values; median values were 0.003 and 0.004 μg/L in the WB countries and the considered EU Member States, respectively. Similar ranges of pesticides were detected in surface waters with medians of 0.001 and 0.002 μg/L in the WB countries and Slovenia/Croatia. Concerning the available data for PFAS (Fig. 2), the concentration range of the reported levels in the WB surface waters was higher than those in the WB wastewater; these results were obtained in the same study (Buljovčić et al., 2022, Table SI2) and the authors concluded that there was no significant difference between the mean values obtained for PFAS in surface water samples collected upstream and downstream to the wastewater discharge point, which suggested that discharged wastewater did not influence the recipient surface water quality. To the best of our knowledge, there is not any PFAS production site in Serbia, and PFAS contamination might be linked to the use and disposal of PFAS-containing products. On the other hand, samples of surface water and wastewater analyzed for the occurrence of PFAS in Croatia and Slovenia came from different studies (Malev et al., 2022; Alygizakis et al., 2019): higher levels were detected in effluents of WWTP (with secondary or tertiary treatment) than in surface water of Sava, with a median of 0.0003 μg/L in the surface water (EU SW in Figs. 2) and 0.002 μg/L (EU WW in Fig. 2).

Among the analyzed compounds in the WB studies, the most frequently detected (i.e. in 4 or more studies) were carbamazepine, azithromycin, trimethoprim followed by ibuprofen, bisphenol A, caffeine, sulfamethoxazole, lorazepam, estrone, metolachlor, carbendazim and two metamizole metabolites (4- formylaminoantipyrine (4-FAA) and 4-acetylaminoantipyrin (4-AAA)). The most frequently detected CECs in surface waters from Slovenia and Croatia were also carbamazepine and caffeine as well as ketoprofen. Concerning the compounds listed in the 4th Watch List established by European Commission as a mechanism for gathering new monitoring data as a support for the future prioritization and EQS (EC Decision, 2022a), 19 out of 26 compounds were analyzed in the collected studies, while 17 substances were detected in surface waters througout the region: sulfamethoxazole, trimethoprim, venlafaxine and O-desmethyl venlafaxine, imazalil, ipconazole, prochloraz, tebuconazole, tetraconazole, famoxadone, clindamycin, metconazole, penconazole, azoxystrobin, diflufenican, fipronil, and ofloxacin. Of these compounds, the following ones were detected in levels above the maximum acceptable method detection or quantification limit (proposed by the 4th Watch List): sulfamethoxazole in 33% of the samples from North Macedonia analyzed by Stipaničev et al. (2017), and venlafaxine, O-desmethyl venlafaxine, famoxadone, and fipronil in 100%, 80%, 100%, and 80% of the samples from Croatia analyzed by Malev et al. (2022).

To compare the levels of selected CECs in surface waters among the considered WB and EU countries, the 8 most studied compounds in the collected articles were recognized and the data are presented in Fig. SI7. These 8 compounds are: azithromycin, trimethoprym, carbamazepine, venlafaxine, diclofenac, ibuprofen, caffeine, and bisphenol A. Due to inconsistency in their analysis among different studies, it is almost impossible to withdraw observations on their spatial and temporal distribution (Fig. SI7); e.g. levels of carbamazepine varied within similar range in both groups of countries, while the levels of caffeine were among the highest of these 8 substances throughout the region. Fig. SI7 illustrates 2012 and 2015 as the years with the most frequent campaigns on the CECs monitoring in surface waters of the WB region, and 2016–2018 in Croatia and Slovenia. The reported frequency of detection of these 8 compounds is given in Table SI4: in most cases, they were detected with a frequency above 50%.

As can be noted (Fig. SI5), azithromycin and azithromycin-derived compounds, as well as erythromycin-derived compounds (erythromycin oxime and anhydrous erythromycin), were found in the Sava River downstream of the pharmaceutical effluent discharge in rather high average concentrations exceeding 1 μg/L (Senta et al., 2017). The average concentration of azithromycin (1.6 μg/L), N-desmethyl azithromycin (4.7 μg/L), erythromycin oxime (6.8 μg/L), and anhydro erythromycin (4.0 μg/L) were above their respective PNEC values (i.e. 0.019 μg/L, 1.3 μg/L, 0.17 μg/L, 0.057 μg/L, respectively). Furthermore, the average content of azithromycin (1.6 μg/L) reported by Senta et al. (2017) exceeded its threshold (0.18 μg/L) set by the latest European Commission's Proposal 2022/0344 (COD). Köck-Schulmeyer et al. (2021) compared the contents of various CECs families in Sava and two other Mediterranean rivers (Adige in Italy and Evrotas in Greece) and concluded that the water pollution load was dominated by

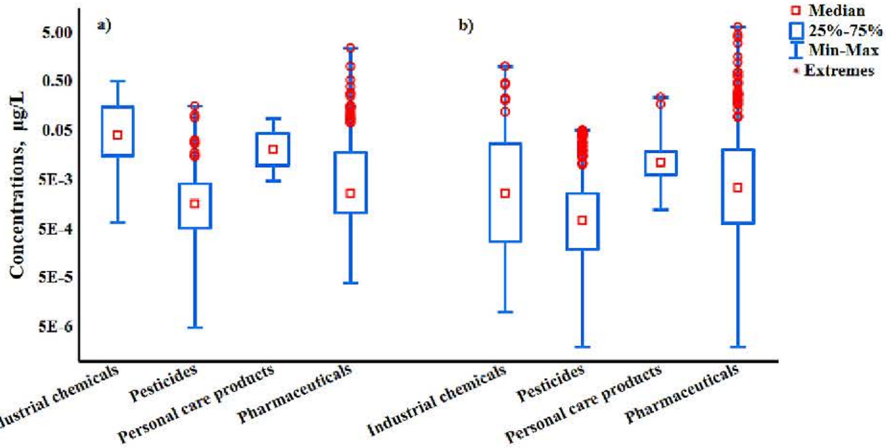

Fig. 3. Box-whisker plots of the averaged levels of CECs detected in studies on surface water from the lower part of the Middle Danube River Basin: a) WB countries, b) EU countries.

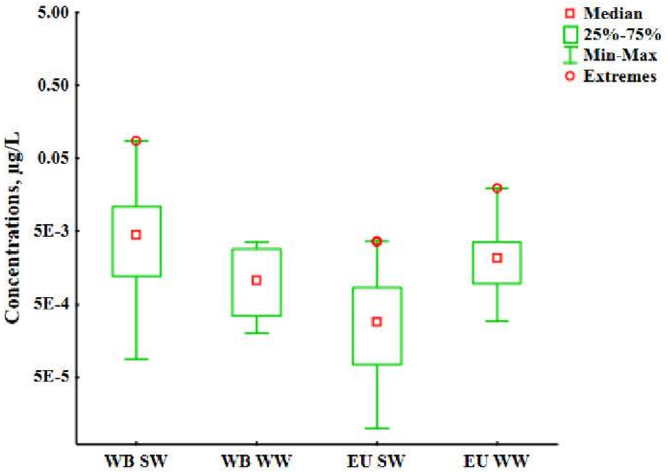

Fig. 2. Box-whisker plots of the averaged levels of PFAS detected in studies on wastewater (WW) and surface waters (SW) from the WB and the EU countries.

similar total number of compounds were examined in wastewater (381), of which 74 have never been detected. The most frequently detected compounds in WB studies were carbamazepine (in 4 out of 7 studies dealing with wastewater), diclofenac (4/7), and naproxen (3/7), whereas in Slovenia and Croatia were azithromycin (5/13), clarithromycin (5/13), bisphenol A (4/13) and bisphenol AF (4/13). If the arbitrarily chosen level of >1 μg/L (Kerketta and Sahoo, 2022) was used to point out the contaminants present in wastewater at very high levels, 16 compounds might be observed in the WB studies, while in Slovenia and Croatia, 18 compounds were detected to be above 1 μg/L. These compounds found in the highest levels in either the discharged untreated wastewater or WWTP effluent samples mostly belonged to different therapeutic groups of pharmaceutically active compounds (analgesics/anti-inflammatories, psychiatric drugs, psychostimulant drugs, antibiotics, β-blocker, diuretics, antihypertensives, antiulcer drugs, antineoplastics, antirheumatic drugs), which may reflect the drugs most often used by local residents Of these compounds, midazolam (21.41 μg/L, Alygizakis et al., 2019), two metabolites of carbamazepine (10,11-epoxy carbamazepine and 2-hydroxy carbamazepine, both ~ 16 μg/L, Petrović et al., 2014) from the group of psychiatric drugs and caffeine (17.20 μg/L, Česen et al., 2018) from the group of psychostimulants were detected in remarkably high concentrations. Other substances recorded in high concentrations in wastewater (>1 μg/L) belonged to analgesics/anti-inflammatories.

The number of analytes analyzed in wastewater samples was notably different (Tables SI2 and SI3); the analysis of a larger number of compounds does not necessarily reflect a higher total concentration of CECs. For example, in the study of Petrović et al. (2014), 75.6 μg/L was the total concentration of 81 compounds analyzed in wastewater, while it was 42.6 μg/L for 48 compounds analyzed in wastewater in the study of Bogunović et al. (2021), and 34.2 μg/L for 280 compounds analyzed in wastewater in the study of Alygizakis et al. (2019). Furthermore, 19.3 μg/L was the total concentration of 48 compounds analyzed in wastewater in the study of Česen et al. (2018), 16 μg/L for 15 compounds analyzed in wastewater in the study of Senta et al. (2019), and 26.7 μg/L for 280 compounds analyzed in wastewater in the study of Alygizakis et al. (2019).

However, a comparison of the CEC levels in wastewater at different locations is not an easy task, as can be seen in Figure SI6. Apart of different sets of analytes chosen to be investigated, the studies differed in type of wastewater, as some studies covered untreated municipal wastewater samples (Terzić et al., 2008; Petrović et al., 2014), while some of the more recent ones (Česen et al., 2018, 2019; Alygizakis et al., 2019) analyzed influents and/or effluents of municipal WWTP; types of the applied treatment and the achieved removal efficiencies have a significant influence on the released CECs. Sampling methods also differed among the studies. Eventually, types and concentrations of CECs in WWTP effluents depend on the socioeconomic composition of the population connected to the WWTPs (Tran et al., 2018) and the wide range of consumer products they used. Results on ibuprofen, one of the most prescribed and consumed drugs, reported in 5 studies from the countries in the lower part of the Middle Danube Basin may additionally illustrate large differences among the levels in wastewater from different studies (Fig. SI6a): it was found from 0.02 μg/L in wastewater effluent from Slovenian WWTPs (Česen et al., 2018) to 20.13 μg/L in municipal wastewater from the area of Novi Sad (Petrović et al., 2014). Similarly, wide ranges of average concentrations were observed for all previously mentioned frequently analyzed substances in wastewater. Azithromycin, in particular, exhibited a range spanning three orders of magnitude (0.005–5.837 μg/L, Fig. SI6d); the ranges for carbamazepine (0.006–0.809 μg/L) and clarithromycin (0.071–0.828 μg/L) are shown in Fig. SI6b and Fig. SI6c, respectively. Differences may also imply different drug consumption rates within the region, as implied in the latest report on a European multi-city study on drugs in wastewater: analysis of municipal wastewater, apart from the importance of studying environmental pollution, is also a developing epidemiological toolkit with the potential to provide timely information on geographical and temporal trends (EMCDDA, 2024).

The levels of ibuprofen, acetaminophen, valsartan, hydrochlorothiazide, azithromycin, and atenolol found in the WBs wastewater were in the range of these detected in the Spanish wastewater influents (Čelić et al., 2019). Nevertheless, there are a few exceptions, such as diclofenac, codeine, sulfamethoxazole, 2-hydroxycarbamazepan, and 10, 11-epoxycarbamazepan, which concentrations were somewhat higher than those found in the Spanish study. The most recent work carried out in Ireland, dealing with the determination of more than 140 CECs in wastewater influents (Rapp-Wright et al., 2023), found the levels of azithromycin, 10,11-epoxycarbamazepan, diclofenac, hydrochlorothiazide, and sulfamethoxazole below 1 μg/L, being lower than those found in the WBs wastewater and the above-mentioned Spanish influents.

4. Occurrence of CECs in surface waters

The samples analyzed in the collected studies were taken from water bodies such as rivers (Danube, Sava, Tisa, Tamis, Pek, etc.), lakes (Palić, Zobnatica, etc.), and the hydro-engineering system of Danube-Tisa-Danube canal (Tables SI2 and SI3). Although many CECs (1207) were considered in the WB studies, the majority (935) were not detected, with most of them being screened by GC-MS-based method within the study of Škrbić et al. (2018), which was discussed previously as having a unique screening approach. In contrast, in Slovenian and Croatian surface waters, the spectrum of analyzed CECs was smaller (659), of which almost 80% were detected. A recent study by Zhou et al. (2019) indicated that out of 477 analyzed emerging pollutants in European surface waters, 284 (60%) were detected in one or more of 33 European countries. The most frequently analyzed classes of selected CECs in the WB surface water are pesticides (52% of the total number of analytes), pharmaceuticals (23%), and industrial chemicals (20%), while PFAS and personal care products have been targeted sporadically. The classes of analyzed CECs in the surface waters studied in Slovenia and Croatia were pharmaceuticals (46%), followed by pesticides (44%), industrial chemicals (8%), and personal care products (3%). These data illustrate uneven coverage of various CECs classes by the studies conducted so far, which most probably could be attributed to analytical capacities of the groups performing the research (e.g. available instruments, sets of analytical standards). Nevertheless, these studies gave snapshots that even limited in the chemicals range as well as in spatial and temporal coverage of contamination, still represent pioneering work that is a basis for developing further regional monitoring plans.

The review revealed a widespread occurrence of CECs in surface water of the WB region, with 272 detected compounds. In the surface pharmaceuticals and personal care products; the highest total concentration of pharmaceuticals per site in Sava was 461 ng/L compared to 368 ng/L in Evrotas and 2041 ng/L in Adige, while the maximum levels of personal care products were 4603 ng/L, 3569 ng/L, and 3055 ng/L, respectively. These authors reported that the highest concentrations among all studied pharmaceuticals in water samples of the Sava River were found for anti-inflammatory drugs such as acetaminophen, ibuprofen, diclofenac, and naproxen (Köck-Schulmeyer et al., 2021).

The other most abundant compound in surface waters was caffeine, which showed an average concentration of 1 μg/L in surface water samples of North Serbia (Škrbić et al., 2018). Caffeine as the most frequently consumed psychoactive stimulant (can be found in food, beverages, spices, tobacco, and medicine (Díaz-Garduño et al., 2017)) was detected in 90% of the analyzed surface water samples from 30 European countries with an average concentration of 885 ng/L, and the highest concentration of 39,813 ng/L found in Belgium (Zhou et al., 2019). In the study by Nannou et al. (2015), caffeine was also the most abundant compound (average of 1524 ng/L) in lake water from Northwest Greece, detected in 100% of the analyzed water samples. However, caffeine has also been found at lower levels elsewhere (e.g., 256 ng/L in the Guadalhorce River, Spain (Llamas-Dios et al., 2021)).

Carbamazepine, one of the most persistent and environmentally studied anticonvulsants (Vázquez-Tapia et al., 2022), was the most studied compound in reviewed studies, with average concentrations ranging from 1.5 ng/L (Slovenian surface waters, Klančar et al., 2018) to 248 ng/L (surface waters of North Serbia, Škrbić et al., 2018). Although carbamazepine is widely distributed and detected, the average contents were far below its maximum allowable concentration (1.6×10^3 μg/L) and annual average EQS (2.5 μg/L) set by the European Commission's Proposal (2022/0344 (COD)). It is interesting to note that the content of carbamazepine in the surface waters of Serbia (Grujić et al. (2009); Lalović et al. (2017); Kovačević et al. (2017); Milić et al. (2018); Petrović et al. (2014); Radović et al. (2012); Škrbić et al. (2018)), varied widely from 4.0 ng/L to 248 ng/L, but below the average concentrations reported for the surface waters of Belgium, Hungary, and Cyprus, found to be up to 572, 771, and 5783 ng/L, respectively (Zhou et al., 2019). The observed differences in the content of carbamazepine can probably be related to the specificity of the sampling locations and the specific resident's consumption of this drug, as well as to the temporal and spatial variability in its environmental content (Brack et al., 2016). All authors agree that carbamazepine is inevitably present in surface waters, considering its constant input, which is a consequence of the treatment of epilepsy that usually lasts a lifetime. All this, together with the environmentally persistent nature of carbamazepine, leads to an increased load on the watercourses with this drug, which is excreted unchanged in only a few percentages (Kasprzyk-Hordern et al., 2009).

Particular attention has also been given to the occurrence of ibuprofen in surface water. It belongs to non-steroidal anti-inflammatory drugs (NSAIDs), which cause great concern due to the widespread consumption for the treatment of inflammation and pain (Shanmugam et al., 2014; Vieno and Sillanpää, 2014) and constitute the largest group of non-prescription drugs sold worldwide. Ibuprofen is among the most frequently studied emerging organic contaminants in the surface waters of the WB studies, whose concentrations ranged from 15.4 ng/L (Milić et al., 2018) to 163 ng/L (Škrbić et al., 2018). Levels of ibuprofen found in surface waters from Slovenia and Croatia (4.1 ng/L (Česen et al., 2018) – 206 ng/L (Malev et al., 2022)) were in a similar range as those detected in Serbian surface waters (Fig.SI7). The annual average EQS proposed for ibuprofen in inland surface waters by EC is 0.22 μg/L (2022/0344 (COD)). A study by Zhou et al. (2019) showed that ibuprofen was among the 45 most studied compounds in European surface waters, which was analyzed in more than 28 European countries, and it was detected in 59% of all analyzed samples, with a mean and maximum levels found to be 337 ng/L and 31,323 ng/L. Although ibuprofen has been reported to show an acceptable removal rate (from 59 to 95%), it is often detected in the WWTP effluents in fairly high concentrations up to 28 μg/L, which may have a direct impact on receiving watercourses (Bueno et al., 2012; Gómez et al., 2007). Due to high consumption, incomplete removal in WWTPs, but also the direct discharge of untreated wastewater into surface watercourses, ibuprofen was frequently detected in surface waters of different countries such as France (up to 8 ng/L (Vulliet and Cren-Olivé, 2011)), Greece (up to 67 ng/l (Stasinakis et al., 2012) or even to 548 ng/L in Nannou et al., 2015), the UK (up to 100 ng/L (Kasprzyk-Hordern et al., 2009)), Finland (up to 1830 ng/L (Meierjohann et al., 2016)), Spain (up to 28.9 ng/L (Čelić et al., 2019) and 89 ng/L (Llamas-Dios et al., 2021)).

Among the most frequently studied compounds in surface waters was also bisphenol A, whose average concentrations were between 16 ng/L (Čelić et al., 2020) and 224 ng/L (Malev et al., 2022), Fig.SI7. These levels were below the maximum allowable EQS (130 μg/L) proposed by the EC Proposal (2022/0344 (COD)). It came into the focus of attention in the last decade due to its weak estrogenic activity (Flint et al., 2012), even though its environmental occurrence has been monitored since the mid-1990s in the freshwater of Europe, it has been present in a wide concentration range, with a 95th-percentile concentration of 0.3 μg/L over the 19-year period (Staples et al., 2018).

5. Occurrence of CECs in groundwaters

Groundwater could be regarded as the largest freshwater body in the European Union, but at the same time, it is the most sensitive resource (GWD, 2006/118/EC). Although groundwater is less susceptible to contamination by CECs than surface water (Lukač Reberski et al., 2022), groundwater contamination with these contaminants represents the most significant global threat. Additionally, groundwater is a vital water resource of each country worldwide, and its potential contamination is of great concern, so knowledge about the occurrence of CEC in this resource is necessary (Sui et al., 2015). Unlike advanced European countries such as Italy (Meffe and de Bustamante, 2014), Spain (Jurado et al., 2012), and the UK (Stuart et al., 2012), where nationwide studies on CECs have been reported, including their occurrence in groundwater, information on the occurrence and presence CECs in groundwater in the WB region, Slovenia, and Croatia are rare. There are 6 studies from Serbia, 2 from Slovenia, and 2 from Croatia that reported the CECs levels in groundwater (Grujić et al., 2009; Kovačević et al., 2017; Petrović et al., 2014; Radović et al., 2012, 2015; Lalović et al., 2017; Koroša and Mali, 2015; Koroša et al., 2016; Senta et al., 2021, Selak et al., 2022, Tables SI2 and SI3). The studied compounds in groundwater within these investigations were mainly pharmaceutical active compounds (120 compounds) followed by pesticides (19).

The pharmaceuticals detected in groundwater belonged to the following therapeutic groups: analgesic and anti-inflammatories (7 compounds), β-blockers (3), antibiotics (including their synthesis intermediates and transformation products, 9), psychiatric drugs (3), analgoantipyretic (metamizole metabolites (2)), antihypertensive (1) and anthelmintics (1). Maximum individual concentrations have been found for azithromycin (140 ng/L, Grujić et al., 2009), N-formyl-4-amino-antipyrine (150 ng/L, Kovačević et al., 2017; Radović et al., 2015), N-acetyl-4-amino-antipyrine (150 ng/L, Radović et al., 2015) trimethoprim (100 ng/L, Grujić et al., 2009), ibuprofen (92 ng/L, Petrović et al., 2014), carbamazepine (88 ng/L, Koroša et al., 2016), ketoprofen (40.8 ng/L, Selak et al., 2022), gebapten (37.1 ng/L, Selak et al., 2022), lorazepam (30 ng/L, Kovačević et al., 2017), naproxen (27.6 ng/L, Petrović et al., 2014), propyphenazone (24.8 ng/L, Petrović et al., 2014), and phenazone (23.4 ng/L, Petrović et al., 2014). Concentrations of other detected pharmaceuticals, such as diclofenac, metoprolol, bisoprolol, salicylic acid, propranolol, albendazole, carazolol, etc. did not exceed 20 ng/L. Among the analyzed pesticides, atrazine, desethylatrazine, metolachlor, simazine, and terbuthylazine were detected, whose maximum concentrations reached 228.8, 103.0, 67.6, 29.6, and 25.7 ng/L, respectively (Koroša et al., 2016). The maximum concentrations of other detected pesticides such as carbendazim, carbofuran, deisopropylatrazine, desethylterbuthylazine, and propazine were up to 20 ng/L (Radović et al., 2015; Koroša et al., 2016). A recent study carried out by Senta et al. (2021) dealt with macrolide antibiotics and their transformation products in groundwater. Similar to the findings for water of Sava river analyzed by Senta et al. (2017), Senta et al. (2021) determined that the concentration of transformation products such as decladinosyl azithromycin (up to 1143 ng/L) and N-demethyl azithromycin (up to 490 ng/L) largely exceeded the concentration of the parent compound, azithromycin, (0.16–17 ng/L), drawing attention to the need for further research. Based on the measured vertical profiles of macrolides content in aquifer sediments, the authors found that their highest concentrations in groundwater were determined at two locations with the highest contamination in deeper sediment layers, which pointed that highly contaminated aquifer sediments should be considered as a significant threat to drinking water supply (Senta et al., 2021). Accordingly, it may be speculated that in the case of the deeper aquifer sediments, the transformation of parent compounds occurs in these sediment layers, which are often a part of the saturated zone of the aquifer that probably enhances the transfer of the transformation products to the adjacent groundwater.

In contrast to sporadic data in the WB region, extensive data from different EU countries were gathered providing insight into the CECs distribution in groundwater based on studies conducted in Spain (Cabeza et al., 2012; Gros et al., 2021; Jurado et al., 2020; López-Serna et al., 2013; Teijon et al., 2010) Germany (Einsiedl et al., 2010; Wolf et al., 2012), the UK (Stuart et al., 2012), Poland (Kapelewska et al., 2018), Hungary (Kondor et al., 2020), Switzerland (FOEN, 2009; Morasch, 2013), Czech Republic (Rozman et al., 2017), and Europe (Bunting et al., 2021; Loos et al., 2010). Among the most frequently detected CECs in groundwater were pharmaceuticals (Silori et al., 2022). The levels ranged from a few ng/L to more than 1 μg/L, which indicated some alarming data (Silori et al., 2022). To ensure the best possible monitoring of European groundwater, the first Voluntary Groundwater Watch List (GWWL) was recently initiated in Europe (CIRCABC, 2019) to identify priority CECs for which groundwater quality standards or threshold values should be set. However, to the best of our knowledge, there is still no data available in the literature on this topic.

6. Occurrence of CECs in drinking waters

Drinking water is obtained mainly from surface water and groundwater, so it is also susceptible to contamination by CECs due to incomplete removal in conventional drinking water treatment plants (DWTP) (Kolkman et al., 2021). The latest revised Drinking Water Directive, DWD (EU, 2020) tackles emerging pollutants, referring to endocrine-disrupting compounds and PFAS. The Directive provides for the establishment of the first watch list for pharmaceuticals in water intended for human consumption, which was adopted in 2022. This list indicates guidance values for 17-beta-estradiol and nonylphenol of 1 ng/L and 300 ng/L, respectively, as well as the limit of their quantification to allow for the measurement of the guidance values with an acceptable degree of precision. Moreover, the recast DWD introduced 2 new parameters for monitoring PFAS, 'PFAS Total' ("the totality of per- and polyfluoroalkyl substances") and 'Sum of PFAS' (a list of 20 PFAS), with limit values of 0.5 μg/L and 0.1 μg/L, respectively, to which Member States must comply with by January 12, 2026.

Literature data about CECs presence in drinking water in the lower part of the Middle Danube Basin are very limited: only two studies from Serbia documented the presence of some CECs in samples of drinking water (Čelić et al., 2020; Petrović et al., 2014; Table SI2). Čelić et al. (2020) analyzed water sampled from public fountains in selected residential areas (n = 30). These authors reported the presence of bisphenol A, nonylphenol, and octylphenol with maximum levels of 35.6 ng/L, 7.9 ng/L, and 3.7 ng/L, respectively, while estradiols E1, E2, and E3, and the metabolites E1-3S and E3-3S were not detected; reported level for nonylphenol did not exceed the guidance level (300 ng/L, EC Decision, 2022b). Petrović et al. (2014) analyzed 81 pharmaceuticals in samples of raw untreated water and chlorinated water collected from public utility company for the Novi Sad city drinking water supply and in a sample of tap water (Novi Sad, Serbia), detecting 14% of the targeted compounds with the maximum levels ranged from 0.4 ng/L for propranolol to 128 ng/L for 10,11-epoxycarbamazepine. Additionally, these authors observed that the treatment and distribution of water in the city water supply did not affect the presence of albendazole, propranolol, and salicylic acid (Petrović et al., 2014).

The presence of pharmaceutical compounds in drinking water has also been documented elsewhere (Tröger et al., 2021; Valbonesi et al., 2021). A recent comprehensive study in 8 European countries (Sweden, Spain, Czech Republic, Netherlands, Switzerland, Germany, Italy, and Belgium) conducted by Tröger et al. (2021), reported a wide range of CECs (177 compounds) in source and drinking water collected from DWTPs; the number of detected CECs in source water samples varied from 6 in Germany to 71 in Spain. There was a significant variation in the concentrations of detected CECs per country (Tröger et al., 2021): the samples from Spain showed the highest total content of detected CECs (7995.2 ng/L), followed by samples from the Czech Republic, the Netherlands, Belgium, and Italy, which were characterized by a medium level (up to 1092.5 ng/L), and then samples from Sweden, Germany, Switzerland, and another sample from Italy, which had relatively low total CEC levels (up to 247.0 ng/L).

7. Future perspectives for wide-range CEC surveillance in the region

The investigative studies on CECs performed so far in the lower part of the Middle Danube Basin gave the snapshots that proved the wide abundance of CECs in various water samples, reaching also drinking water. It might be presumed that detected CECs in the waters of the region are only the tip of an iceberg, while the full spectrum of those non-targeted chemicals is left unrecorded, so their levels remain unknown. Most of the studies considered here were based on conventional analytical approaches targeting from a few to several tens of CECs. The only 5 studies included in this review that targeted several hundreds of compounds can be regarded as rather specific and sporadic. It is interesting to note that 11 out of 38 reviewed studies were produced as a result of international (bilateral) collaboration. Among these studies are those that reported the results on several tens to hundreds of analyzed CECs. It seems that the regional analytical capacities were generally limited to target analysis of CECs in water, at least for the period covered by this review. Although some of these studies proved that the HRMS instruments have been used for the CECs monitoring in the region, none have been used for suspect or non-target screening analysis.

A suspect screening based on liquid chromatography with HRMS has been imposed recently as a promising and reliable addition to target analysis not only in the scientific community but also for authorities and regulators (Hollender et al., 2023). Suspect screening analysis relies on lists of chemicals expected to be present in the sample, and it is typically performed without reference standards, but with prior information on exact mass and isotope pattern from the known molecular formula or the expected adduct(s); sometimes it is referred to as analysis of "known unknowns" (Hajeb et al., 2022; Hollender et al., 2023; Paszkiewicz et al., 2022; Schymanski et al., 2015). On the other hand, non-target HRMS analysis aims to analyze "unknown unknowns" without *a priori* criteria; because no structural information is available in advance, a full non-target identification starting from the exact mass, isotope, adduct, and fragmentation information needs to be performed (Hajeb et al., 2022; Hollender et al., 2023; Paszkiewicz et al., 2022; Schymanski et al., 2015). Both of these approaches might be covered by the general term "non-target screening", because many aspects and methods are the same for both; in general, they are laborious, time-consuming, and computationally challenging, with much more "identification burden" linked to the analysis of "unknown unknowns" (Hollender et al., 2023; Lai et al., 2021). Besides obtaining an insight into the broader range of substances detected in samples with various levels of confidence than the one obtained by conventional target analytical approaches, suspect and non-target screening enables archiving of the HRMS data, keeping in this way the most comprehensive information on the chemical status of the sample that can be subjected to the later assessment. Additionally, the sharing of electronic HRMS data according to FAIR (Findable, Accessible, Interoperable, Re-useable) principles enables maximization and internationalization of the local research efforts, being eventually retraceable and verifiable for the final purpose of use by legislators and policymakers (Hollender et al., 2023). The digital archiving and sharing of HRMS spectra via open science can also foster the knowledge exchange necessary for boosting and harmonizing the relevant research competencies needed for the effective implementation of suspect screening analysis in environmental monitoring. To the best of our knowledge, only a laboratory at the Faculty of Technology Novi Sad (University of Novi Sad), Serbia, owns the capacities that enable non-target analysis in the WB region (LC-HRMS and the dedicated vendor software for HRMS data processing towards suspect and non-target screening) (Farre et al., 2023). With this material capacity and the training that has been conducted within Horizon Europe project TwiNSol-CECs (GA 101059867, www.twinsol-cec.com) coordinated by the Faculty of Technology Novi Sad, Serbia, the aim is precisely to perform the first suspect screening analysis of the surface water in Serbia in collaboration with IDAEA-CSIC, Barcelona, Spain, as the project partner known for development of multi-residue analytical methods (Llorca et al., 2021; Picardo et al., 2020b, 2020a). Nevertheless, this capacity must be further harmonized and linked with other researchers, teams, and institutions in the region involved in the CECs monitoring in water, including also those spotted via this review in Serbia, North Macedonia, Bosnia and Herzegovina, Croatia, and Slovenia. This review pointed out the significant background of the Serbian, Croatian, and Slovenian researchers in the CECs monitoring in the past decades (Table SI2 and SI3). Some researchers from these countries have established important links with prestigious international teams known in the field of environmental monitoring. Even more, among them, there is a proven interest and expertise available in non-target analysis (Schymanski et al., 2015). Table SI5 summarizes regional strengths and gaps in knowledge and capacities for the wide-range surveillance of CECs within the lower part of the Middle Danube Basin. The stronger regional and international cooperation is needed not just to fill the gaps in monitoring capacities, but also to foster the flow of relevant information and two-way exchange of best practices and knowledge, establishing a platform capable to influence and guide future monitoring strategies and schemes in the region in line with latest EU initiatives and directions on water quality and safety.

8. Conclusion

This review gave a comprehensive overview of the work performed on the CECs monitoring of different types of water in the WB and EU countries in the lower part of the Middle Danube River Basin. The majority of collected data are presented in graphs included in the Supplementary Information, helping in easy visualization and comparison of data on the levels of pharmaceuticals, pesticides, PFAS, personal care products, and industrial chemicals analyzed in surface and wastewater from the WB countries, Slovenia and Croatia, and representing a unique database of information on the CECs presence in this region. An assessment of the gathered results showed that many CECs are present in the regional aquatic environment, including some of those listed in the watch lists. Pharmaceutically active compounds and pesticides were among the most frequently analyzed CECs: the ranges of their occurrence in surface and wastewater significantly differed, with wider ranges and many extreme values observed for pharmaceuticals, indicating also a variety in their consumption rates. Less than 10% of analyzed substances in surface water througout the region were above the relevant PNEC values. The compounds found in high quantities and also those in levels above the values proposed by the latest EU decisions, may be considered as candidates for further regional monitoring schemes and prioritization efforts for substances of regional/national concern.

Nevertheless, consolidated knowledge of the current status of waters points out studies rather limited in terms of the number of compounds measured and the geographical distribution of sampling points, with the lack of continuity in the aforementioned studies. Accordingly, new studies should be based on novel approaches such as those based on HRMS suspect screening methods harmonized with the existing European and worldwide research efforts in order to fill data gaps and to reveal the chemical status of the regional's water resources. International research projects, collaboration with well-experiences laboratories in Europe and beyond, and open science data exchange are possible directions needed to facilitate the regional strengths in advanced and comprehensive analytical approaches. The research teams and capacities observed by this review represent a good starting point for further bilateral, regional, and international cooperation needed to foster the monitoring efforts and community.

CRediT authorship contribution statement

Nataša Đurišić-Mladenović: Writing – original draft, Methodology, Investigation, Conceptualization. **Jelena Živančev:** Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Igor Antić:** Visualization, Investigation. **Dušan Rakić:** Visualization, Investigation. **Maja Buljovčić:** Visualization, Investigation. **Biljana Pajin:** Supervision. **Marta Llorca:** Supervision. **Marinella Farre:** 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.

Acknowledgements

This study was conducted under the TwiNSol-CECs project, which received funding from a Horizon Europe program under grant agreement No. 101059867, and under the projects no. 451-03-66/2024-03/200134 and 451- 03-65/2024-03/200134, funded by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.125128.

Data availability

Data will be made available on request.

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