Occurrence of pharmaceuticals in the Danube and drinking water wells: Efficiency of riverbank filtration[☆]

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ABSTRACT

Surface waters are becoming increasingly contaminated by pharmaceutically active compounds (PhACs), which is a potential risk factor for drinking water quality owing to incomplete riverbank filtration. This study examined the efficiency of riverbank filtration with regard to 111 PhACs in a highly urbanized section of the river Danube. One hundred seven samples from the Danube were compared to 90 water samples from relevant drinking water abstraction wells (DWAW) during five sampling periods. The presence of 52 PhACs was detected in the Danube, the quantification of 19 agents in this section of the river was without any precedent, and 10 PhACs were present in >80% of the samples. The most frequent PhACs showed higher concentrations in winter than in summer. In the DWAWs, 32 PhACs were quantified. For the majority of PhACs, the bank filtration efficiency was >95%, and not influenced by concentrations measured in the river. For carbamazepine lidocaine, tramadol, and lamotrigine, low (<50%) filtration efficiency was observed; however, no correlations were observed between the concentrations detected in the Danube and in the wells. These frequently occurring PhACs in surface waters have a relatively even distribution, and their sporadic appearance in wells is a function of both space and time, which may be caused by the constantly changing environment and micro-biological parameters, the dynamic operating schedule of abstraction wells, and the resulting sudden changes in flow rates. Due to the changes in the efficiency of riverbank filtration in space and time, predicting the occurrence and concentrations of these four PhACs poses a further challenge to ensuring a safe drinking water supply.

1. Introduction

Along with treated and untreated wastewater, numerous pharmaceutically active compounds (PhACs) are also discharged into rivers as a result of the communal consumption of pharmaceuticals, presenting an increasing ecological risk all over the world (aus der Beek et al., 2016; Couto et al., 2019; Jakab et al., 2020; König et al., 2017; Loos et al., 2009; Quesada et al., 2019; White et al., 2019; Zhou et al., 2019). The presence of certain PhACs (e.g. the antiepileptic drug carbamazepine (CBZ), the non-steroidal anti-inflammatory drug (NSAID) diclofenac (DCL), or illicit drugs) has already been detected in drinking water (Bradley et al., 2014; Davoli et al., 2019; Jones et al., 2005; Kleywegt et al., 2011; Leung et al., 2013; Mendoza et al., 2014; Padhye et al., 2014; Sun et al., 2015). Riverbank filtration systems (RFS) and aquifers along polluted rivers are even more exposed to anthropogenic contamination. RFS is a natural water filtration system between river and shallow groundwater where surface water infiltrates through alluvial sediments to drinking water abstraction wells (Ascott et al., 2016; Bradley et al., 2014). Although RFS can attenuate the groundwater pollution with

different biological, physical, and chemical processes, this medium is highly exposed to anthropogenic influences (Hiscock and Grischek, 2002; van Driezum et al., 2019). Certain inorganic and organic micropollutants (eg. PhACs) can contaminate aquifers and they can reach drinking water wells where shallow drinking water aquifers are closely connected to rivers (Hamann et al., 2016; Heberer, 2002; Hollender et al., 2018). Although no legal limiting values exist for the pharmaceutical contamination levels of natural and drinking water, the monitoring of PhACs in surface water has become increasingly important in the past few years due to the potential risks to environmental and human health (Reis-Santos et al., 2018; Sui et al., 2015). As a result, in addition to certain antibiotics, hormones, such as E1 (estrone), E2 (17-Beta-estradiol), EE2 (17-Alpha-ethinylestradiol), and DCL, are also present on the watch list of the European Union, following with the Water Framework Directive (Barbosa et al., 2016; Castiglioni et al., 2018).

The Danube is the largest river in the EU with a total length of 2780 km. Its catchment area covers 801,000 km^2 with approximately 81 million inhabitants in 19 countries (Schmedtje et al., 2005), and it is exposed to a huge amount of anthropogenic contamination (Kirschner et al., 2017). In Slovakia, Hungary and Serbia, the largest cities along the Danube, like capitals Bratislava, Budapest and Belgrade use much more than 50% of riverbank filtrated water for their drinking water supply (Storck et al., 2015). Several surveys (Joint Danube Surveys in 2001, 2007, and 2013; *JDS1, JDS2, JDS3*) have been conducted by the *International Commission for the Protection of the Danube River* (ICPDR) to study the pharmaceutical contamination of the entire length of the river. Within the framework of the latest survey (JDS3 in 2013), the presence of several hundred molecules was studied along the entire length of the Danube, and dozens of pharmaceutical compounds were detected in the water (Ginebreda et al., 2018; Neale et al., 2015). Surveys have also been conducted along shorter sections of the Danube, revealing differing dynamics of certain substances (Chiţescu et al., 2015; Chiţescu and Nicolau, 2015; Letić et al., 2015; Milić et al., 2018; Petre et al., 2016; Radović et al., 2015; Varga et al., 2010). The water discharge of the Danube at Hungary varies 1000−10,000 m^3 s^{-1} with a maximum at early spring owing to snowmelt and a minimum at early fall. As the amount of the treated wastewater input is stable, the varying water discharge can trigger considerably concentration changes in the river owing to dilution, possibly affecting even the bank filtration efficiency (Ascott et al., 2016).

River water is primarily treated by passing the water through the geological layer to the wells. Certain contaminants are adsorbed by the sediments, and the most effective form of treatment, microbiological degradation, also occurs during this process. However, water treatment can never be perfect (Heberer, 2002). The efficiency of a filtration system may be influenced by several environmental factors; therefore, it can change rapidly in both space and time (Henzler et al., 2014). The most critical factors are believed to be the properties of the sediment/soil, hydrogeological settings, temperature, travel times and distances, dissolved organic compounds and oxygen content, pH, and the properties of the target molecule (Petrović et al., 2009). Tests aiming to determine the efficiency of RFS have been mainly carried out in a laboratory environment as model experiments on artificial soil columns or as field model experiments (Bertelkamp et al., 2016; Henzler et al., 2014); however, no universal conclusions have been reached (Abdelrady et al., 2019; Oberleitner et al., 2020). Measurements taken by Maeng et al. (2010) in Lake Tegel revealed that increased CBZ levels in the lake water did not result in a CBZ increase in the wells, which indicates that the riverbank filtration efficiency can change over time. In the case of smaller rivers, travel time and, in particular,

travel distance play a crucial role in reducing contaminant concentrations (Hamann et al., 2016; Huntscha et al., 2013; Kruć et al., 2019; Oberleitner et al., 2020). As a general trend, it was established that certain persistent PhACs, such as CBZ (JDS3; van Driezum et al., 2019; Kovačević et al., 2017), penetrate the oxidative alluvial aquifers along the Danube as well, while others are prevented from doing so as a result of varying affinity for adsorption and biodegradation. Nagy-Kovács et al. (2018) found equal distributions of CBZ and DCL in the Budapest section of the Danube, but filtration efficiency was significantly different in the north and south sections under similar hydrogeological conditions (north: CBZ: 20%, DCL: 32%; south: CBZ: 4%, DCL 44%, respectively). The authors also pointed out that due to the different pumping operational schedules, it was not possible to determine whether the travel distance or the travel time was more responsible for the attenuation under conditions of water abstraction in large quantities. Consequently, a further study of fluctuations of in situ filtration efficiency in space and time measured in abstraction wells could have far-reaching scientific implications.
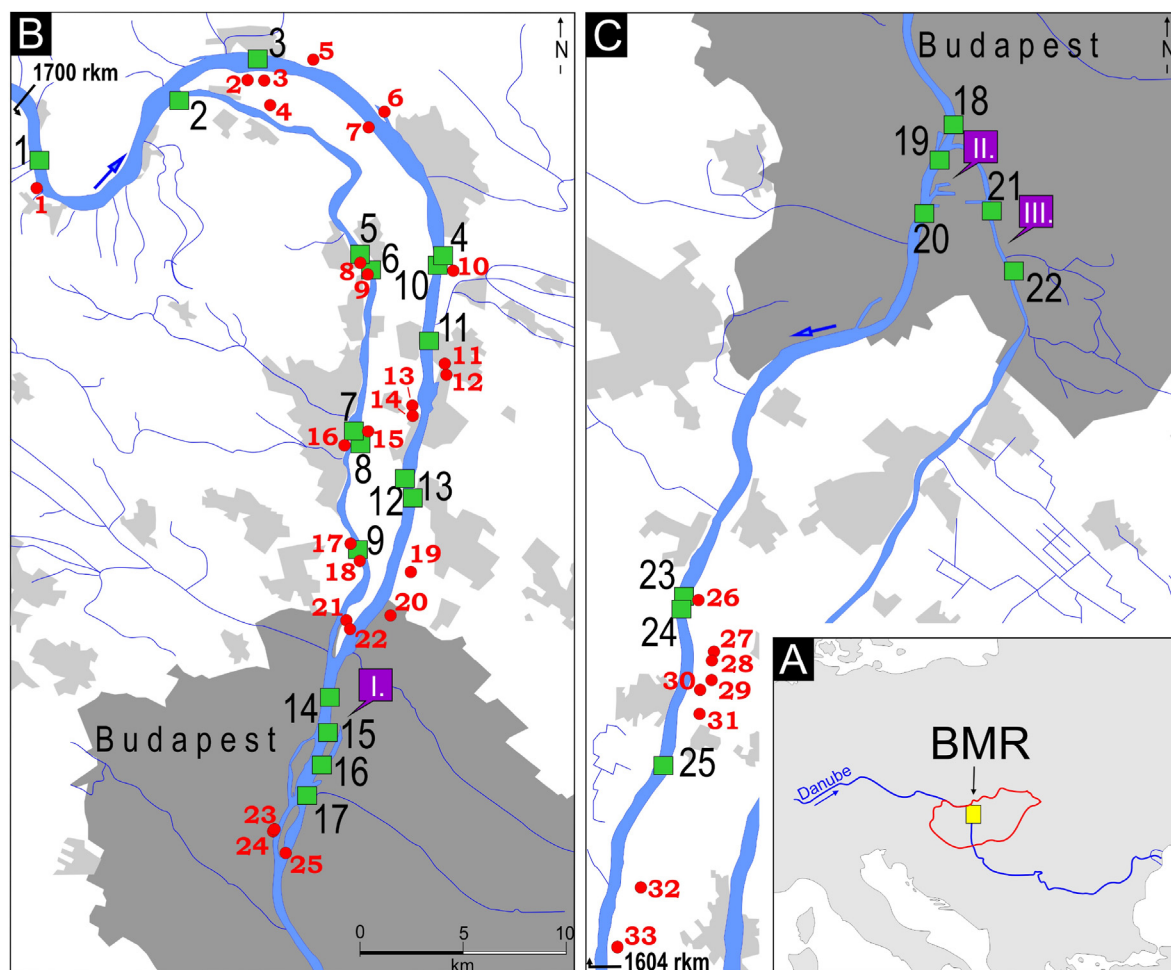
The present study was completed within the framework of a research project conducted over several years and supported by the Hungarian government with the aim of analyzing pharmaceutical contamination in the Budapest Metropolitan Region. It was hypothesized that the efficiency of riverbank filtration was not related to the PhAC concentrations measured in the river. The research of the Central-Hungarian section of the Danube was conducted i) to determine the pharmaceutical contamination of the Danube and the abstraction wells operating along its banks, and its main spatiotemporal features through an analysis based on significantly more samples and pharmaceuticals than before and ii) to determine the efficiency of riverbank filtration systems in the removal of individual PhACs and identify the compounds presenting the highest threat to the security of the drinking water supply.

2. Materials and methods

2.1. Study area

The study was performed along the Hungarian section of the Danube, stretching almost 100 river kilometers (rkm) in the Budapest Metropolitan Region (BMR) (Fig. 1). The average water discharge of the river at Budapest is 2300 m^3 s^{-1}. The study was carried out at a permanent low discharge without relevant seasonal fluctuations. In this section of the river, about 7.2 m^3 s^{-1} of treated wastewater is discharged into the Danube directly or indirectly, which is less than 1% of the total water flow. Three big wastewater treatment plants (WWTPs) are responsible for the 80% of the discharged wastewater, which together transfer approximately 500,000 m^3 day^{-1} of treated wastewater into the river. The average discharge of the North-Pest WWTP is 180,000 m^3 day^{-1}; the capacity of the Central WWTP is 250,000 m^3 day^{-1}; and the capacity of the South-Pest WWTP discharging treated wastewater into the Ráckeve-Soroksár branch of the Danube is 80,000 m^3 day^{-1}. The treated wastewater also enters directly the river from 15 WWTP effluents (more than 70% of the total discharge) or its subsidiaries from more than 100 smaller WWTPs or communal wastewater disposal systems (HCSO, 2019; WMD, 2010). According to the Catchment Management Plan of Hungary, more than 90% of the discharged communal wastewater is treated in the WWTPs (WMD, 2010; WMD, 2016). The impact of untreated wastewater on the water quality of the Danube is no longer particularly significant.

The two large drinking water treatment plants operating in the area provide riverbank filtration-treated drinking water to more than two million people in Budapest and its vicinity. This means

Fig. 1. Sampling area in Budapest Metropolitan Region, Hungary. Location of the study site in Europe (A); sampling sites in the northern (B) and southern (C) water resources; green squares represent the Danube sampling sites; red dots represent the drinking water abstraction wells sampling sites; wastewater treatment plants are marked with roman numerals: I: North-Pest; II: Central; III: South-Pest. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

that more than 90% of the volume of the drinking-water supply in BMR is riverbank-filtrated water. The Budapest Waterworks operates 756 drinking water abstraction wells (DWAWs), mainly in the area of Szentendre Island and Csepel Island, with an average water production of 456,000 m^3 day^{-1}. The Danube Regional Waterworks, on average, produces 161,000 m^3 day^{-1} from the wells along with the upstream of the Budapest section of the Danube. The majority of the wells are located quite close to the Danube (<200 m), whereas the range is 16.5−813 m. Water filtration is done by the geological layer, which mainly consists of Pleistocene fluvial gravels and sands of the Pleistocene on the basement of impermeable tard clay. The thickness of the gravels and sand varies between 90 and 130 m, constructing a homogeneous filtration material in the studied area (Kármán et al., 2014). Owing to the geological circumstances, the filtering system is oxidative (Szalai, 1998; Szalai et al., 2004). The vast majority of the water extracted from the wells (>95%) comes from the Danube (Deák et al., 1992).

2.2. Sampling

To determine the degree of pharmaceutical contamination of the Danube, 107 water samples were collected along the 96 river kilometer section between 1700 rkm and 1600 rkm during five sampling periods (Period I: 29−30. 06. 2017; Period II: 21−22. 02. 2018; Period III: 04. 05. 2018; Period IV: 30. 08. 2018; Period V: 19.

11. 2019). Checking seasonal variations in the concentration of PhACs, three sampling campaigns (Periods I, III, and IV) were carried out during the summer, and two other samplings (II and V) were carried out during the winter. Dilution of wastewater by the runoff may occur during extremely heavy rains or flashfloods, but no such phenomenon was observed during the investigation thus the WWTPs produced their average contribution prior to the sampling periods. Samples were taken from a boat, 5 m from the bank, and 200 mm below the surface as grab samples; before each sampling, original nitrile latex gloves were worn during the handling of the water samples. Each sampling was taken at low water levels, and there were no flood events during the research period.

To determine the contamination level of the DWAWs, 90 untreated samples were collected from wells producing RFS-treated water during five sampling periods (Period I: 14. 07. 2017; Period II: 07. 03. 2018; Period III: 14−15. 05. 2018; Period IV: 10−13. 09. 2018; Period V: 26−29. 11. 2018). The sampling of the wells was conducted as close to ten days following the sampling of the Danube as it was possible, taking into account the mean 10−12 day travel time from the river to the wells (Kármán et al., 2014). Samples were taken from the wells' sampling taps as grab samples.

Water samples were collected directly from the river and the drinking well taps, respectively. For the performance of a general water chemistry analysis, samples were collected in 500 ml brown

borosilicate glass containers after they were rinsed 2 to 3 times. To measure the organic material content, a 50 mL sample was taken into a white borosilicate container, and 500 μL of 2 M hydrochloric acid (VWR International, Pennsylvania, USA) was added to it. For the PhACs test, 2.5 L of water was collected in brown borosilicate glass containers with teflon faced caps (Thermo Fisher Scientific) as grab samples and 2 mL HPLC purity formic acid (VWR International, Pennsylvania, USA) was added to it. For the elemental analysis 15 ml water sample was taken from the Danube river with an original plastic syringe and transferred into polypropylene centrifuge tubes free from metal pollutants through a 0.45 μm syringe filter, and then 100 μL of high-purity cc. nitric acid (VWR International, Pennsylvania, USA) was added to the sample. In the case of drinking water wells, samples for elemental analysis were taken via well taps first in the original polypropylene plastic bottle having 50 mL volume (VWR International, Pennsylvania, USA), and after that, the same sampling procedure was repeated.

Each sample was immediately cooled in a closed container until it arrived to the laboratory less than 4h.

2.3. Chemical analysis

2.3.1. General water chemistry

Temperature, conductivity, pH, dissolved oxygen concentration, and turbidity were measured in the river, using a portable Hanna Multi Meter (Hanna Instrument, USA), and turbidimeter (VWR International, USA). The other physico-chemical parameters were determined in the lab. Total organic carbon (TOC) and total nitrogen (TN) concentrations were measured by applying a Multi N/C 3100 TC−TN analyzer (Analytik Jena, Germany). The concentrations of anions (fluoride, chloride, sulfate, bromide, nitrate) and cations (ammonium, calcium, magnesium, sodium, potassium) were determined with a Dionex ICS 5000+ dual channel ion chromatography system (Thermo Fischer Scientific, USA). Phosphate, nitrite, alkalinity, and total hardness were measured by standard titrimetric and spectrophotometric methods (Eaton et al., 2005). The heavy metal concentration of the samples was determined using a PlasmaQuant MS Elite inductively coupled plasma mass-spectrometer (Analytik Jena, Germany).

2.3.2. PhAC analysis

Sample preparation processes and instrumental analysis have been reported earlier (Jakab et al., 2020; Maasz et al., 2019). Briefly, prior to sampling filtration (GF/F 0.7 μm glass microfibre filter, #516−0345, VWR) the corresponding mass-labelled internal standards (IS) were added to the samples used for quantification. Drug residues were concentrated on Strata X−CW (#8B−S035−FCH, Phenomenex) solid-phase extraction (SPE) cartridges using an automata SPE system (AutoTrace 280, Thermo Scientific). The extraction was carried out within the 20h of the sampling. Ensuring the needed sensitivity derivatization of steroid agents was conducted using dansyl-chloride. The SFC-MS/MS system used for multiple-reaction-monitoring mode quantitation consisted of a WATERS Xevo TQ-S Triple Quadrupole mass spectrometer and a WATERS ACQUITY UPC2 system. MassLynx software (V4.1 SCN950) was used for recording data in triplicate, whereas the evaluation was carried out with TargetLynx XS software. All the SFC-MS/MS tests were conducted on an ACQUITY UPC2 BEH analytical column (#186007607, Waters). The 111 quantified PhACs, analytical parameters of SFC-MS/MS method, limit of detection (LOD), limit of quantification (LOQ), and validation values are listed in Table S1. Using method blank samples, we ensured that the environmental samples were free from laboratory contamination. The analytical methods were validated and verified in each sampling period applying further quality assurance-quality control samples (QA/

QC). All extracts were analyzed <30 days.

2.4. Data analysis

To estimate spatial and temporal changes in concentrations, descriptive statistics, such as mean, standard deviation, and coefficient of variation (CV) were used. Data distribution was analyzed by the Shapiro-Wilk test. Since the individual variables did not exhibit normal distribution patterns, the correlation between the variables was quantified using the Spearman correlation coefficient with a 95% significance level. The seasonal differences in PhAC concentrations owing to their non-normal distribution were analyzed by the Mann-Whitney U test with a 95% significance level. The efficiency of riverbank filtration was determined for PhACs, which were identified in at least one-third of the samples collected from the Danube. To establish the efficiency of riverbank filtration, PhAC concentrations measured in the bank filtrates were compared to those found in the Danube. Filtering out the distorting effects of point source pollution the average contamination level of three relevant water samples (nearest samples from the Danube to the well of which at least one was collected upstream, above the well) was compared to the concentrations measured in the well.

The efficiency of the riverbank filtration system (ERFS) was calculated for each PhAC based on the frequency of occurrence (fro) and the concentration (con) as follows (eqs. (1) and (2)):

$$ERFS_{fro} = \left(1 - \frac{\sum fro_{well}}{\sum fro_{Danube}} \right) \times 100, \qquad (1)$$

$$ERFS_{con} = \left(1 - \frac{\sum con_{well}}{\sum con_{Danube}} \right) \times 100, \qquad (2)$$

where $ERFS_{fro}$ denotes the efficiency of the riverbank filtration system based on the frequency of occurrence; fro denotes the frequency of occurrence of a PhAC; $ERFS_{con}$ denotes the efficiency of the riverbank filtration system based on a comparison of the total PhAC concentrations measured in the Danube and bank filtrates; and con denotes the concentration of a PhAC.

Filtration efficiency calculated based on measuring point couples had no normal distribution in the case of any of the compounds. Hence, to compare the filtration efficiency of individual wells and the water aquifers north and south of Budapest, a median-based comparison of independent samples was performed instead of a parameterized test (eq. (3)). Where the concentration measured in a well exceeded the concentration in the Danube, the filtration efficiency was assumed to be 0%:

$$ERFS_{mp} = Me \left(\left(1 - \frac{Con_{well}}{Con_{r, Danube}} \right) \times 100 \right), \qquad (3)$$

where $ERFS_{mp}$ denotes the efficiency of the riverbank filtration system based on measuring pairs; con_{well} denotes the concentration of a certain PhAC in a given well; and $con_{r, Danube}$ denotes the average concentration of a certain PhAC, calculated from the results of three relevant Danube samples. Statistical calculations were carried out using IBM SPSS Statistics for Windows (version 22, IBM Corp., Armonk, NY, USA).

3. Results and discussion

3.1. Measured concentrations in the danube water samples

General water chemistry parameters and heavy metal content in the 107 Danube samples (Kondor et al., 2020) − considering

seasonal fluctuations as well − did not differ significantly from previously published data (Ionescu et al., 2015; Simeonov et al., 2011; Takić et al., 2012). Fifty-two of the monitored 111 PhACs were detected over a LOQ (Table 1). Based on these results, direct traces of poorly treated or untreated wastewater can be barely detected. Eight PhACs occurred only once, while 44 compounds were detected in several samples. The detection of 19 PhACs in the investigated section of the Danube was without precedent. Among these, the antipsychotic agent tiapride, the anxiolytic cinolazepam (CNL), and the cardiovascular drugs perindopril and propafenone occurred with frequencies greater than 50%. The antidepressant

lacosamide was also detected in one-third of the samples. Altogether 15 PhACs were found in at least half of the samples and 10 compounds occurred with frequencies greater than 80%. CBZ, lidocaine (LID), lamotrigine (LTG), tramadol (TRA), and DCL, which are on the EU watch list, were consistently detected in the river. The antiepileptic drug CBZ has already been identified as a potential environmental risk in the Danube (Shao et al., 2019). Moreover, the cardiovascular drug bisporolol (BSP) was identified in every sample, and the occurrence of metoprolol (MTP) and perindopril was over 90%.

Previous analyses (Fick et al., 2017; JDS1; JDS2; JDS3; Ginebreda

Table 1
Concentrations of all pharmaceutically active compounds (PhACs) found to exceed their limit of quantification (LOQ) value in Danube (MIN: measured minimum value, MAX: measured maximum value, Mean: average of the measured values > LOQ).

Pharmacological classification	PhACs	Frequency of detection	Frequency of occurrence	LOQ	MIN	MAX	MEAN	SD
		N	%	ng L^{-1}				
Alkaloids	atropine[a]	2	1.9	0.05	0.18	4.31	2.24	n.a.
	caffeine	50	46.7	10	10.3	3400	591	758
	theophyllin[a]	20	18.7	10	16.3	119	45.9	31
Antipsychotics, antidepressants	amitriptillin	2	1.9	0.1	0.50	0.73	0.61	n.a.
	bupropion[a]	2	1.9	0.5	0.56	0.60	0.58	n.a.
	citalopram	*103*	*96.3*	*0.1*	*0.18*	*15*	*1.61*	*1.85*
	clozapine	71	66.4	0.1	0.43	64.7	2.84	8.44
	metoclopramide	1	0.9	0.2	1.05	1.05	1.05	n.a.
	mirtazapine	39	36.4	0.1	0.14	18.9	1.49	3.01
	quetiapine	25	23.4	0.1	0.32	6.29	0.94	1.14
	tiapride[a]	73	68.2	0.1	0.97	308	21.5	42.4
	trazodone	52	48.6	0.05	0.16	3.52	1.26	1.06
Antiepileptics	*carbamazepine (CBZ)*	*106*	*99.1*	*0.1*	*26.08*	*498*	*77.2*	*60*
	lacosamide[a]	34	31.8	0.5	0.81	60.32	8.45	11.71
	lamotrigine (LTG)	*92*	*86*	*5*	*13.9*	*2780*	*171*	*287*
Anxiolytics	alprazolam	25	23.4	0.1	0.12	4.3	0.38	0.83
	cinolazepam(CNL)[a]	82	76.6	0.1	0.38	45.07	2.9	5.98
	diazepam	13	12.1	0.1	0.11	0.22	0.15	0.04
	nitrazepam	1	0.9	0.1	1.87	1.87	1.87	n.a.
	nordiazepam	27	25.2	0.1	0.1	0.98	0.18	0.16
	oxazepam (OXA)	*88*	*82.2*	*0.1*	*0.45*	*7.13*	*2.65*	*1.34*
	temazepam	26	24.3	0.1	0.21	0.60	0.37	0.09
	zolpidem	20	18.7	0.01	0.02	0.62	0.28	0.14
Cardiovascular drugs	*bisoprolol(BSP)[a]*	*107*	*100*	*0.5*	*0.54*	*70.1*	*3.80*	*7.52*
	esmolol[a]	1	0.9	0.1	0.11	0.11	0.11	n.a.
	losartan	78	72.9	0.1	0.30	109	4.2	12.6
	metoprolol (MTP)	*105*	*98.1*	*0.1*	*0.91*	*233*	*11.4*	*23.6*
	perindopril[a]	*99*	*92.5*	*0.1*	*0.51*	*81.5*	*5.16*	*11.3*
	propafenone[a]	61	57.0	0.5	0.51	32.4	2.57	4.46
	propranolol	35	32.7	0.1	0.14	8.08	0.58	1.33
	trimetazidine[a]	9	8.4	20	20.5	275	57.7	81.8
	verapamil[a]	10	9.3	0.05	0.06	0.47	0.15	0.13
	warfarin[a]	24	22.4	0.1	0.12	0.69	0.27	0.13
Dissociative anaesthetics, psychedelic drugs, and their metabolites	benzoylecgonine	47	43.9	0.1	0.14	43.9	3.55	6.97
	cocaine	43	40.2	0.05	0.06	24.3	1.28	3.78
	ketamin	44	41.1	0.5	0.56	111	8.72	17.3
Hormones	levonorgestrel[a]	1	0.9	1	9.82	9.82	9.82	n.a.
	E1	45	42.1	0.05	0.09	2.33	0.39	0.32
	aE2	1	0.9	0.05	0.17	0.17	0.17	n.a.
	bE2	10	9.3	0.05	0.11	0.4	0.24	0.1
	E3	8	7.5	0.05	0.06	0.25	0.12	0.08
	EE2	1	0.9	0.05	0.10	0.10	0.10	n.a.
Local anaesthetics	bupivacaine[a]	7	6.5	0.1	0.16	0.29	0.22	0.05
	lidocaine (LID)	*106*	*99.1*	*0.1*	*2.45*	*298*	*13.6*	*28.6*
	ropivacain[a]	7	6.5	0.1	0.11	0.20	0.14	0.03
	tetracaine[a]	1	0.9	0.1	3.69	3.69	3.69	n.a.
NSAID's	*diclofenac (DCL)*	*94*	*87.9*	*0.5*	*1.71*	*115*	*22.5*	*22.9*
	naproxen[a]	6	5.6	0.1	2.80	92.2	26.4	33.7
	paracetamol	1	0.9	20	34.4	34.4	34.4	n.a.
Opioids, morphine derivatives	methadone[a]	14	13.1	0.02	0.43	16.2	1.77	4.15
	pethidine[a]	10	9.3	0.1	0.14	0.53	0.33	0.13
	tramadol (TRA)	*92*	*86.0*	*0.1*	*1.44*	*262.4*	*23*	*30.7*

n.a. not applicable.

[a] First time detection in the affected section of the Danube (asterisk: PhACs detected for the first time from the affected section of the Danube. Italic: Frequency of occurrence >80%.

et al., 2018; Loos et al., 2010; Petrović et al., 2014; etc.) showed that the pharmaceutical contamination of the BMR section of the Danube (see Fig. 1., section A) did not differ from that of the surrounding areas, but the population density of the BMR and the quantity of untreated wastewater discharged into the Danube had an impact on the water quality of the river. Based on the data of general chemistry and heavy metals however, the untreated wastewater had only low impact on the water quality of the Danube in the sampling period. Although the comparison of results with earlier research findings seems inappropriate due to differences in sampling methods, locations (e.g. sampling close to the riverbank vs. streamline), and sampling periods, some points should be highlighted. In the three samples collected from the affected section of the Danube, JDS3 (2015) did not detect the presence of the beta-blocker BSP, which was found in all samples in our research, and the presence of citalopram occurred with over 95% frequency. The presence of perindopril, occurring with a frequency of over 90%, had not even been studied before. Compared to the results of JDS3, higher concentrations of several persistent PhACs were detected, which may be the result of sampling close to the riverbank. While the concentrations of two antiepileptic drugs (CBZ and LTG) were lower in the JDS3 study (CBZ: 32.3 ng L^{-1}, LTG: 60 ng L^{-1}; Ginebreda et al., 2018), in the present research, high frequency of occurrence was accompanied by high average concentration levels. Although LID was identified at lower concentrations compared to these other substances, it had more than three times the concentration established during the JDS3 (4.27 ng L^{-1}). The average concentration of the frequently occurring MTP, TRA, and DCL were nearly the same as the findings of previous studies; it was over 10 ng L^{-1}. Only in the case of oxazepam (OXA) was a lower contamination level detected than that detected by JDS3 (6.63 ng L^{-1}). DCL exhibited an exceptionally high frequency of occurrence among the PhACs on the EU watch list. It had an average concentration of 22.5 ng L^{-1} in 94 positive samples, while the average concentration of the hormone E1 (estrone), which was detected in 46 samples, was 0.4 ng L^{-1}. The compound detected in the largest amount was caffeine, but there were differences between concentrations in samples obtained at different sampling locations.

Bertelkamp et al. (2016) pointed out that due to its high adsorption capacity, organic matter is able to filter out large quantities of PhACs. However, in the present study, the quantity of dissolved organic substances proved to be unrelated to the PhAC concentrations most frequently measured in the Danube. Besides highlighting the different adsorption affinities of certain molecules (Petrović et al., 2009), this also sheds light on the low filtering capacity of dissolved organic matter and the high filtering capacity of those in a solid phase (Szabó et al., 2020).

The coefficient of variation (CV) was influenced by three samples taken at different times in different places, which were much more contaminated than the rest (samples ID 7, 37, and 100, see Kondor et al., 2020). One of these samples (sample ID 37 from sampling site 22, see Fig. 1) was collected close to the effluent of a WWTP, while the other two were taken farther away from the large wastewater treatment plants (sample ID 7 from sampling site 23: more than 25 km downstream, and sample ID 100 from sampling site 13: approx. 10 km upstream). The general water chemistry properties of these samples were not different from those of other samples, but for certain compounds (e.g. LTG, CBZ, MTP etc.), much higher contamination was detected, while the PhAC compositions of the three samples were also different. Presumably, these samples became contaminated as a result of local riverbank pollution or untreated wastewater discharge. These three samples represent only 2.8% of the total number of samples, this also suggests that the

role of untreated wastewater was negligible in the sampling period. Excluding these samples, only the CV value of perindopril was over 100%, and it remained under 50% for LTG, CBZ, and LID. These results indicate a homogeneous distribution of frequently occurring contaminants in both space and time, which, in the case of a river of this size, is only influenced by certain local factors, such as untreated wastewater discharge, relatively close to the bank. The samples revealed significantly lower concentrations in summer compared to the winter for LID, TRA, MTP, OXA, DCL, citalopram, BSP, and perindopril; however, the seasonal concentration did not differ for CBZ and LTG. This is in accordance with the results of Varga et al. (2010), who also reported lower concentrations of contaminants in winter in the Danube, supposing a lower degree of biological- and photo-degradation. Even though the present study focuses on treated wastewater contribution, there are additional possible sources to increase the PhACs concentrations such as direct load from baths (Jakab et al., 2020), damaged sewers, farms, and boats. However, their impact is very limited for DWAWs.

3.2. Drinking water abstraction wells

The nitrate-ammonium composition measured in the well water samples (Kondor et al., 2020) proved that the filtering system is still oxidative. Although 32 of the targeted 111 PhACs were quantified in the 90 DWAW samples, most of the micropollutants only occurred in a few samples or in an extremely low concentration (Table 2, Kondor et al., 2020). Twelve of the components occurred only once, and in the cases of 20 PhACs the average of the concentrations over LOQ did not exceed 1 ng L^{-1}. Only four PhACs were over the 50% frequency of occurrence value. The most persistent PhAC was CBZ. Like the Danube samples, it was detected in more than 90% of the drinking water samples, and its average concentration was quite similar to the concentrations measured in surface water. LTG occurred in more than half of the samples over LOQ, and in the positive samples, it was present with almost the same concentration as in the water of the Danube. The average concentration of LID remained two orders of magnitude below concentrations measured in surface waters, and the concentration of TRA remained one order of magnitude below that value. Due to the low LOQ value applied during the study, the frequency of the other three PhACs was over 10%: the anxiolytic benzodiazepine CNL and OXA were frequent, and the appearance of benzoylecgonine, which is the stable metabolite of cocaine, indicates that the spread of cocaine use can present a threat to drinking water supply security (Campestrini and Jardim, 2017; Mendoza et al., 2014). In interpreting the findings, we must also consider the fact that the possible synergistic effects of compounds that enter the groundwater in low concentrations but belong to similar pharmaceutical categories also present a risk factor.

The CV of CBZ was similar in the DWAW and Danube samples. In contrast, the CV of TRA in the wells was higher, while the CV values of LTG and LID were lower than those calculated in the Danube. Each PhAC that revealed seasonal changes in the Danube and was found in the DWAW samples (LID, CBZ, TRA) also provided seasonal dynamics in the well waters. Even though in well waters, higher PhAC concentrations were found in summer. LTG in DWAWs, as in the case of the Danube did not show seasonal changes. These results suggest that the efficiency of riverbank filtration greatly varies among PhACs, and for the most persistent ones (LID, CBZ, TRA, LTG) it is not affected by concentrations in the Danube. As an alternative, the results would imply an additional permanent water and contamination source to the DWAW, however, former stable isotope results (Kármán et al., 2014) and the chemical parameters and heavy metal concentrations of the present study refute this

Table 2
Concentrations of all pharmaceutically active compounds (PhACs) found to exceed their limit of quantification (LOQ) value in well water (MIN: measured minimum value, MAX: measured maximum value, Mean: average of the measured values > LOQ).

Pharmaceutical classification	PhACs	Frequency of detection	Frequency of occurrence (FRO)	LOQ	MIN	MAX	MEAN	SD
		N	(%)	ng L^{-1}				
alkaloids	drotaverin	1	1.1	*0.1*	*0.84*	*0.84*	0.84	n.a.
	caffeine	8	8.8	*10*	*10.21*	*22.07*	16.9	4.10
antidepressants	citalopram	5	5.5	*0.1*	*0.13*	*0.58*	0.28	0.20
	quetiapine	4	4.4	*0.1*	*0.15*	*6.05*	2.08	2.69
	mirtazapine	3	3.3	*0.1*	*0.39*	*3.84*	1.62	1.92
	bupropion	2	2.2	*0.5*	*0.65*	*2.39*	1.99	n.a.
	clozapine	2	2.2	*0.1*	*0.37*	*0.91*	0.64	n.a.
	metoclopramide	1	1.1	*0.2*	*1.79*	*1.79*	1.79	n.a.
	tiapride	1	1.1	*0.1*	0.52	0.52	0.52	n.a.
	trazodone	1	1.1	*0.05*	0.12	0.12	0.12	n.a.
	risperidone	1	1.1	*0.1*	5.55	5.55	5.55	n.a.
	paliperidone	1	1.1	*0.1*	1.1	1.1	1.10	n.a.
antiepileptics	*carbamazepine (CBZ)*	85	94.4	0.1	0.49	176	47.6	37.9
	lamotrigine(LTG)	48	53.3	5	5.18	849	126	130
anxiolytics	cinolazepam (CNL)	19	21.1	*0.1*	*0.17*	*1.13*	0.5	0.23
	oxazepam (OXA)	13	14.4	*0.1*	*0.23*	*1.58*	0.69	0.44
	alprazolam	5	5.5	*0.1*	*0.12*	*0.3*	0.17	0.07
	nordiazepam	4	4.4	*0.1*	*0.11*	*0.38*	0.19	0.13
	diazepam	3	3.3	*0.1*	*0.16*	*0.25*	0.19	0.05
	temazepam	1	1.1	*0.1*	*0.15*	*0.22*	0.22	n.a.
	zolpidem	1	1.1	*0.01*	*0.04*	*0.04*	0.04	n.a.
cardiovascular drugs	verapamil	7	7.7	*0.05*	*0.24*	*4.78*	1.35	1.86
	perindopril	5	5.5	*0.1*	*0.22*	*1.11*	0.52	0.34
	losartan	3	3.3	*0.1*	*0.15*	*0.66*	0.37	0.26
	metoprolol (MTP)	1	1.1	*0.1*	*0.73*	*0.73*	0.73	n.a.
	bisoprolol (BSP)	1	1.1	*0.5*	*0.66*	*0.66*	0.66	n.a.
DAPSHM	benzoylecgonine	13	14.4	*0.1*	*0.13*	*1.20*	0.39	0.37
	cocaine	1	1.1	*0.05*	*0.27*	*0.27*	0.27	n.a.
	ketamin	2	2.2	*0.5*	*0.63*	*1.15*	0.89	n.a.
local anaesthetics	*lidocaine (LID)*	74	82.2	0.1	0.11	6.1	0.97	0.97
NSAID's	diclofenac (DCL)	1	1.1	*0.5*	*1.55*	*1.55*	1.55	n.a.
Opioids, morphine derivatives	*tramadol (TRA)*	62	68.8	0.1	0.12	26.72	2.62	3.78

Italic: Frequency of occurrence > 50%.
n.a. not applicable.

hypothesis.

3.3. Efficiency of riverbank filtration system

Among the twenty-two PhACs detected in at least one-third of the Danube samples, 15 compounds were almost completely removed from DWAWs by riverbank filtration (ERFS$_{con}$, ERFS$_{fro}$ >90%), including the frequently occurring BSP and DCL (Kondor et al., 2020). This is in line with the hypothesis of the study. Although the degradable DCL had been detected by some authors in high concentrations along the Danube and also in filtered water (Kovačević et al., 2017; Nagy-Kovács et al., 2018.), the present study did not confirm those findings. This PhAC was detected in DWAWs only randomly and in low concentrations, which is similar to the findings of other studies (van Driezum et al., 2019; Hamann et al., 2016; Kruć et al., 2019).

CBZ usually penetrated the riverbank (Table 3). The filtration efficiency of CBZ was still higher than the values previously published for the same section of the Danube by Nagy-Kovács et al. (2018). In the case of LTG neither the ERFS$_{con}$ nor the ERFS$_{fro}$ reached 50%. In the case of LID and TRA, the ERFS$_{con}$ and the ERFS$_{fro}$ were widely separated. In the case of LID, the compound penetrated the RFS in more than 80% of the cases, but its magnitude decreased by one order. TRA penetrated filtration in 70% of the cases, but almost 90% of the compound was removed by riverbank filtration. In the case of three PhACs (OXA, benzoylecgonine, CNL) that occurred less frequently in DWAWs, ERFS$_{con}$ and ERFS$_{fro}$ were separated from each other; while the former was nearly 95%, the latter did not reach 90%. However, filtration efficiency does not

necessarily mean that a given PhAC has been completely eliminated because it often remains in the natural environment for surprisingly long periods of time in the forms of different metabolites, such as lamotrigine (LTG) or OXA, which can be detected even after several years (Chefetz et al., 2019; Klaminder et al., 2015).

While the presence of CBZ in drinking water is already widely known, there is less information available about the persistence of LID, TRA, and LTG. In the case of the four most frequently occurring PhACs in drinking water, the ERFS is only partly similar to the values found in the literature. In our research, higher concentrations were found in the Danube riverbank filtrates than identified by earlier research. This may be partly attributed to the fact that, in the present study, higher concentrations were measured in the Danube as well.

To further refine the interpretation of the results, for the PhACs occurring most frequently in the Danube and in riverbank filtrates, filtration efficiency was calculated in pairs based on the quotient of the given DWAW and the related PhAC concentration in the Danube (the average contamination of the three relevant Danube samples, see Section 2.4). Efficiency was calculated for a given compound at a given time in every DWAW sample, and then the median of the entire dataset was taken. In the cases of LID and CBZ, the ERFS$_{mp}$ ~ ERFS$_{con}$, but the CV values varied. For LTG and TRA, the values of ERFS$_{mp}$ > ERFS$_{con}$, and the CV values were also higher for the former. These results indicate that the filtration efficiency of wells for LID was similar in time and space (the values were not too dispersed). In the cases of the other PhACs, efficiency was rather different for various individual compounds and locations. Although the highest contamination values were measured in wells near the

Table 3
Efficiency of riverbank filtration system (ERFS) (%), and literature values for certain pharmaceutically active compounds (PhACs) in the case of filed investigations of bank filtrates.

PhACs	Detected average concentrations of PhACs in riverbank filtrates (ng L^{-1})			Removal rate in %		
	Current study	Riverbank filtrates along the Danube	Other riverbank filtrates	ERFS$_{con}$ in current study	ERFS$_{fro}$ in current study	ERFS in literature
Carbamazepine	BDL − 176.06	2−57[b] 23−37[c] 24−29[e]	63.6−179[d] 2.89−313[i] 15−21[k] 0−282[l]	27.2	5.6	*65.4*[b] 0−51.8[d] 4−20[e] <10[h],[a] <25[k] 0−44[j] *<50 − 100*[l]
Lidocaine	BDL − 6.10	NA	15[f] BDL − 2.1[k] BDL − 214[i]	94.6	17.8	incomplete[f] 80−95[k]
Tramadol	BDL − 8.98	NA	BDL − 73.7[d] 31[f] 0−281[i] BDL − 15[j] 3.1−8.8[k]	87.9	29.5	3.2−100[d] incomplete[f] 37.5−100[j] 0−30[k] 0−100 [l]
Lamotrigine	BDL − 849.19	NA	BDL − 54[d] 10−48[j]	41.3	40	0−100[d] 0−43[j]

BDL = below detection limit; NA = not available; Italic: redox dependent.
g(Benotti et al., 2012).
[a] (Hamann et al., 2016).
[b] (Kovačević et al., 2017).
[c] (Krakkó et al., 2019).
[d] (Kruć et al., 2019).
[e] (Nagy-Kovács et al., 2018).
[f] (Rúa-Gómez − Püttmann 2012a)
[h] (Laws et al., 2011).
[i] (Bradley et al., 2014).
[j] (Hollender et al., 2018).
[k] (Huntscha et al., 2013).
[l] (Oberleitner et al., 2020).

Danube, the efficiency of riverbank filtration did not show a strong correlation with the distance of the wells from the river (r < 0.04) (Figs. S1−S4). All this suggests that in the case of alluvial porous aquifers, a few hundred meters is not enough distance for complete filtration.

The efficiency of riverbank filtration was also analyzed in terms of the differences between northern and southern water resources of BMR. Although there was a relevant difference between the two areas in terms of sample numbers (n = 68 (N); n = 22 (S)), in the case of CBZ the efficiency of filtration was higher in the south (ERFS$_{con}$ = 39.8%, ERFS$_{mp}$ = 58.5%), than the ERFS$_{con}$ = 4% determined by Nagy-Kovács et al. (2018) on the same water resource, which also refers to the variability of ERFS. In the water resources in the north, ERFS$_{con}$ was 23.6%, and ERFS$_{mp}$ was 28.1, which was similar to the data published before (ERFS$_{con}$ = 20%, Nagy-Kovács et al., 2018).

For compounds penetrating riverbank filtration most frequently, the relationship between the extent of contamination detected in the wells and concentrations measured in the Danube was also studied. It was concluded that there was no linear correlation between the concentrations measured in the two water sources neither in the case of LID nor in the case of TRA, and bank filtration efficiency was not influenced by concentrations measured in the river (Fig. 2). Consequently, the concentration of these compounds occurred entirely randomly in the DWAWs, independent of the contamination levels in the surface water. Thus, it is increasingly difficult to forecast the emergence of these contaminants in drinking water resources.
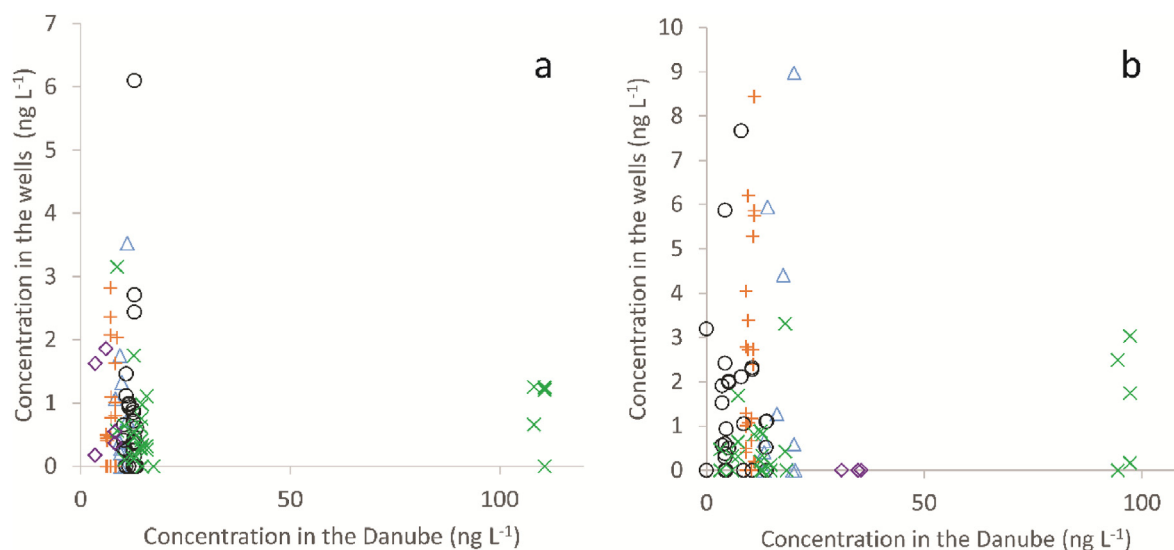
The usually low filtration efficiency corresponding to relatively stable CBZ concentrations in the Danube in one sampling period

was random in a given area. However, it had some correlation with the Danube; higher surface contamination levels were linked to higher DWAW concentrations, although the correlation was not linear (R = 0.4). This tendency was also present in the case of LTG, but it was less pronounced (Fig. 3). The ERFS for both CBZ and LTG was independent of concentrations detected in the river.
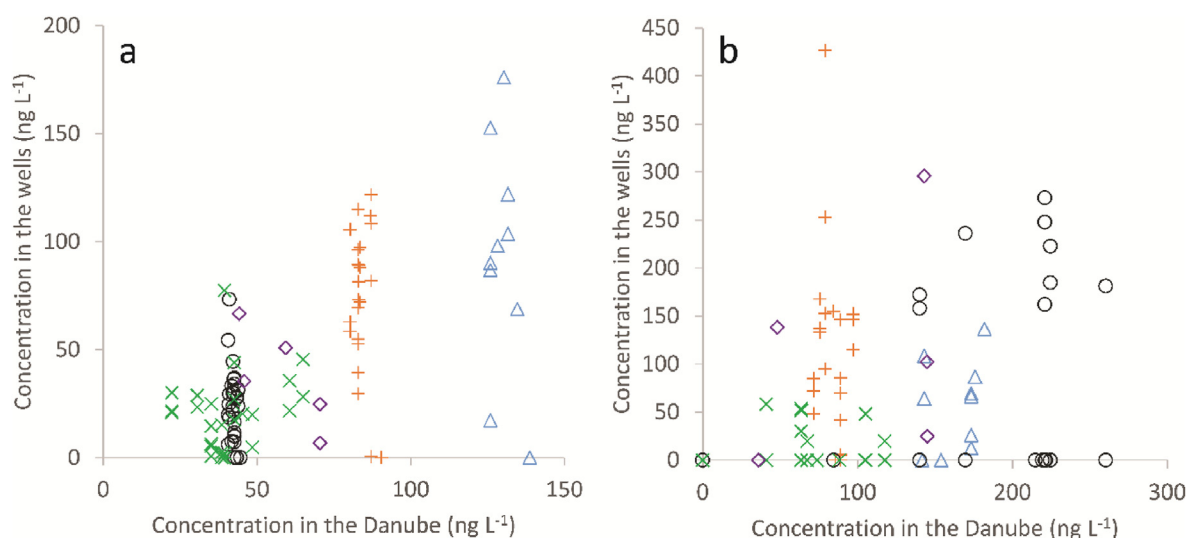
The fate, mobility, and persistence of pharmaceuticals is highly determined by changing local biotic and abiotic environmental factors, such as the pH, temperature, intensity of sunlight, composition of sediments, and microbial activities, which can alter the transformation or adsorption of molecules in natural media (Pal et al., 2010; Li et al., 2014; Patel et al., 2019). The adsorption, however, is the main process controlling the concentration, mobility, toxicity, and the fate of PhACs in the environment and especially in the soil (Yamamoto et al., 2016). The main driver of PhACs sorption in the soils and sediments is rather the soil organic matter (Lambert, 1968) than clay minerals (Szabó et al., 2020). Besides the quantity, the source, the degree of decomposition, spatial dispersion, and the chemical properties of organic matter also affect the adsorption (Cornelissen et al., 2005; Jakab et al., 2018; Ping and Lou, 2019).

CBZ is known to be a persistent and very stable PhAC (Yamamoto et al., 2009; Tixier et al., 2003), which was further confirmed by the findings of the present research. It was detected in high concentrations in the Danube and bank filtrates, indicating low, but sporadically changing filtration efficiency (Table 3). Even though the biotic (microbial) and abiotic (photo-) degradation of TRA is also found to be small (Bergheim and Gieré, 2012), its concentration decreased in the DWAWs. This indicates that not only the biotransformation of a given PhAC is an essential factor in the

Fig. 2. Measured lidocaine (a) and tramadol (b) concentrations in the Danube and the drinking water abstraction wells. Colors refer to the sampling period as follows: blue triangle: 07/03/18; orange cross: 14/05/18; black circle: 10/09/18; green x: 26/11/18; purple diamond: 14/07/17. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 3. Measured carbamazepine (a) and lamotrigine (b) concentrations in the Danube and the drinking water abstraction wells. Colors refer to the sampling period as follows: blue triangle: 07/03/18; orange cross: 14/05/18; black circle: 10/09/18; green x: 26/11/18; purple diamond: 14/07/17. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

evaluation of filtration efficiency, but the adsorption of the molecules is also believed is a principle parameter affecting pharmaceutical mobility in porous media. The organic matter is considered to be the most important component in the adsorption of hydrophobic organic pollutants (Chiou et al., 1979; Li et al., 2014; Bielská et al., 2018). Thus, the small decrease in the concentration of CBZ and LTG indicates that the sediment and rock in which the PhACs passed through likely to have low organic matter content.

It was also documented that mineral surface (Martínez-Hernández et al., 2014) greatly influence the sorption of compounds, especially for the ionized molecules. Therefore, it is crucial to clarify whether the given PhAC is present in an ionized or non-ionized form at a given pH because several pharmaceutical molecules are weak bases or acids (Newton and Kluza, 1978; Raymond and Born, 1986). LID and TRA are present in an ionized form in the natural waters – TRA is used as tramadol-HCl, LID used as

lidocaine-HCl. This means that one hand, it is highly degradable due to its hydrophilicity (Rúa-Gómez and Püttmann, 2012b), and, on the other hand, they can bind to the mineral phases with electrostatic interaction between the particle surface and ionized compounds. Since the sediment surface was predominantly negatively charged, it could bind the positively charged TRA and LID with electrostatic forces or with ligand exchange surface complexation onto Al and/or Fe-oxides/hydroxides of the sediment. It was demonstrated by Martínez-Hernández et al. (2014), who found that the sorption of cationic species onto the sediment was slightly higher than that of anionic species, while the sorption of neutral species was very low.

In addition, ERFS is likely influenced by the operational schedule of high yield DWAWs. For each frequent PhAC, not only spatial differences can be detected; filtration efficiency may vary over time for a given well, regardless of the seasons (Kondor et al., 2020).

4. Conclusions

The present study detected 52 PhACs in the Danube and found that riverbank filtration removes most PhACs independently from the concentration in the river. Consequently, this type of water supply is basically safe for drinking water service. Even though, in the cases of four PhACs (LTG, CBZ, LID, TRA) the ERFS calculated in different ways was rather low. In the Danube, concentrations of the most frequent contaminants were lower in summer than in the winter sampling period, which may reflect on the role of biological decomposition of PhACs. With regard to persistent PhACs, filtration efficiency in water wells with a large extraction capacity is random in terms of space and time, owing to the constantly changing environment and the varying discharge of abstraction wells. Although these factors make forecasts concerning the persistent PhACs entering the drinking water supply and the protection of drinking water resources extremely difficult, the present study reveals new information about anthropogenic stress and helps to determine the level of risks of PhACs along this section of the Danube.

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 results presented in this paper.

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Attila Csaba Kondor: Conceptualization, Writing - original draft, Writing - review & editing, Project administration, Methodology. **Gergely Jakab:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Anna Vancsik:** Data curation. **Tibor Filep:** Writing - original draft. **József Szeberényi:** Visualization. **Lili Szabó:** Data curation. **Gábor Maász:** Resources. **Árpád Ferincz:** Resources. **Péter Dobosy:** Resources. **Zoltán Szalai:** Conceptualization, Methodology.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2020.114893.

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