Science of the Total Environment 922 (2024) 171186

Contents lists available at ScienceDirect

Science of the Total Environment

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

Drought impact on pharmaceuticals in surface waters in Europe: Case study for the Rhine and Elbe basins

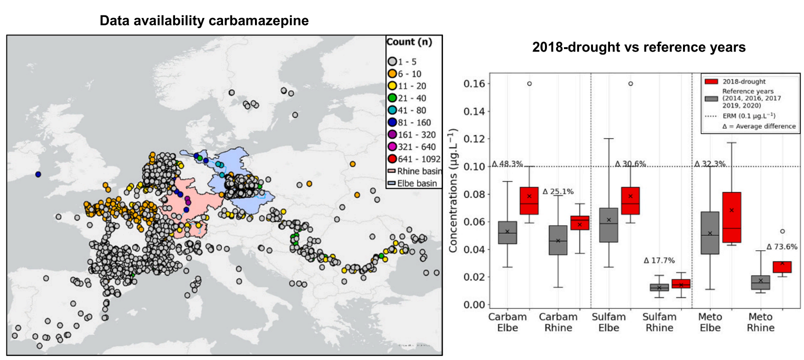
Mark P. Lentz, Duncan J. Graham, Michelle T.H. van Vliet *

Department of Physical Geography, Utrecht University, P.O. Box 80.115, 3508 TC Utrecht, the Netherlands

HIGHLIGHTS

- Spatial patterns of carbamazepine, sulfamethoxazole, diclofenac, metoprolol in European rivers were analyed.
- Impact of 2018-drought on four pharmaceuticals were statistically analysed for Elbe and Rhine rivers.
- Increased concentrations of carbamazepine, sulfamethoxazole and metoprolol were driven by less dilution.
- Decreased diclofenac concentrations were driven by increased decay due to higher water temperature.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Kevin V. Thomas

Keywords:
Water quality
Pharmaceuticals
Droughts
Rivers
Elbe
Rhine
Europe

ABSTRACT

Hydrological droughts are expected to increase in frequency and severity in many regions due to climate change. Over the last two decades, several droughts occurred in Europe, including the 2018-drought, which showed major adverse impacts for nature and different sectoral uses (e.g. irrigation, drinking water). While drought impacts on water quantity are well studied, little understanding exists on the impacts on water quality, particularly regarding pharmaceutical concentrations in surface waters. This study investigates the impact of the 2018-drought on concentrations of four selected pharmaceuticals (carbamazepine, sulfamethoxazole, diclofenac and metoprolol) in surface waters in Europe, with a major focus on the Elbe and Rhine rivers. Monitoring data were analysed for the period of 2010–2020 to estimate the spatiotemporal patterns of pharmaceuticals and assess the concentration responses in rivers during the 2018-drought compared to reference years. Our results indicate an overall deterioration in water quality, which can be attributed to the extremely low flow and higher water temperatures (∼ + 1.5 °C and + 2.0 °C in Elbe and Rhine, respectively) during the 2018-drought. Our results show an increase in the concentrations of carbamazepine, sulfamethoxazole, and metoprolol, but reduced concentrations of diclofenac during the 2018-drought. Significant increases in carbamazepine concentrations (+45 %) were observed at 3/6 monitoring stations in the upstream part of the Elbe, which was mainly attributed to less dilution of chemical loads from wastewater treatment plants under drought conditions. However, reduced diclofenac concentrations could be attributed to increased degradation processes under higher water temperatures ($R^2 = 0.60$). Moreover, the rainfed-dominated Elbe exhibited more severe water quality deterioration than the snowmelt-dominated Rhine river, as the Elbe's reduction in dilution capacity was larger. Our findings

* Corresponding author.
E-mail address: m.t.h.vanvliet@uu.nl (M.T.H. van Vliet).

https://doi.org/10.1016/j.scitotenv.2024.171186
Received 27 June 2023; Received in revised form 20 January 2024; Accepted 20 February 2024
Available online 24 February 2024

highlight the need to account for the impacts of climate change and associated increases in droughts in water quality management plans, to improve the provision of water of good quality for ecosystems and sectoral needs.

1. Introduction

Hydrological droughts are one of the most devastating natural disasters, which have severe impacts on ecological and environmental aspects of the affected region in terms of both water quantity and quality (Ahmadi et al., 2019). Hydrological droughts occur when river flow and water storages in lakes, reservoirs or aquifers fall below normal levels (Prudhomme et al., 2013; Trenberth et al., 2013). Droughts are triggered due to a precipitation shortage and increased evaporation (meteorological drought) and can propagate through the hydrological system, affecting soil moisture (agricultural drought), groundwater, and surface waters (Dai, 2012; van Loon and Van Lanen, 2012). Studies have shown that over the next 50 years, most of the world's major rivers are projected to show large increases in the frequency and severity of hydrological drought conditions due to climate change (Hirabayashi et al., 2008; Mosley, 2015; Prudhomme et al., 2013). The 2018-drought in north-western Europe was one of the most severe droughts this century, with long periods of high temperatures (July–August) in Germany (maximum 39.5 °C) (DWD annual report 2018) and the Netherlands (maximum 38.2 °C) (van der Wiel et al., 2021). This resulted in extreme low flow conditions in the Elbe and Rhine rivers (Buras et al., 2020; Mallast et al., 2020) and significant adverse impacts on various sectors, such as irrigation, drinking water, and energy (Naumann et al., 2021).

Although the effects of recent droughts on water quantity (e.g. discharge and groundwater levels) have been extensively studied, it is important to emphasize that surface water quality can also deteriorate during these extreme events (Wright et al., 2014). Most studies on the impact of streamflow drought on river water quality focused on physical-chemical parameters, such as temperature, salinity (Jones and van Vliet, 2018), nutrients and inorganic micro-pollutants (Mortazavi-Naeini et al., 2019; Mosley, 2015). However, research on the response in pharmaceutical concentrations in rivers during these drought events is scarce (Palma et al., 2020; Sjerps et al., 2017; Wolff and van Vliet, 2021). The presence of pharmaceutical active compounds in surface water (i.e. streams, rivers, lakes, and reservoirs) is a growing concern because most of these substances are difficult to remove through wastewater treatment processes. These processes are not designed to eliminate contaminants of emerging concern from.

wastewater, posing challenges and potential adverse impacts on ecosystems and drinking water quality when concentrations exceed water quality standards for aquatic ecosystem health and drinking water production (Deo, 2014). The high production and extensive use of pharmaceuticals result in the continuous release of these compounds into surface waters (Tang et al., 2021). In the European Union, >3000 different pharmaceuticals from various therapeutic classes are used for human applications (Patel et al., 2019). Furthermore, a comprehensive analysis revealed the detection of over 713 different pharmaceutical active compounds and 127 transformation products in surface waters globally, with concentrations exceeding detection limits. Among these active compounds, 16 (e.g., diclofenac, carbamazepine, and ibuprofen) were identified in surface water, groundwater, and even in purified potable water across all regions of the world (Aus der Beek et al., 2015). The overall concentrations in surface waters are low (range ng.L^{-1} - μg.L^{-1}) and sometimes below the detection limit (limit of detection on average 2 ng.L^{-1}) (Aus der Beek et al., 2015). However, the ecotoxicological effects that these low concentrations can have on the aquatic environment and drinking water potential are of major concern (Sjerps et al., 2017). This is particularly the case for pharmaceuticals that act like conservative substances, which are substances that are highly persistent in the environment and have characteristics that are resistant to biological or biochemical degradation.

The major contributors of pharmaceuticals in surface water are from point sources such as wastewater treatment plants (WWTPs), waste streams from hospitals and sewage treatment plants (STP) (Deo, 2014; Lin et al., 2008; Tang et al., 2021), with households, residential care homes, and healthcare services being the most important sources of pharmaceuticals (Mackuľak and Brandeburová, 2019). WWTPs treat wastewater through a combination of biological, chemical, and physical treatments. However, not all pharmaceuticals are completely removed. Persistent pharmaceuticals in treated wastewater are then discharged into surface waters (Tang et al., 2021). Furthermore, it should be noted that pharmaceutical compounds have the potential to undergo transformation. Various chemical and biological processes can transform the pharmaceuticals and transformation products during wastewater treatment (e.g. hydrolysis, oxidation, de-conjugation, photodegradation) (Rapp-Wright et al., 2023).

Transformation products can have the same toxicity as their parent compound when the active substructure (toxicophore) remains intact with transformation. In some cases, the transformation can generate new toxicophores, potentially leading to increased toxicity in similar doses (e.g. sulfamethoxazole and N4-acetyl-sulfamethoxazole) (de Jongh et al., 2012; Escher and Fenner, 2011). Moreover, transformation compounds can transform back to the parent compound which may increase the pharmaceutical concentrations in the effluent, compared with the concentrations observed in the influent (Rapp-Wright et al., 2023).

Most studies concerning pharmaceuticals have investigated the removal efficiency in WWTPs (e.g. Khasawneh and Palaniandy, 2021), environmental risk assessment regarding the occurrence of pharmaceutical active compounds in the aquatic environment (e.g. Meyer et al., 2016; Zhou et al., 2009) and processes affecting pharmaceutical concentrations such as dilution (e.g. Guzel et al., 2018; Palma et al., 2020), bio-chemical degradation (e.g. Osorio et al., 2012; Zind et al., 2021) and adsorption (e.g. Daneshvar et al., 2010; Petrovic et al., 2011). However, these studies generally neglect the impact of drought on pharmaceutical concentrations. During streamflow droughts, emissions from point sources are less diluted, potentially resulting in increased concentrations of some pharmaceutical compounds in surface waters (Mosley, 2015; Osorio et al., 2012; Wolff and van Vliet, 2021; van Vliet et al., 2023). Additionally, reduced streamflow can lead to longer residence times due to lower flow velocity. The combination of reduced water volumes and higher air temperatures often leads to elevated water temperatures, potentially altering processes like decay of organic matter and respiration (Mosley et al., 2012). However, our understanding of the complex and dynamic behaviour of pharmaceuticals across multiple river basins during these extreme events remains limited. This is partly due to the lack of monitoring data of pharmaceutical concentrations during droughts, although some river basins, such as the river Rhine and Elbe in Europe, show potential based on their data availability for studying these impacts.

This study therefore aims to analyse the impacts of the 2018-drought on concentrations of four selected pharmaceuticals in the Rhine and Elbe rivers in Europe. Here, we focus on four pharmaceuticals belonging to four therapeutic classes: anti-epileptics (carbamazepine), antibiotics (sulfamethoxazole), β-blockers (metoprolol), all of which are conservative substances, and the anti-inflammatory (diclofenac), which is a labile substance, to capture a range of concentration responses during droughts. The first part of this study focuses on the analyses of the spatiotemporal patterns of the selected pharmaceuticals by evaluating publicly available water quality monitoring data for major river basins in Europe spanning the period of 2010–2020. Additionally, the second part of the study aims to assess the impact of the 2018-drought on the selected pharmaceuticals for the Rhine and Elbe rivers, and to quantify the influence of two external factors (i.e. river flow changes and water temperature) on the responses in pharmaceutical concentrations during this extreme event. Here we statistically analysed the responses based on high-frequency monitoring data obtained from 12 monitoring stations located in the German part of the Rhine and Elbe rivers for 2010–2020. This is achieved by comparing the pharmaceutical concentrations during the 2018-drought to concentrations under normal hydrological conditions (reference years 2014–2020) with similar levels of pharmaceutical contamination.

2. Methods

2.1. Data collection

Five different databases on European and river basin levels were used to obtain monitoring data of pharmaceuticals concentrations (Table 1). Data requirements were set to determine suitable river basins for this study. Monitoring stations had to have at least monthly measurements of pharmaceutical concentrations over multiple years. Both databases per river basin (e.g. Elbe, Rhine and Danube) and on the country level were considered. Each database has a different time period and frequency of pharmaceutical concentration measurements. Despite these variations, all databases provide instantaneous measurements of pharmaceutical concentrations (in μg.L^{-1}) (Table 1). Moreover, data presented in published articles or reports were not used in this study, as high temporal pharmaceutical monitoring series were required to compare the 2018-drought with reference years.

The analysis focuses on four pharmaceuticals: carbamazepine, sulfamethoxazole, diclofenac, and metoprolol. This selection of pharmaceuticals is based on the following criteria: availability of concentration data on at least a monthly level, characteristics of pharmaceuticals including both conservative (i.e. carbamazepine, sulfamethoxazole, and metoprolol) and labile (i.e. diclofenac) substances, previous detection (Filipe et al., 2017; Kovalakova et al., 2020; Sathishkumar et al., 2020; Yuan et al., 2019), ecotoxicological relevance such as antibiotics (e.g. sulfamethoxazole) (Kovalakova et al., 2020) and anti-epileptics (e.g. carbamazepine) (Oropesa et al., 2016), and their classification as contaminants of emerging concern (see Supplementary Table S1, which shows the predicted no-effect concentrations 'PNEC' value). Carbamazepine, sulfamethoxazole, and metoprolol are pharmaceuticals that exhibit low removal rates in wastewater treatment processes (Palma et al., 2020). Additionally, degradation rates, sorption capacities, and biotransformation capabilities are also low for these selected pharmaceuticals except for diclofenac (Mandaric et al., 2019; Palma et al., 2020; Yuan et al., 2019). This leads to the accumulation and persistence of these pharmaceutical compounds in the environment. Spatial patterns of the data availability for each pharmaceutical compound over the 2000–2020 period (Fig. 1) show that a large number of concentration measurements are available for multiple major river basins (e.g. Rhine, Elbe, Danube, Meuse, and Seine). However, drought impact analyses were only feasible for the Rhine and Elbe rivers, as these were the only river basins with a sufficient amount of pharmaceutical concentration data. Statistical analyses of the responses in pharmaceutical concentrations under drought were therefore focused on the Rhine and Elbe basins.

2.2. Study area

The Elbe and Rhine are two major rivers located in Central and Western Europe (Fig. 1b). The Elbe river rises high in the "Riesengebirge" (Giant Mountains) in the Czech Republic and enters the North Sea near Cuxhaven in Germany (Wiegel et al., 2004). The Elbe flows over a distance of 1090 km with a drainage basin of 148,268 km^2, of which two-thirds (~100,000 km^2) is located in Germany and one-third is in the Czech Republic (Huang, 2012). The Rhine river rises in the Swiss Alps and enters the North Sea in the Rhine-Meuse Delta near Rotterdam with an approximate length of 1230 km (Leuven et al., 2009). The drainage basin has an area of approximately 185,000 km^2, with roughly two-thirds (120,000 km^2) in Germany and covering a large portion of Switzerland and the Netherlands as well as parts of France, Luxemburg, and Belgium (van der Weijden and Middelburg, 1989). The climate of the Elbe basin can be described as humid and temperate, while the Rhine basin has a temperate and marine climate. There is an annual precipitation of 592 and 700 mm and an average temperature of 9.0 °C and 10.0 °C for the Elbe and Rhine, respectively (Pfeiffer and Ionita, 2017). The headwaters of the Elbe and the largest tributary in the Czech Republic (Vltava) have a snowmelt-dominated regime, while the largest tributary in Germany (Saale) has a rain-dominated regime. Other major tributaries include the Mulde and Schwarze Elster (Wiegel et al., 2004). From May until November most of the discharge of the Rhine is meltwater originating from the Swiss part of the river catchment. From December till May the river is, however, rainfall dominated as most of the precipitation in the Alps is retained as snow. The major tributaries are the Main and Mosel (Uehlinger et al., 2009).

Table 1
Pharmaceutical, discharge and water temperature databases used for this research, with corresponding links, time periods and frequency of measurements.

Database	Links	Time period	Frequency
Pharmaceuticals			
Norman Empodat database	https://www.norman-network.com/nds/empodat/chemicalSearch.php?s	2000–2020	Irregular timesteps
Elbe-data portal (Fis Fgg Elbe)	https://www.elbe-datenportal.de/FisFggElbe/content/start/BesucherUnbekannt.action	2008-2020	Monthly/bi-weekly/weekly
Danubis ICPDR database	http://www.icpdr.org/wq-db/home	2003-2019	Every 6 years
EEA: waterbase	https://www.eea.europa.eu/data-and-maps/data/waterbase-water-quality-icm-2	2000-2020	Monthly/yearly
IPCR – IKSR database	https://iksr.bafg.de/iksr/dl_auswahl.asp?S=3&JA=2019	2008-2019	Monthly/bi-weekly
Discharge and water temperature			
Elbe-data portal (Fis Fgg Elbe)	https://www.elbe-datenportal.de/FisFggElbe/content/start/BesucherUnbekannt.action	2008-2020	Daily
Service-portal Hamburg	https://serviceportal.hamburg.de/HamburgGateway/FVP/FV/BSU/wasserguete/wfWasserguete AnfrageKarte.aspx?sid=37#	2008–2020	Daily
Umwelt Sachsen	https://www.wasser.sachsen.de/daten-und-berichte-archiv-9541.html	2008-2020	Daily
Federal Institude of hydrology	https://www.bafg.de/EN/06_Info_Service/02_WaterQuality/waterQuality	2008-2020	Daily
IPCR – IKSR database	https://iksr.bafg.de/iksr/dl_auswahl.asp?S=3&JA=2019	2008-2019	Bi-weekly
Rijkswaterstaat water data	https://www.rijkswaterstaat.nl/water/waterdata-en-waterberichtgeving/waterdata	2008-2019	Daily

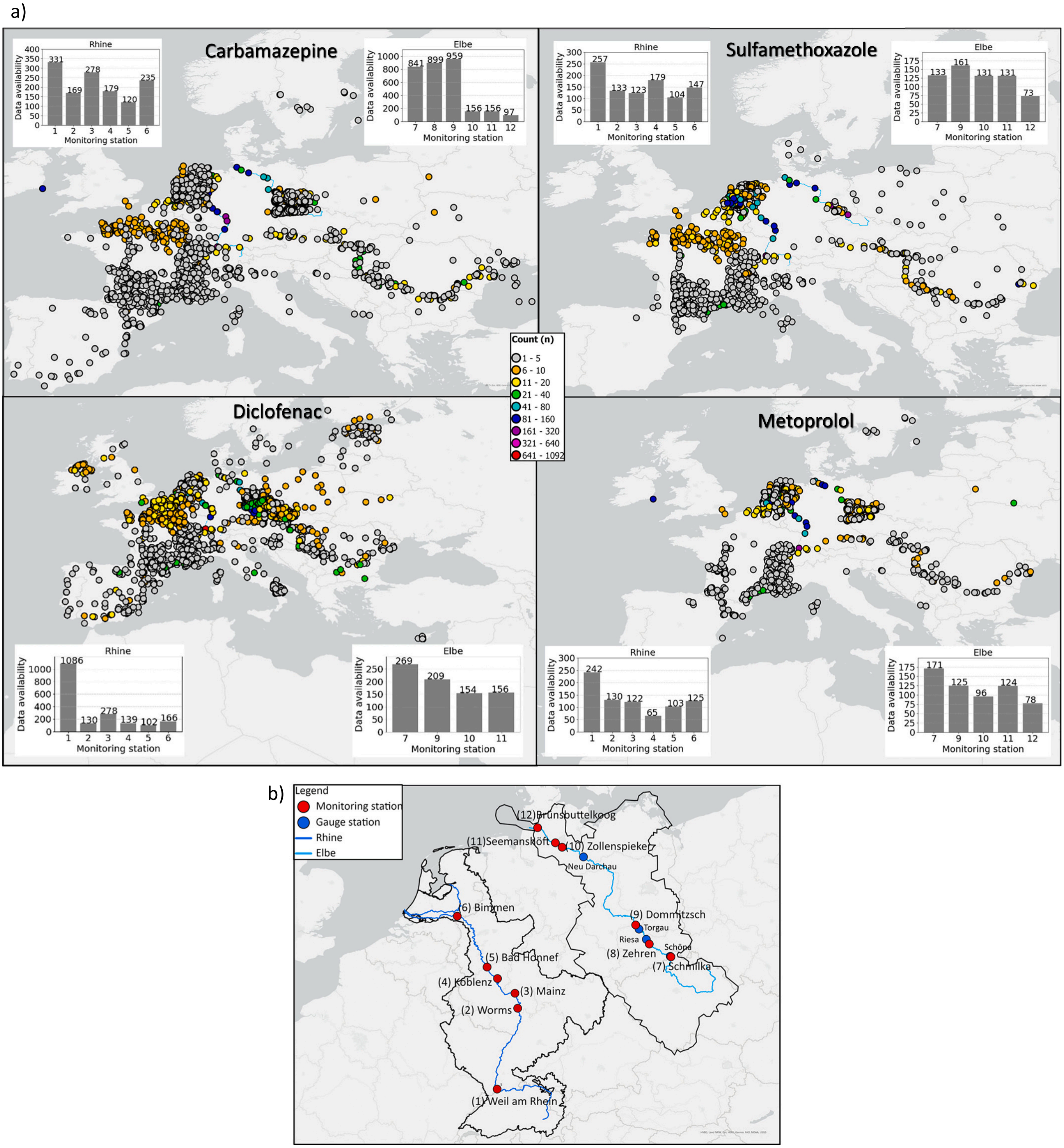


Fig. 1. (a) Map of all publicly available monitoring stations and the number of measurements for carbamazepine (top left), sulfamethoxazole (top right), diclofenac (bottom left) and metoprolol (bottom right) for the period 2000–2020. Bar-charts show the data availability of the monitoring stations alongside the Elbe and Rhine river, the numbers correspond with the location in panel (b). (b) River catchment of the Rhine and Elbe, with the location of the monitoring stations (red dots) Weil am Rhein, Worms, Mains, Koblenz, Bad Honnef and Bimmen (Rhine) and Schmilka, Zehren, Dommitzsch, Seemanshöft, Zollenspieker and Brünsbuttelkoog (Elbe). Blue dots represent the discharge stations closest to the water quality monitoring stations.

2.3. *Drought identification*

The 2018-drought was characterized by long periods of extreme low flow conditions in Germany and the Netherlands and high temperatures (July–August), resulting in a compound drought-heatwave event (van der Wiel et al., 2021). It was one of the hottest years recorded in Germany since the beginning of the weather recordings in 1881 (Mallast et al., 2020). The number of summer days in 2018 was 74 days (air temperature > 25 °C), with remarkably high temperatures (> 30 °C) during the period from the end.

Of July to mid-August (DWD annual report 2018, accessed 2023). Furthermore, next to the high temperatures, there was a precipitation deficit with an average of 250 mm between June–December in the Elbe and Rhine basins (van der Wiel et al., 2021), resulting in all time low water levels recorded in the Elbe river (Mallast et al., 2020). Consequently, due to the combination of high air temperatures and a severe precipitation deficit, the June–October months can be seen as the most extreme period of the 2018-drought, with a mean recurrence time of approximately 30 years (Sluijter et al., 2018).

Streamflow droughts can be defined considering both the magnitude and timing of low river discharges or by when the discharge is below a given threshold (Laaha et al., 2017). For this study, the constant threshold method is used and is defined based on when the daily discharge is lower than the 20-percentile (van Loon and van Lanen, 2012; Laaha et al., 2017). The threshold is calculated per monitoring station over the period 2012–2020 and 2011–2019 for the rivers Elbe and Rhine, respectively. Daily discharge ($m^3.s^{-1}$) and water temperature data were obtained at each of the selected monitoring sites from multiple databases (Table 1). To compare the 2018-drought with average (non-extreme) hydrological regimes, four reference years were selected as they overall represent common hydrological conditions and similar pharmaceutical concentrations. The 2018-drought began in the first week of June and continued until the end of autumn. Therefore, this research will focus on the June–October period for the 2018-drought and compare it to the June–October period of the reference years. For the Elbe, the reference years are 2014, 2016, 2017 and 2020 and for the Rhine the reference years are 2014, 2016, 2017 and 2019. The year 2015 for both rivers and 2019 for the Elbe river were excluded as references as those were also relatively dry years (Supplementary Table S2). The median and average discharges and the total amount of days that the discharge is below the 20-percentile threshold were compared between the drought period (June–October of 2018) and the corresponding period of the reference years. Furthermore, the median water temperatures of the 2018-drought were compared to the individual reference years for the period June–August.

2.4. Monitoring stations in the Rhine and Elbe

The study area contains the German part of the river catchments. Five sites for the Elbe and six sites for the Rhine river were identified as having suitable data availability (i.e. at least monthly measurements) for this study (Fig. 1, Supplementary Table S3). Pharmaceutical data for both rivers are investigated at the following monitoring stations: Schmilka, right bank (km 3.9 from Czech border), Dommitzsch, left bank (km 172.6), Zollenspieker (km 598.7), Seemanshöft (km 628.9) and Brunsbüttelkoog (km 694.0) along the Elbe. For the Rhine we focussed on the monitoring stations Weil am Rhein (km 165.0 from Lake Constance at the Swiss-German border), Worms (km 443.0), Mainz (km 498.0), Koblenz/Rhine (km 590.0), Bad Honnef (km 632.0) and Bimmen (km 858.0 at the Dutch-German border) (Fig. 1b). Most stations have monthly measurements of pharmaceutical concentration data available from 2010 onwards (see Supplementary Table S3). One additional monitoring station alongside the Elbe (Zehren, left bank 89.6 km) is used, although this station only has data available for carbamazepine (weekly level).

Daily mean discharge ($m^3.s^{-1}$) and water temperature (°C) data were obtained at each of the selected monitoring sites (Table 1 and Supplementary Table S3). However, only four sites (Schmilka, Zehren, Dommitzsch and Zollenspieker) out of the six sites from the Elbe where adequate pharmaceutical data was available had an appropriate availability of discharge measurements for analysis. Since discharge is not directly measured at all water quality monitoring stations, we utilize discharge measurements from nearby discharge stations (blue dots in Fig. 1b). These discharge stations are located in Schmilka (Schöna), Zehren (Riesa), Dommitzsch (Torgau), and Zollenspieker (Neu Darchau), respectively. All discharge stations are in a range of 50 km upstream or downstream from the monitoring stations (as this is the range of a medium river basin where the discharge is still representative). Additionally, daily mean discharge ($m^3.s^{-1}$) and water temperature (°C) data for the Rhine are directly measured at all six selected water quality stations.

For all stations along the Elbe the pharmaceutical concentrations are measured monthly, except for carbamazepine at Schmilka, Zehren and Dommitzsch where the concentrations are measured on a weekly basis. For the stations Weil am Rhein, Worms and Mainz along the Rhine pharmaceuticals are measured bi-weekly, while for Koblenz, Bad Honnef and Bimmen the pharmaceutical data is measured at a monthly timestep. Not all reference years are available for some pharmaceuticals and monitoring stations. Therefore, the stations where more than two reference years are missing have been excluded from the analysis (Supplementary Table S3).

2.5. Analyses of drought impact on pharmaceuticals

The spatial patterns of the four pharmaceuticals are analysed for all the available monitoring stations in Europe with available data for the 2018-drought. The study period 2010–2020 was selected to estimate the overall average pharmaceutical concentrations. Moreover, as the drought study focusses on the Elbe and Rhine rivers, the temporal patterns within these river basin areas were analysed in greater detail.

The pharmaceutical data for the June–October period during the 2018-drought were compared to the selected reference years (i.e. 2014, 2016, 2017, and 2020 for the Elbe and of 2014, 2016, 2017, and 2019 for the Rhine). For the analysis, samples with pharmaceutical concentrations below the limit of detection (LOD) or quantitation (LOQ) were replaced by values equal to half the individual detection limit (Mandaric et al., 2019; Sjerps et al., 2017; Wolff and van Vliet, 2021). To test whether pharmaceutical concentrations during the 2018-drought deviated significantly from the reference periods, descriptive statistics (e.g. mean, median, standard deviation) were used. The Mann-Whitney *U* test and unpaired *t*-test were performed to assess whether differences in pharmaceutical concentrations were statistically significant with a 95 % confidence level (Jones and van Vliet, 2018; Pereira et al., 2017; Wolff and van Vliet, 2021). In the case of a non-normal distribution ($p < 0.05$) (tested by the Shapiro-Wilk test (Mandaric et al., 2019; Wolff and van Vliet, 2021)), the correlation between the variables can be quantified using the Mann-Whitney U test. Otherwise, if the data are normally distributed ($p > 0.05$), an unpaired t-test can be performed. Furthermore, considering both the ecotoxicological and drinking water quality perspectives, it is unwanted to exceed the target concentrations for pharmaceuticals and water temperature outlined in the European River Memorandum (ERM) by the Internationale Arbeitsgemeinschaft der Wasserwerke im Rheineinzugsgebiet (IAWR) et al. (2020). The ERM represents a collective agreement among 170 European drinking water companies operating within major European river basins (i.e. Rhine, Elbe, Danube, Meuse, etc) to establish minimum quality criteria for river water. It is important to note that surpassing the ERM target value does not carry legal consequences. However, these targets are set with high standards in line with precautionary and sustainability principles. Additionally, they take into consideration the effectiveness of natural treatment methods. Maintaining the composition of river water below these ERM target values enables the utilization of natural purification methods for drinking water preparation (IAWR et al., 2020). Consequently, the ERM target values, which are set at 0.1 μg.L^{-1} for all four pharmaceuticals and 25 °C for water temperature, were used as basis to evaluate the impact of the 2018-drought by looking at the magnitude, frequency, and duration of the exceedance of this ERM target value.

Finally, relationships between the measured pharmaceutical concentrations and the corresponding measurements of river discharge and water temperature were established. This was done for the 2018-drought (January–December) and the corresponding reference years for each river basin. The conservative nature of some pharmaceuticals, such as carbamazepine, suggests that their concentrations in surface water can be described as a simple function of both river discharge and emission load (Sjerps et al., 2017). Considering the relatively stable nature of point source emissions (i.e., background concentration and emission load) for the pharmaceuticals within the limited time period analysed in this study, changes in discharge are expected to mainly influence the concentration responses by affecting chemical dilution. The effects of variability in discharge on water quality is estimated by fitting an empirical relation between pharmaceutical concentrations and discharge based on van der Weijden and Middelburg (1989) (see Supplementary Eq. 1). However, the concentration of pharmaceuticals in surface waters is influenced by various processes, including degradation, transformation, and sorption, which are all temperature sensitive. Therefore, the dependency between the pharmaceutical concentrations and water temperature was also assessed using multiple linear regression analyses. The goodness of fit for both relationships is described by the squared correlation coefficient (R^2), which specifies the proportion of variability in pharmaceutical concentration that can be accounted for by changes in either discharge or temperature. The classification used to determine the strength of the relationship can be found in Supplementary Table S10.

3. Results

3.1. Hydro-meteorological drought conditions

Two discharge stations, one downstream and one further upstream within the study area of the Elbe river (Schmilka-Schöna and Zollenspieker-Neu Darchau) and Rhine river (Koblenz and Bimmen), were selected to illustrate the impact of the 2018-drought on river discharge compared to the reference years (2014–2020). The results indicate that the June–October period of 2015 was also characterized by low flow conditions in the Elbe and Rhine basins (Fig. 2), with notably low median discharges at all four monitoring stations (see Supplementary Table S2). The 2015-drought was not as extreme as the 2018-drought, however, it is not appropriate to consider these data from 2015 as reference years since they do not represent typical hydrological conditions. The median and average discharge values at all four stations were significantly lower ($p < 0.05$) during the 2018-drought compared to the reference years (Supplementary Table S2). At Schmilka, for example, the median discharge was 93.4 $m^3.s^{-1}$ during the 2018-drought whereas during the reference periods the median discharge values were: 173 $m^3.s^{-1}$ (2014), 166 $m^3.s^{-1}$ (2016), 121 $m^3.s^{-1}$ (2017) and 186 $m^3.s^{-1}$ (2020) (Fig. 2a, Supplementary Table S2). For the Rhine near Koblenz, there was a median discharge of 808 $m^3.s^{-1}$, compared to the reference periods: 1580 $m^3.s^{-1}$ (2014), 1530 $m^3.s^{-1}$ (2016), 1280 $m^3.s^{-1}$ (2017) and 1380 $m^3.s^{-1}$ (2019) (Fig. 2c, Supplementary Table S2). Moreover, during the 2018-drought, the discharge at Koblenz (Rhine) was lower than the 20th percentile threshold for 114 days, compared to 6 days, 39 days, 18 days, and 21 days for the same period (Jun-Oct) of the reference years. Furthermore, at Schmilka (Elbe), the discharge was lower than the 20th percentile discharge for 139 days compared to 22 days, 41 days, 78 days, and 20 days for the reference years, respectively (Supplementary Table S2). Similar results were found downstream for both rivers at the discharge station Zollenspieker-Neu Darchau (Elbe) and Bimmen (Rhine) (Fig. 2b and d) (Supplementary Table S2). In mid- June 2018 the discharge started to decline and stayed below the 20-percentile threshold until late November and early

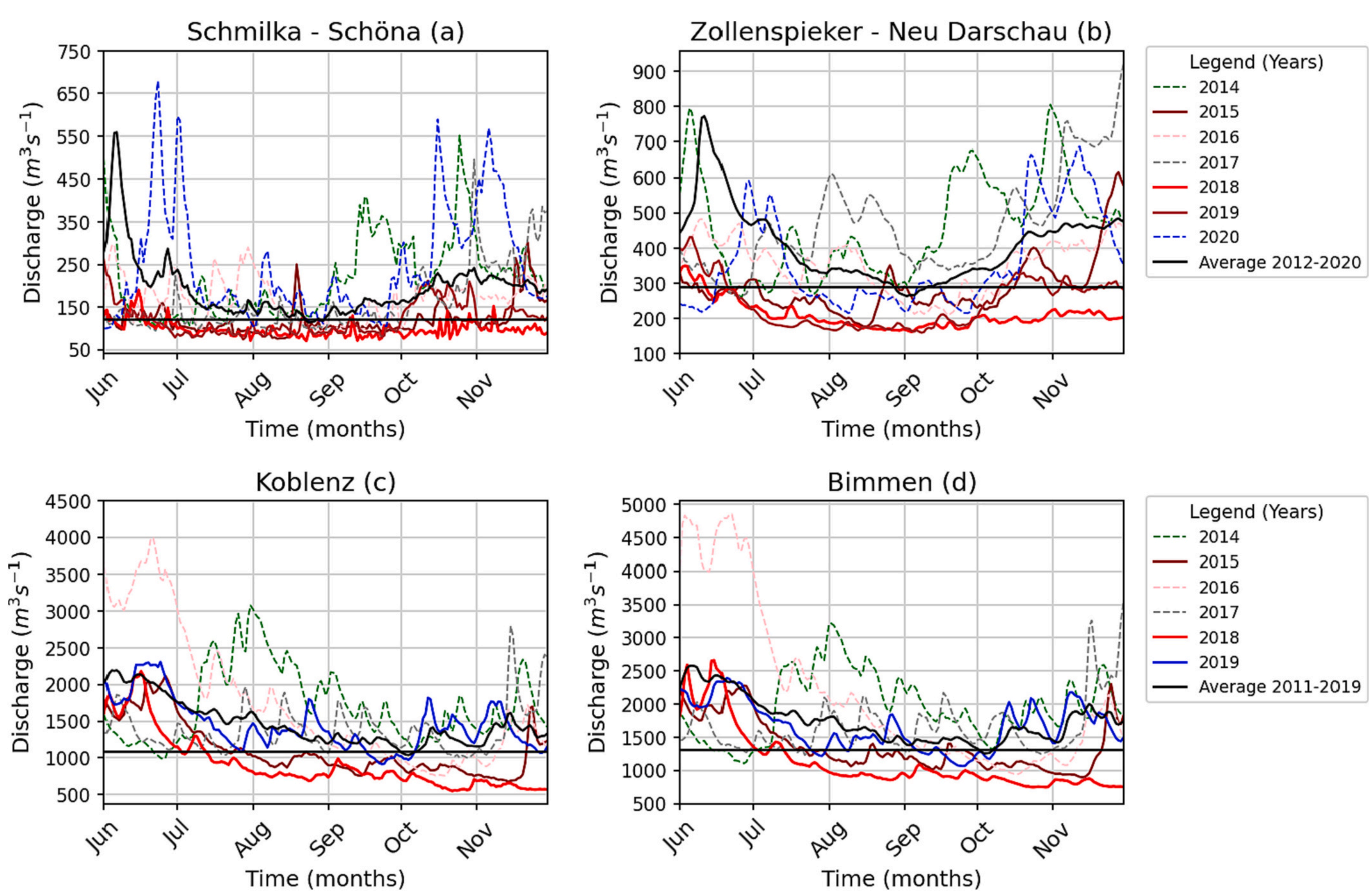


Fig. 2. Discharge at discharge stations Schmilka-Schöna (a) and Zollenspieker-Neu Darchau (b) along the Elbe and Koblenz (c) and Bimmen (d) along the Rhine during the drought of 2018 and reference years and the average discharge of the period 2012–2020 (Elbe) and 2011–2019 (Rhine). The horizontal thresholds represent the 20-percentile line calculated per monitoring station. Furthermore, the drought of 2015 and 2019 for the Elbe and 2015 for the Rhine are included to compare with the 2018-drought.

December for the Rhine and Elbe, respectively.

During the 2018-drought, water temperatures in the period June–August were increased compared to the reference periods for both the Elbe and Rhine rivers (Fig. 3a-d). The median water temperatures in this period during the 2018-drought were 22.7 °C and 22.4 °C (Fig. 3a-b) at the stations Schmilka and Zollenspieker (Elbe), respectively. Water temperatures were on average + 1.9 °C and + 1.2 °C warmer than the reference periods (June–August). Furthermore, the ERM target value of 25 °C was exceeded 13 out of 92 (Schmilka) and 15 out of 92 (Zollenspieker) times during this drought. This exceedance occurred during one consecutive period starting from July 19th until August 10th and July 26th until August 9th, with maximum temperatures of 26.7 °C and 26.6 °C at Schmilka and Zollenspieker, respectively. For the Rhine the water temperatures were even higher than the Elbe for the period June–August. The ERM target value of 25 °C was exceeded 34 out of 92 (Koblenz) and 16 out of 92 (Bimmen) times. The longest period of exceedance occurred between July 15th and August 11th (total of 28 days) at Koblenz (maximum water temperature of 28 °C) and July 24th until August 8th at Bimmen (maximum water temperature of 26.6 °C).

3.2. Analyses of drought impact on pharmaceuticals

3.2.1. Spatiotemporal patterns

The spatial distributions of carbamazepine, sulfamethoxazole, diclofenac and metoprolol in surface waters of several European river basins are shown in Fig. 4. The majority of the 211 monitoring stations for carbamazepine and 82 monitoring stations for sulfamethoxazole are located in the river basins of the Elbe, Rhine, and Meuse, spanning across Germany, France, Belgium, and the Netherlands. Among these stations, 25 for carbamazepine and 12 for sulfamethoxazole concentrations exceeded the ERM target value of 0.1 μg.L^{-1}. Moreover, for 83 out of 334 monitoring stations for diclofenac and 18 out of 126 monitoring stations for metoprolol the average concentrations surpassed the ERM target value of 0.1 μg.L^{-1}. Based upon the data availability for the 2018-drought and reference years, the next part of the analysis focuses on the Elbe and Rhine rivers and the monitoring stations in the German part of the river basins.

The spatial patterns of carbamazepine and sulfamethoxazole in the Elbe and Rhine rivers are generally similar. Analysis of monitoring data indicates an increase in average concentrations moving downstream (Fig. 4, see Fig. 1 for location monitoring stations), except for sulfamethoxazole, for which an opposite spatial distribution can be observed in the Elbe basin (see Supplementary Table S4). Specifically, the lowest average concentrations of carbamazepine are measured at the monitoring station Schmilka (0.048 μg.L^{-1}) (Fig. 4) with concentrations increasing until Seemanshöft (0.091 μg.L^{-1}). After Seemanshöft, concentrations decrease, with an average concentration of 0.072 μg.L^{-1} at Brunsbüttelkoog (Supplementary Table S4). Similarly, carbamazepine exhibits comparable patterns in the Rhine river, with low average concentration at Weil am Rhein (0.021 μg.L^{-1}) and high average concentrations at Bimmen (0.052 μg.L^{-1}) (see Supplementary Table S4). When looking more closely at the Elbe and Rhine rivers, the spatial patterns

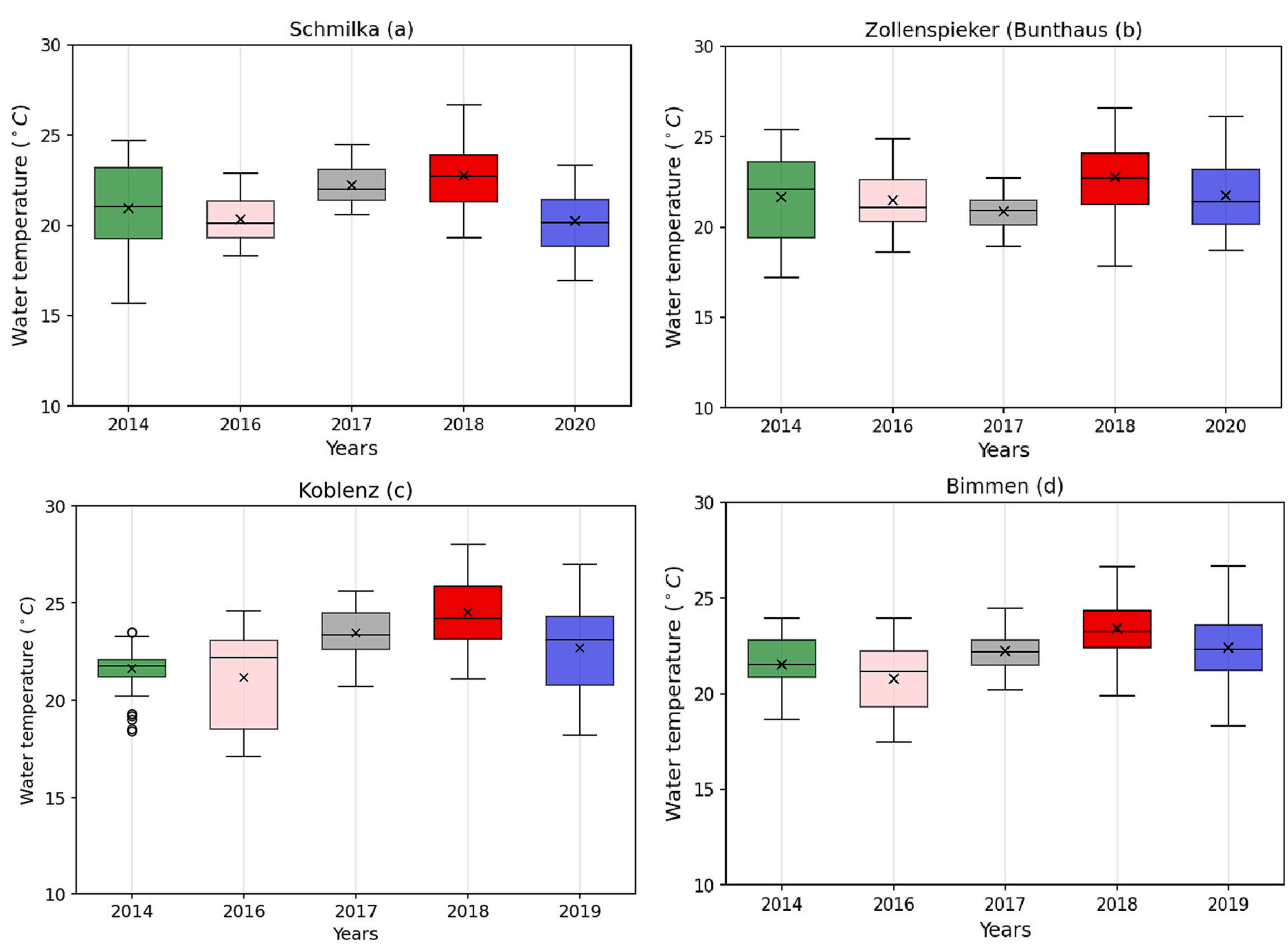


Fig. 3. Boxplots summarizing the distribution in water temperature for the June–August period for a selection of monitoring stations which are most illustrative for the Elbe and Rhine rivers for the 2018-drought and reference years. Two monitoring stations alongside the Elbe, Schmilka (a) and Zollenspieker-Bundshaus (b) and the two monitoring stations alongside the Rhine, Koblenz (c) and Bimmen (d) are presented. The colours of the boxplots align with the respective years highlighted in Fig. 2.

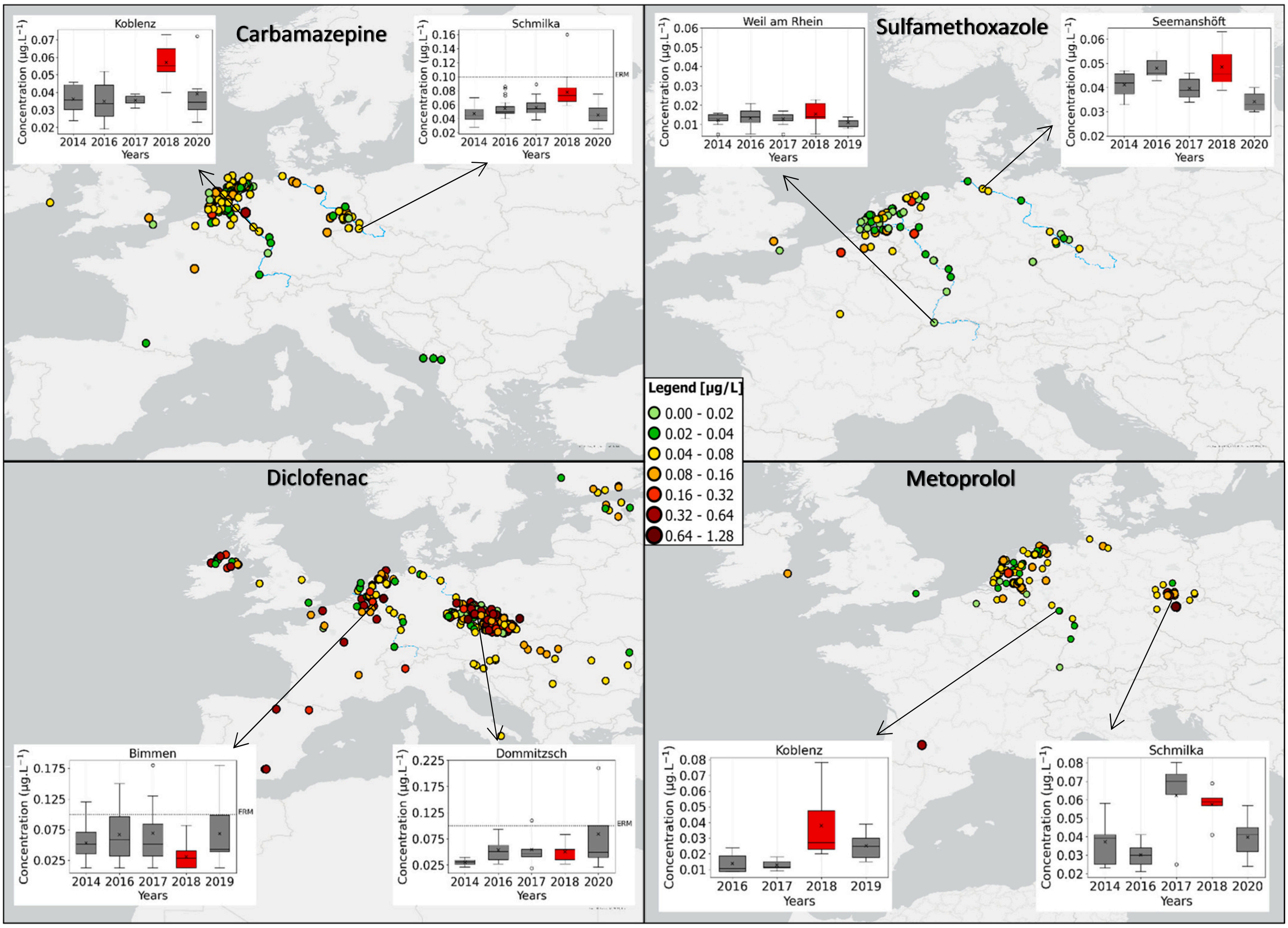


Fig. 4. Spatial patterns of the average concentrations of carbamazepine (top left), sulfamethoxazole (top right), diclofenac (bottom left) and metoprolol (bottom right) in (μg.L^{-1}) for the period 2010–2020. Monitoring stations where the concentrations are above the ERM target value (0.1 μg.L^{-1}) are larger. The boxplots display the monitoring stations which show the most illustrative results per pharmaceutical for the Elbe and Rhine rivers for the 2018-drought and reference years.

show a dynamic system, with both increasing and decreasing average concentrations between monitoring stations for both diclofenac and metoprolol (Fig. 4, Supplementary Table S4).

The analysis indicates substantial fluctuations in pharmaceutical concentrations throughout the year, except for sulfamethoxazole, where overall consistent concentrations are observed throughout the years (Fig. 5c-d). The seasonal variation in pharmaceutical concentrations for both rivers show similar trends, with notably higher concentrations observed in autumn (October–December) and lower concentrations in winter months (January–March) for carbamazepine. These patterns were observed upstream as well as downstream the Elbe river (Fig. 5a-d, Supplementary Figs. S1-S4). However, maximum concentrations for carbamazepine at upstream monitoring stations were found between August and October. For the Rhine river, similar seasonal patterns are observed for carbamazepine (Fig. 5a-d, Supplementary Figs. S1-S4), except at the monitoring station Weil am Rhein, with minimum concentrations in the spring (April and June) during the melt season and increased concentrations in the winter period (January–March), when most precipitation is retained as snow and discharge is low.

For diclofenac and metoprolol, different seasonal patterns were observed, with increased concentrations in winter and autumn and decreased concentrations in spring and summer (Fig. 5e-h, Supplementary data Figs. S5-S8). Minimal differences in median concentrations between the four seasons were observed at upstream monitoring stations Schmilka and Weil am Rhein for both diclofenac and metoprolol. However, downstream of both rivers, the seasonal variation for both pharmaceuticals were more prominent. The highest concentrations for diclofenac and metoprolol were measured between January and March, with median values of 0.095 μg.L^{-1} and 0.119 μg.L^{-1} at Seemanshöft, respectively. At Bimmen, the highest maximum and median concentrations for both pharmaceuticals were measured between January–March, with median values of 0.077 μg.L^{-1} and 0.076 μg.L^{-1} for diclofenac and metoprolol, respectively.

3.2.2. Pharmaceutical concentrations under drought

The responses in carbamazepine, sulfamethoxazole, diclofenac and metoprolol concentrations were studied during the 2018-drought relative to the reference periods (June–October). Overall, increased concentrations were found for carbamazepine, sulfamethoxazole and metoprolol during the summer and fall of 2018 (Fig. 4 and Fig. 5). Increased carbamazepine concentrations were observed at almost all monitoring stations for both the Elbe and Rhine rivers. The Mann-Whitney U test showed for 3 out of 6 stations in the river Elbe (i.e. Schmilka, Dommitzsch and Zehren) statistically significant increases ($p < 0.05$) during the 2018-drought compared to the reference years (Fig. 5, Supplementary Fig. S1 and Table S6). Average concentration increases of +48 % (stdev 13.7 %), +41 % (stdev 19.1 %) and +47 % (stdev 25.3 %) were found for the monitoring stations Schmilka, Zehren and Dommitzsch, respectively, compared to the reference years. Likewise, most monitoring stations of the Rhine showed increased

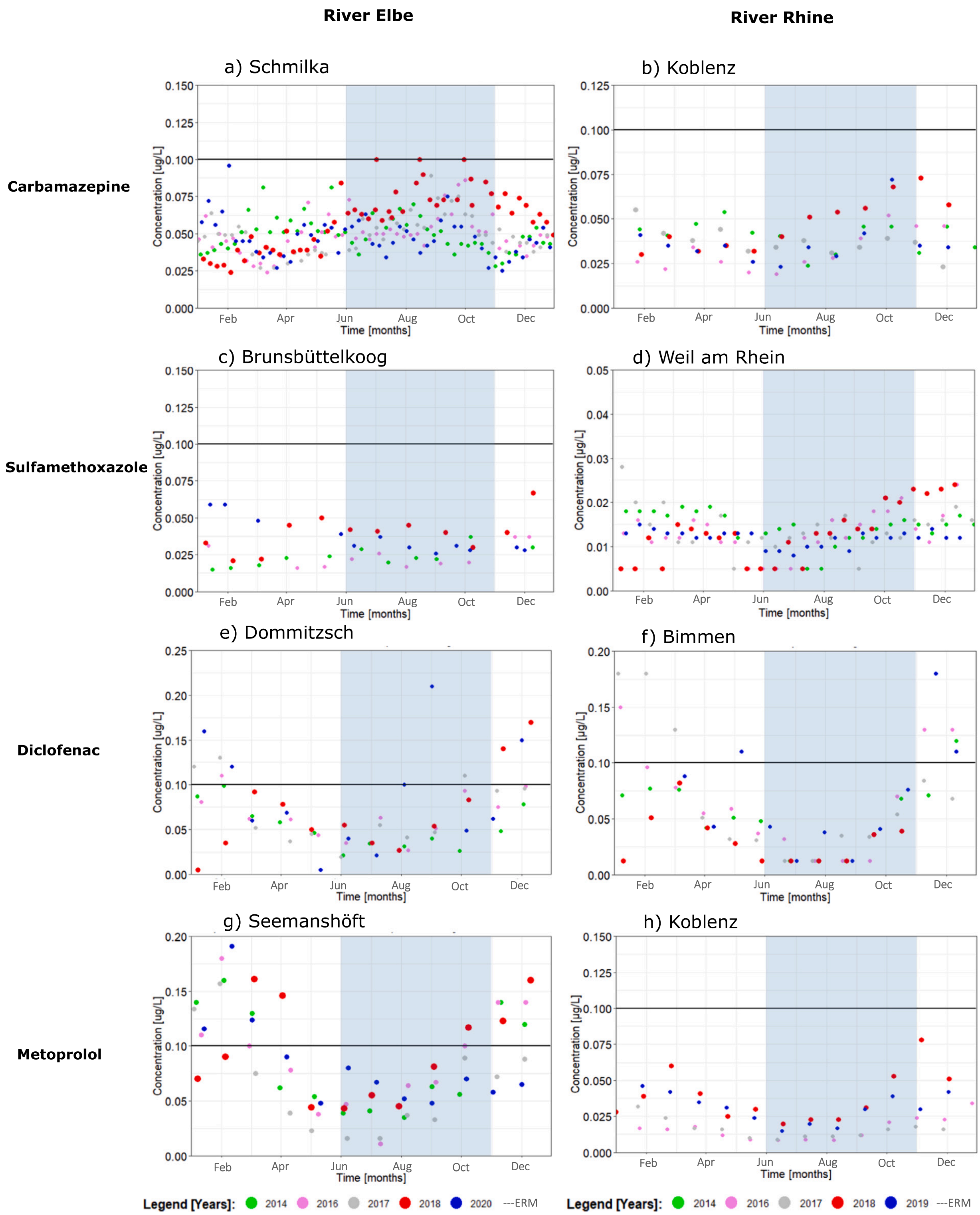


Fig. 5. Concentrations of carbamazepine (a-b), sulfamethoxazole (c-d), diclofenac (e-f) and metoprolol (g-h) for a selection of monitoring stations which are most illustrative for the Elbe and Rhine rivers during the drought of 2018 and the reference period. (The figures for the other monitoring stations are shown in the Supplementary data Fig. S3-S8). Blue shade represents the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 μg.L^{-1} (note the different values on the y-axis).

concentrations during the drought period compared to the reference years with statistically significant increases ($p < 0.05$) at Koblenz (+57 %) (Fig. 4, Fig. 5 and Supplementary Table S6). Furthermore, for the remaining monitoring stations statistically insignificant ($p > 0.05$) increases were observed although average concentration increases were considerable (e.g. +21 % Mainz and +23 % Bimmen) with respect to carbamazepine (Supplementary Table S6).

The sulfamethoxazole and metoprolol concentrations during the 2018-drought were generally higher compared to the reference years (except for metoprolol compared to 2017 at Schmilka) for both rivers (Fig. 4). The monitoring station at Brunsbüttelkoog (Elbe) exhibited significantly higher sulfamethoxazole concentrations ($p < 0.05$)

(average 0.040 μg.L^{-1}) compared to the reference years (average 0.026 μg.L^{-1}) (Fig. 4, Supplementary Fig. S3). Furthermore, at Worms and Koblenz (Rhine) significantly higher metoprolol concentrations ($p < 0.05$) were observed compared to most reference years (Supplementary Table S9). The average concentrations of metoprolol for the 2018-drought were 0.035 μg.L^{-1} and 0.038 μg.L^{-1} for Worms and Koblenz, respectively, compared to the average of the reference years (0.023 μg. L^{-1} and 0.017 μg.L^{-1}) (Supplementary Table S9). The remaining stations showed mostly statistically insignificant ($p > 0.05$) changes in sulfamethoxazole and metoprolol during the 2018-drought (Supplementary Tables S7 and S9). In the case of diclofenac, lower concentrations were generally found during the drought (Fig. 4). Nonetheless, the concentration decrease was statistically insignificant ($p > 0.05$) for both rivers (Supplementary Table S8).

Additionally, increased concentrations of carbamazepine, sulfamethoxazole and metoprolol were observed for the months November and December (Fig. 5) in 2018, when the discharge of the Elbe and Rhine rivers was still below the threshold (Fig. 2). Overall higher concentrations were observed for all pharmaceuticals for the Elbe river compared to the Rhine river. For carbamazepine and sulfamethoxazole, the ERM target value was not exceeded at monitoring stations along the Rhine river. However, in the Elbe river, carbamazepine concentrations exceeded the ERM target value for almost all monitoring stations during the 2018-drought, except for Schmilka and Brunsbüttelkoog where the concentrations were either below (Brunsbüttelkoog) or equal to (Schmilka) the ERM target value of 0.1 μg.L^{-1}. At Seemanshöft and Zollenspieker, the concentration surpassed the ERM threshold for 6 out of 12 measurements between June and December (except August) (Supplementary Fig. S1). The highest concentrations of carbamazepine were recorded at Zollenspieker, reaching 0.175 μg.L^{-1} (Supplementary Fig. S1). In contrast, sulfamethoxazole only exceeded the threshold value of 0.1 μg.L^{-1} once in December at Schmilka, with a maximum concentration of 0.120 μg.L^{-1}. Finally, during the 2018-drought diclofenac and metoprolol did not exceed the ERM target values for both rivers, except once for metoprolol at the monitoring stations Seemanshöft and Brunsbüttelkoog (Elbe river).

3.2.3. Drivers of changes in pharmaceutical concentrations under drought

The correlation analysis between pharmaceutical concentrations and river discharge for the drought and reference years for both rivers indicates a clear inverse C-Q relationship for carbamazepine and sulfamethoxazole (and metoprolol for some stations alongside the Rhine river). This means that high pharmaceutical concentrations correspond with low flow conditions and vice versa, supporting the process of dilution as a main driving factor (Fig. 6). For the Elbe river, stronger inverse relations are observed upstream near Schmilka ($R^2 = 0.47$ and $R^2 = 0.30$; Table S5) compared to downstream near Zollenspieker ($R^2 = 0.35$ and $R^2 = 0.06$; Table S5) where the relations are weak to very weak

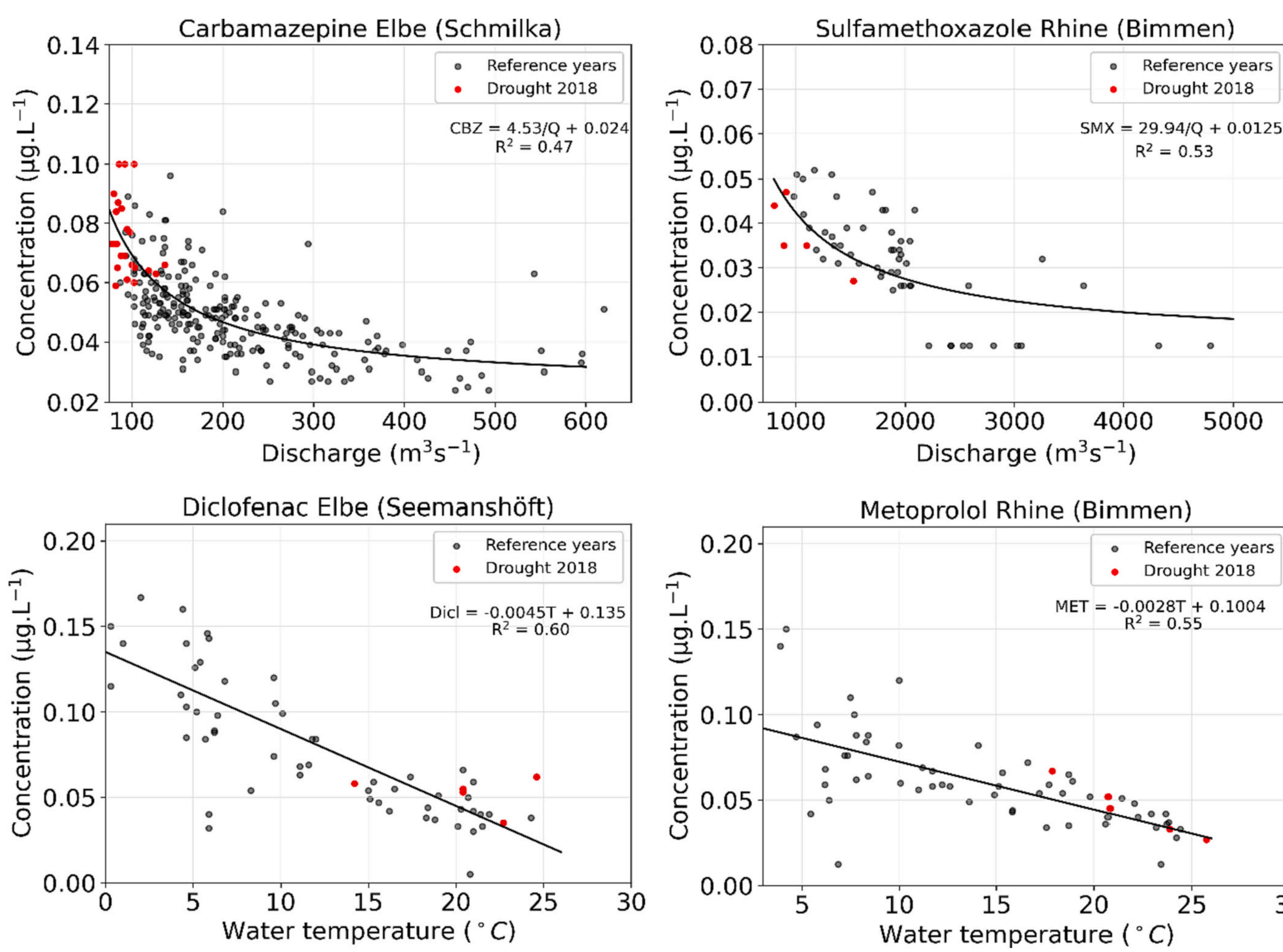


Fig. 6. The relation between the discharge and the carbamazepine and sulfamethoxazole concentrations for one station alongside the Elbe (Schmilka) and the Rhine (Bimmen) rivers and the relation between the water temperature and diclofenac and metoprolol concentrations for the drought year and corresponding reference years. The red dots represent the measurements of the 2018-drought (June–October). The black line in the concentration-discharge relation plot represents the relation by van der Weijden and Middelburg (1989) (Supplementary data Eq. 1). The black line in the concentration-water temperature plot represents the linear relation.

(Fig. 6, Supplementary Figs. S9- S10 and Table S5 and 10), for carbamazepine and sulfamethoxazole, respectively. For the Rhine river, moderate to strong relations were obtained for carbamazepine with an R^2 up to 0.68 (Koblenz), while for sulfamethoxazole the R^2 ranged from 0.34 (Koblenz) to 0.56 (Weil am Rhein) (Supplementary Table S5 and S10). Moreover, for metoprolol, weak relationships were found for the upstream stations along the Rhine river with the R^2 ranging between 0.22 (Koblenz) to 0.42 (Worms), while for all other monitoring stations along both rivers no clear C-Q relations for diclofenac and metoprolol ($R^2 < 0.1$) were found (Supplementary Table S5).

As discussed in Section 3.2.1, strong seasonal variation was observed for diclofenac and metoprolol, with elevated concentrations during winter months when river flow is at its peak, and low concentrations during summer when river flow is at its lowest (Fig. 2 and Fig. 5, Supplementary Fig. S12). This suggests that factors other than river flow influence the dynamics of metoprolol and diclofenac. To investigate further, we examined the relationship between water temperature and pharmaceutical concentrations. The analysis revealed clear negative linear relations between water temperature and pharmaceutical concentrations for both diclofenac and metoprolol, with lower pharmaceutical concentrations under higher water temperatures and vice versa (Fig. 6). Furthermore, stronger relations were obtained for both the Elbe and Rhine rivers at downstream stations. For the Elbe, R^2 ranges between 0.20 (Schmilka) versus 0.60 (Seemanshöft) for diclofenac and 0.13 (Schmilka) versus 0.68 (Zollenspieker) for metoprolol (Fig. 6, Supplementary Fig. S11). For the Rhine river, the R^2 ranges between the 0.50 and 0.58 (diclofenac) and 0.35 and 0.55 (metoprolol), between the monitoring stations Weil am Rhein and Bimmen, respectively (Fig. 6, Supplementary Fig. S11). However, no clear relations were found between water temperature and carbamazepine and sulfamethoxazole for both the Elbe and Rhine rivers.

4. Discussion and conclusions

The 2018-drought resulted in extreme low flow conditions between the period June–December and increased water temperatures for both the Elbe ($\sim +1.5$ °C) and Rhine ($\sim +2.0$ °C) rivers (June–August) were found. During this period, higher concentrations for the pharmaceuticals carbamazepine, sulfamethoxazole, and metoprolol were observed compared to the reference years (2014, 2016, 2017 and 2020 Elbe and 2014, 2016, 2017 and 2019 Rhine), whereas overall decreased concentrations were measured for diclofenac compared to these reference years. The varied responses of the four pharmaceuticals during the 2018-drought depend on their conservative or reactive characteristics.

4.1. Drought impact on pharmaceutical concentrations

The higher concentrations found for carbamazepine and sulfamethoxazole during the 2018-drought compared to the reference years can be directly linked to the inverse concentration-discharge (C-Q) relations (Section 3.2.3). This can also account for the seasonal variability of both pharmaceuticals, which is in accordance with previous studies for the Rhine (Sjerps et al., 2017; Wolff and van Vliet, 2021) and Elbe rivers (Meyer et al., 2016) but also, rivers in the Mediterranean (Mandaric et al., 2019; Palma et al., 2020). This C-Q relation of van der Weijden and Middelburg (1989) describes a dilution-based model and applies to conservative compounds and substances that are slowly degradable such as carbamazepine, sulfamethoxazole, but also metoprolol (Kovalakova et al., 2020; Sjerps et al., 2017; Wiegel et al., 2004; Yuan et al., 2019). However, no significant relations were found for metoprolol in the Elbe river. In contrast, only weak relations with discharge were observed at monitoring stations located in the upstream section of the Rhine river. These findings contradict the previous findings of Wolff and van Vliet (2021) for the Rhine river, where strong relationships were observed downstream at monitoring station Lobith located at the German-Dutch border. Additionally, Sjerps et al. (2017) observed no substantial C-Q relation at Lobith. These different findings may be attributed to variations in the water quality databases and sampling years used in the respective studies. The increased concentrations found for carbamazepine, sulfamethoxazole and metoprolol for both rivers during the 2018-drought could, therefore, be accounted for by a lower dilution factor. The main source of these pharmaceuticals are from WWTPs (Wiegel et al., 2004), with multiple large WWTPs downstream for both rivers (serving >500.000 people) (see Supplementary Fig. S13). In the case of the Rhine, there is a cluster of three large WWTPs in the Ruhr area that collectively treat wastewater for over 3.3 million people. Similarly, for the Elbe, there are two large WWTPs in Hamburg that treat wastewater for over 3 million people. During the extreme low flow conditions of the 2018-drought, wastewater is less diluted and when pollutant emissions remain constant the concentrations are increased, which agrees with findings of previous studies (Osorio et al., 2012; Wolff and van Vliet, 2021).

Given that the responses in carbamazepine concentrations were not statistically significant at the downstream stations of the Elbe (Zollenspieker and Seemanshöft), increased residence time may have favoured degradation processes (Mandaric et al., 2019) and can explain the difference in response between upstream compared to downstream the monitoring stations. As the upstream flow velocity is higher and the residence time is lower, substances are easily transported and less likely to be degraded. Moreover, the concentration changes found for the other pharmaceuticals were overall statistically insignificant, which indicates that processes other than dilution may dominate.

Significant relations were found between water temperature and both diclofenac and metoprolol, which could explain the seasonal variation (Section 3.2.1) as it could not be accounted for by flow changes. Consequently, it is most likely that the seasonal variation is caused by varying removal efficiencies in WWTPs and in the aquatic environment, which are highly influenced by water and air temperatures (Chauveheid and Scholdis, 2019; Sacher et al., 2008). Diclofenac is mainly removed out of the system by photo-transformation and biodegradation (Meierjohann et al., 2016), which can explain the overall decreased diclofenac concentrations during the 2018-drought compared to the reference years, but this depends on the physicochemical characteristics of the pharmaceutical compounds. Increased travel time and decreased river depth (low flow conditions) form favourable conditions for driving factors such as temperature, solar irradiation, and turbidity, which are mainly responsible for the degradation processes of diclofenac (Mandaric et al., 2019; Yuan et al., 2019).

Furthermore, the main processes responsible for the removal of metoprolol out of the system are biodegradation and adsorption (Daneshvar et al., 2010; Guzel et al., 2018). This could also explain the stronger relation found between water temperature and diclofenac and metoprolol concentrations at the stations downstream the Elbe and Rhine rivers (Section 3.2.3). Downstream conditions are more favourable (i.e. longer residence time) for decay and other processes that are temperature dependent. Although metoprolol concentrations are significantly influenced by processes depending on water temperatures, our results overall showed increased metoprolol concentrations during the 2018-drought compared to the reference years. Hence, this gives the impression that metoprolol is more dependent on discharge (dilution) than on water temperature (decay), which is also observed in other studies (Mandaric et al., 2019; Palma et al., 2020; Wolff and van Vliet, 2021).

The main source of all pharmaceuticals (i.e. carbamazepine, sulfamethoxazole, metoprolol, and diclofenac) is from WWTPs. As there is an increase in WWTPs which discharge into the river Elbe (Wiegel et al., 2004) and Rhine (Burgos et al., 2008; Sacher et al., 2008) along these rivers (see Supplementary Fig. S13), overall higher concentrations are found at downstream monitoring stations compared to upstream located monitoring stations. Additionally, tributaries such as Neckar, Main (Rhine) and Saale (Elbe), which exhibit a high percentage of municipal wastewaters for which relatively high concentrations of pharmaceuticals have been found contribute to the overall contamination (Sacher et al., 2008; Wiegel et al., 2004). Furthermore, drought events have the potential to alter the transport dynamics of pharmaceutical compounds. During dry periods, pharmaceuticals may be temporarily retained in catchments and subsequently released during subsequent wet conditions, leading to intermittent pulses of pollutant transport (Mosley, 2015; van Vliet et al., 2023). However, this phenomenon is predominantly pertinent to veterinary pharmaceuticals, as manure typically remains confined to agricultural fields during droughts. Nevertheless, our understanding of this process is limited. Sewer overflows also contribute to pulses of pharmaceuticals compounds to rivers, but these mainly occur during heavy rainstorms and floods, rather than drought events. Further research is necessary to investigate the impact of consecutive drought-heavy rainfall events (van Vliet et al., 2023).

While overall the same pharmaceutical responses for both rivers were observed, a higher percentage reduction in discharge (Section 3.1) can account for a stronger water quality deterioration of the Elbe compared to the Rhine river. In summer and early autumn, the Elbe is rainfed dominated (pluvial river system), while the Rhine river is both rainfed and snowmelt dominated (Nival-pluvial river system) (Huang et al., 2013) resulting in relatively higher streamflow. During the 2018-drought, the Elbe therefore had a lower dilution capacity compared to the Rhine river (Supplementary Table S2), which resulted in higher pharmaceutical concentrations particularly for carbamazepine (total cumulative average of 0.095 $\mu g.L^{-1}$ 2018-drought compared to 0.077 $\mu g.L^{-1}$ reference years) and sulfamethoxazole (total cumulative average of 0.055 $\mu g.L^{-1}$ 2018-drought compared to 0.048 $\mu g.L^{-1}$ reference years).

4.2. Uncertainties

Higher concentrations were found for several pharmaceuticals in surface waters during the 2018-drought, although in some cases these increases were statistically insignificant. Throughout this study, uncertainties may arise due to several assumptions that were made related to the analysis of pharmaceutical concentrations. First of all, uncertainties in the concentration data of pharmaceuticals required for this study must be considered. Concentration data were downloaded for all monitoring stations alongside the Elbe and Rhine river, however, no considerations were made regarding the method of data collection at each site. For example, the time of data sampling can influence the pharmaceutical concentrations due to complicated short-term dynamics. Brunsch et al. (2018) showed that pharmaceutical concentrations at the outlet of sewer treatment plants, as in the aquatic environment can fluctuate during the day. This can be attributed to changing weather conditions with dry and rainy periods succeeding each other. Nelson et al. (2011) found that daily concentration fluctuations could be attributed to consumption patterns. For example, higher sulfamethoxazole concentrations were observed in WWTP effluent during the afternoon, which could be linked to morning influents from waking residents. Furthermore, it is assumed in our study that the pharmaceutical concentrations during the study period were emitted to the surface water at a constant rate, with no increasing or decreasing trend in the human consumption. Secondly, the artificially set values of half the detection limit are assumed to be reliable as is widely used in other studies (Mandaric et al., 2019; Sjerps et al., 2017). However, it makes the measurements during drought and non-drought conditions less representative, as the detection or quantification limit can differ per pharmaceutical, monitoring station and year (See Supplementary Table S11).

Finally, it is assumed that the concentrations measured during the drought and reference years are well represented despite the unequal number of measurements and unequal sampling throughout the years. Grab samples capture a specific moment, which may not represent the true temporal variability of the pharmaceutical concentration. Pharmaceutical concentrations can vary over time due to various factors such as weather conditions, flow rates, and human activities. Using only grab samples may not capture these fluctuations accurately. Moreover, grab samples might miss episodic events or peak pollution instances that can have a significant impact on water quality. For instance, pollution events caused by stormwater resulting in sewer overflows which may not align with the timing of grab samples, leading to underrepresentation or missed detection of pollution events (Brunsch et al., 2018). For instance, at the Weil am Rhein monitoring station there was a large water quality monitoring campaign in the years 2015 and 2016. During this campaign the daily diclofenac concentrations were monitored and could be downloaded from the EEA database. In addition, the IKSR database only provides the bi-weekly measurements including the measured concentrations for the period 2015 and 2016 which corresponds to the EEA data. Fig. 7 shows the diclofenac concentrations in which the EEA data is plotted along with the IKSR data. This suggest that the bi-weekly measurements are generally a good representation of the seasonal variation of the diclofenac concentrations. However, the maximum bi-weekly concentration of the IKSR data is under-representing the maximum daily concentration of the EEA data by 30 % (0.058 $\mu g.L^{-1}$ vs. 0.075 $\mu g.L^{-1}$, February 2015) and 27 % (0.079 $\mu g.L^{-1}$ vs. 0.1 $\mu g.L^{-1,}$ December 2015), respectively. Especially for stations downstream where the variability in concentration during the year is higher (differences minimum and maximum concentrations is larger) (Section 3.2.1), this can give an under-representation of the maximum concentrations. This indicates that small datasets (monthly measurements) with instantaneous measurements might lack the temporal resolution needed to capture fluctuations in concentrations over time. If significant variations occur between measurements, they could be overlooked, potentially leading to a misunderstanding of concentration trends. Moreover, the limited number of compounds investigated might not fully represent the entire class of pharmaceutical substances within the system, raising concerns about the generalizability of the results to a broader range of chemicals and potential impact on the aquatic environment. In addition, the study may lack some context as it solely focuses on concentrations without accounting for essential factors such as source pathways and the presence of transformation products. Furthermore, the study did not fully account for the presence of metabolites and transformation products. Consequently, when assessing the ecotoxicological impact of a particular pharmaceutical and only concentrating on the parent compound, this could underestimate the overall impact because the total concentration of the parent compound, metabolites, and transformation products can be much higher.

In addition, it is important to clarify the difference between the sampling date and the moment that the concentrations are measured in the laboratory. The database of the EEA and IKSR have the same bi-weekly measurements for the diclofenac concentrations at Weil am Rhein for the year 2012. However, the dates attributed to the measurements do not correspond between the two data bases. The data of the EEA database is 6/7 days later than the same measurements of the IKSR. This can potentially impact the results by inadvertently comparing concentrations at different times, resulting in inaccurate assessments. For example, this can be an issue when fitting relations of pharmaceutical concentration with discharge or water temperature, since the discharge and water temperature fluctuate on daily basis.

4.3. Outlook

The analysis of monitoring data throughout Europe spanning the 2010–2020 timeframe revealed that 12 %, 15 %, 25 %, and 14 % of the monitoring stations exhibited average concentrations exceeding the ERM target value of 0.1 $\mu g.L^{-1}$ for carbamazepine, sulfamethoxazole, diclofenac, and metoprolol, respectively. Despite irregular sampling throughout the year and variations in the frequency of measurements among different monitoring stations, a substantial spatial extent exists where water quality standards are consistently exceeded. Moreover,

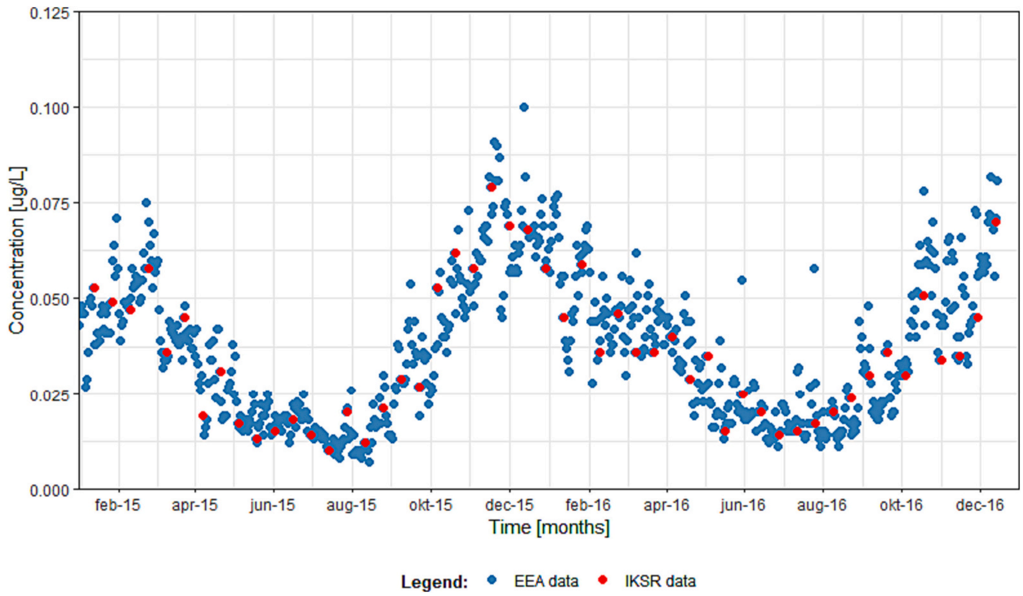


Fig. 7. Uncertainties that arise when measuring the diclofenac concentrations for the period 2015–2016 with a different frequency at monitoring station Weil am Rhein (Rhine). EEA data (Blue) shows the daily measured concentrations, while the IKSR data (Red) shows the bi-weekly measurements.

carbamazepine, sulfamethoxazole, and metoprolol showed increased concentrations during the 2018-drought for both the Elbe and Rhine rivers. The ERM target value of 0.1 $\mu g.L^{-1}$ was not exceeded for carbamazepine, sulfamethoxazole, and metoprolol for the Rhine during the June–October period of 2018. In contrast for the Elbe, the ERM target values for both metoprolol and especially for carbamazepine were exceeded during the 2018-drought. The carbamazepine concentrations exceeded the ERM target value at four out of six monitoring stations. At Zollenspieker and Seemanshöft the concentrations exceeded 0.1 $\mu g.L^{-1}$ in early June and remained above this threshold until January 2019. This resulted in a period of eight months during which the ERM target values were exceeded. For Dommitzsch and Zehren this was respectively shorter, where in late June the concentrations exceeded 0.1 $\mu g.L^{-1}$ and fluctuated around this threshold until late November. During this period of severe drought, the impact on the secondary and tertiary economic sectors was minimal and drinking water supply was continuously maintained (Conradt et al., 2023). However, the effects of the drought propagated throughout the natural ecosystem, resulting in devastating consequences for ecosystems, as well as substantial economic losses in forestry and agriculture (Conradt et al., 2023).

Studies show that long-term exposure to carbamazepine concentrations results in chronical diseases in aquatic vertebrates like zebrafish and rainbow trout, leading to reduced egg viability and altered feeding behaviour (da Silva Santos et al., 2018; Li et al., 2011). Furthermore, carbamazepine can cause a variety of toxicological effects in algae, insects, and crustacean, by affecting reproduction ability and behaviour (Duarte et al., 2021; Jarvis et al., 2014; Oropesa et al., 2016). Moreover, long-term exposure to diclofenac and metoprolol can affect the antioxidant defence mechanism of freshwater fish, as diclofenac is already measured at high toxicity levels in the liver and kidneys of fish (Sathishkumar et al., 2020). During the 2018-drought overall decreased diclofenac concentrations were however observed with concentrations also below the limit of detection (LOD < 0.005 $\mu g.L^{-1}$). Probably the largest concern is the widespread use and disposal of antibiotics, resulting in the antibacterial resistance of bacterial communities used for biological degradation in WWTPs. This may also result in a decrease in efficiency rate to remove other pollutants (Duarte et al., 2021; Larcher and Yargeau, 2012; Oldenkamp et al., 2019). Recently, the European Commission therefore adopted a proposal to revise the list of priority substances in surface water for the European Water Framework Directive for most of these pharmaceuticals considered in our study (carbamazepine, sulfamethoxazole, diclofenac).

Considering a future perspective, increases in the frequency and intensity of droughts are expected in many parts of Europe due to climate change, which may result in higher air and water temperatures and longer dry spells (Hirabayashi et al., 2008; Mosley, 2015; Prudhomme et al., 2013). Additionally, the potential increase in pharmaceutical consumption due to a growing and ageing human population and more extensive use of veterinary medicine with an increasing number of livestock could further increase concentrations of certain pharmaceuticals compared to present-day levels (Sjerps et al., 2017). As a result, the concentrations may exceed the maximum ERM target values more often and with a higher magnitude in both the Elbe and Rhine rivers during future droughts, which could have major consequences for the aquatic environment and drinking water potential. Consequently, it is important to closely monitor and strongly focus on reducing the emissions of not only pharmaceuticals but also other contaminants of emerging concern (~350.000 chemical compounds (Chen et al., 2023; Wang et al., 2020)) in the rivers. This may require: 1) expanding and optimizing existing wastewater treatment plants to effectively remove pharmaceutical compounds and other emerging contaminants from wastewater; 2) strengthening and enforcing regulations related to pharmaceutical and emerging contaminant waste disposal and effluent standards for manufacturing facilities and healthcare institutions; and 3) educating the public about the appropriate disposal of unused or expired medications to prevent improper flushing down the drain. These efforts are vital for safeguarding water quality and preserving aquatic life, particularly during future droughts.

CRediT authorship contribution statement

Mark P. Lentz: Conceptualization, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Duncan J. Graham:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Michelle T.H. van Vliet:** Conceptualization, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgement

DJG and MTHvV were financially supported by a VIDI grant (Project No. VI.Vidi.193.019) of the Netherlands Scientific Organisation (NWO). In addition, MTHvV acknowledges funding by the European Union European Research Council (ERC, B-WEX, Project 101039426).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.171186.

References

Ahmadi, B., Ahmadalipour, A., Moradkhani, H., 2019. Hydrological drought persistence and recovery over the CONUS: A multi-stage framework considering water quantity and quality. Water Res. 150, 97–110. https://doi.org/10.1016/j.watres.2018.11.052.

Aus der Beek, T., Weber, A., Bergmann, A., Gruttner, G., Carius, A., 2015. Pharmaceuticals in the Environment: Global Occurrence and Potential Cooperative Action under the Strategic Approach to International Chemicals Management (SAICM). IWW Rheinisch-Westfälisches Institut für Wasser.

Brunsch, A.F., ter Laak, T.L., Rijnaarts, H., Christoffels, E., 2018. Pharmaceutical concentration variability at sewage treatment plant outlets dominated by hydrology and other factors. Environ. Pollut. 235, 615–624. https://doi.org/10.1016/j.envpol.2017.12.116.

Buras, A., Rammig, A., Zang, C.S., 2020. Quantifying impacts of the 2018 drought on European ecosystems in comparison to 2003. Biogeosciences 17 (6), 1655–1672. https://doi.org/10.5194/bg-17-1655-2020.

Burgos, R.P., Passier, H., Bakker, I., Delsman, J., van Vliet, M., 2008. Old Contaminated Sediments in the Rhine Basin During Extreme Situations.

Chauveheid, E., Scholdis, S., 2019. Removal of pharmaceuticals by a surface water treatment plant. Water Supply 19 (6), 1793–1801. https://doi.org/10.2166/ws.2019.054.

Chen, Y., Li, M., Gao, W., Guan, Y., Hao, Z., Liu, J., 2023. Occurrence and risks of pharmaceuticals, personal care products, and endocrine-disrupting compounds in Chinese surface waters. J. Environ. Sci. https://doi.org/10.1016/j.jes.2023.10.011.

Conradt, T., Engelhardt, H., Menz, C., vincente-Serrano, S.M., Farizo, B.A., Peña-Angulo, D., López-Moreno, j.I., 2023. Cross-sectoral impacts of the 2018-2019 Central European drought and climate resilience in the German part of the Elbe River basin. Reg. Environ. Chang. 23 (1), 32. https://doi.org/10.1007/s10113-023-02032-3.

Dai, A., 2012. Erratum: drought under global warming: a review. WIREs Clim. Chang. 3 (6), 617. https://doi.org/10.1002/wcc.190guzel.

Daneshvar, A., Svanfelt, J., Kronberg, L., Prévost, M., Weyhenmeyer, G.A., 2010. Seasonal variations in the occurrence and fate of basic and neutral pharmaceuticals in a Swedish river–lake system. Chemosphere 80 (3), 301–309. https://doi.org/10.1016/j.chemosphere.2010.03.060.

Deo, R.P., 2014. Pharmaceuticals in the surface water of the USA: a review. Curr. Environ. Health Rep. 1 (2), 113–122. https://doi.org/10.1007/s40572-014-0015-y.

Duarte, D.J., Niebaum, G., Lämmchen, V., Heijnsbergen, E., Oldenkamp, R., Hernández-Leal, L., Schmitt, H., Ragas, A.M.J., Klasmeier, J., 2021. Ecological Risk Assessment of Pharmaceuticals in the Transboundary Vecht River (Germany and The Netherlands). Environ. Toxicol. Chem. 41 (3), 648–662. https://doi.org/10.1002/etc.5062.

Escher, B.I., Fenner, K., 2011. Recent advances in environmental risk assessment of transformation products. Environ. Sci. Technol. 45 (9), 3835–3847.

Filipe, O.M., Mota, N., Santos, S.A., Domingues, M.R.M., Silvestre, A.J., Neves, M.G.P., Simões, M.M., Santos, E.B., 2017. Identification and characterization of photodegradation products of metoprolol in the presence of natural fulvic acid by HPLC-UV-MSn. J. Hazard. Mater. 323, 250–263. https://doi.org/10.1016/j.jhazmat.2016.05.072.

Guzel, E.Y., Cevik, F., Daglioglu, N., 2018. Determination of pharmaceutical active compounds in Ceyhan River, Turkey: seasonal, spatial variations and environmental risk assessment. Hum. Ecol. Risk Assess. Int. J. 25 (8), 1980–1995. https://doi.org/10.1080/10807039.2018.1479631.

Hirabayashi, Y., Kanae, S., Emori, S., Oki, T., Kimoto, M., 2008. Global projections of changing risks of floods and droughts in a changing climate. Hydrol. Sci. J. 53 (4), 754–772. https://doi.org/10.1623/hysj.53.4.754.

Huang, S., 2012. Modelling of Environmental Change Impacts on Water Resources and Hydrological Extremes in Germany (Doctoral dissertation, Universitätsbibliothek der Universität Potsdam).

Huang, S., Hattermann, F.F., Krysanova, V., Bronstert, A., 2013. Projections of climate change impacts on river flood conditions in Germany by combining three different RCMs with a regional eco-hydrological model. Clim. Chang. 116, 631–663.

IAWR, IAWD, AW, AWWR, RIWA-Maas, RIWA-schelde, 2020. Europees Rivierenmemorandum voor de kwalitatieve waarborging van de winning van drinkwater.

Jarvis, A.L., Bernot, M.J., Bernot, R.J., 2014. Relationships between the psychiatric drug carbamazepine and freshwater macroinvertebrate community structure. Sci. Total Environ. 496, 499–509. https://doi.org/10.1016/j.scitotenv.2014.07.086.

Jones, E., van Vliet, M.T.H., 2018. Drought impacts on river salinity in the southern US: implications for water scarcity. Sci. Total Environ. 644, 844–853. https://doi.org/10.1016/j.scitotenv.2018.06.373.

de Jongh, C.M., Kooij, P.J.F., de Voogt, P., ter Laak, T.L., 2012. Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water. Sci. Total Environ. 427–428, 70–77. https://doi.org/10.1016/j.scitotenv.2012.04.010.

Khasawneh, O.F.S., Palaniandy, P., 2021. Occurrence and removal of pharmaceuticals in wastewater treatment plants. Process. Saf. Environ. Prot. 150, 532–556. https://doi.org/10.1016/j.psep.2021.04.045.

Kovalakova, P., Cizmas, L., McDonald, T.J., Marsalek, B., Feng, M., Sharma, V.K., 2020. Occurrence and toxicity of antibiotics in the aquatic environment: a review. Chemosphere 251, 126351. https://doi.org/10.1016/j.chemosphere.2020.126351.

Laaha, G., Gauster, T., Tallaksen, L.M., Vidal, J.P., Stahl, K., Prudhomme, C., Wong, W.K., 2017. The European 2015 drought from a hydrological perspective. Hydrol. Earth Syst. Sci. 21 (6), 3001–3024.

Larcher, S., Yargeau, V., 2012. Biodegradation of sulfamethoxazole: current knowledge and perspectives. Appl. Microbiol. Biotechnol. 96 (2), 309–318. https://doi.org/10.1007/s00253-012-4326-3.

Leuven, R.S., van der Velde, G., Baijens, I., Snijders, J., van der Zwart, C., Lenders, H.R., bij de Vaate, A., 2009. The river Rhine: a global highway for dispersal of aquatic invasive species. Biol. Invasions 11, 1989–2008.

Li, Z.H., Zlabek, V., Velisek, J., Grabic, R., Machova, J., Kolarova, J., Li, P., Randak, T., 2011. Acute toxicity of carbamazepine to juvenile rainbow trout (Oncorhynchus mykiss): effects on antioxidant responses, hematological parameters and hepatic EROD. Ecotoxicol. Environ. Saf. 74 (3), 319–327. https://doi.org/10.1016/j.ecoenv.2010.09.008.

Lin, A.Y.C., Yu, T.H., Lin, C.F., 2008. Pharmaceutical contamination in residential, industrial, and agricultural waste streams: risk to aqueous environments in Taiwan. Chemosphere 74 (1), 131–141. https://doi.org/10.1016/j.chemosphere.2008.08.027.

van Loon, A.F., van Lanen, H.A.J., 2012. A process-based typology of hydrological drought. Hydrol. Earth Syst. Sci. 16 (7), 1915–1946. https://doi.org/10.5194/hess-16-1915-2012.

Mackuľak, T., Brandeburová, P., 2019. Occurrence of Pharmaceuticals in the Waters of the Danube Region. waterquality.danube-region, 1-57.

Mallast, U., Staniek, M., Koschorreck, M., 2020. Spatial upscaling of CO_2 emissions from exposed river sediments of the Elbe River during an extreme drought. Ecohydrology 13 (6). https://doi.org/10.1002/eco.2216.

Mandaric, L., Kalogianni, E., Skoulikidis, N., Petrovic, M., Sabater, S., 2019. Contamination patterns and attenuation of pharmaceuticals in a temporary Mediterranean river. Sci. Total Environ. 647, 561–569. https://doi.org/10.1016/J.SCITOTENV.2018.07.308.

Meierjohann, A., Brozinski, J.M., Kronberg, L., 2016. Seasonal variation of pharmaceutical concentrations in a river/lake system in Eastern Finland. Environ. Sci. Process Impacts 18 (3), 342–349. https://doi.org/10.1039/c5em00505a.

Meyer, W., Reich, M., Beier, S., Behrendt, J., Gulyas, H., Otterpohl, R., 2016. Measured and predicted environmental concentrations of carbamazepine, diclofenac, and metoprolol in small and medium rivers in northern Germany. Environ. Monit. Assess. 188 (8) https://doi.org/10.1007/s10661-016-5481-2.

Mortazavi-Naeini, M., Bussi, G., Elliott, J.A., Hall, J.W., Whitehead, P.G., 2019. Assessment of risks to public water supply from low flows and harmful water quality in a changing climate. Water Resour. Res. 55, 10386–10404. https://doi.org/10.1029/2018WR022865.

Mosley, L.M., 2015. Drought impacts on the water quality of freshwater systems; review and integration. Earth Sci. Rev. 140, 203–214. https://doi.org/10.1016/j.earscirev.2014.11.010.

Mosley, L.M., Zammit, B., Leyden, E., Heneker, T.M., Hipsey, M.R., Skinner, D., Aldridge, K.T., 2012. The impact of extreme low flows on the water quality of the lower Murray river and lakes (South Australia). Water Resour. Manag. 26 (13), 3923–3946. https://doi.org/10.1007/s11269-012-0113-2.

Naumann, G., Cammalleri, C., Mentaschi, L., Feyen, L., 2021. Increased economic drought impacts in Europe with anthropogenic warming. Nat. Clim. Chang. 11 (6), 485–491. https://doi.org/10.1038/s41558-021-01044-3.

Nelson, E.D., Do, H., Lewis, R.S., Carr, S.A., 2011. Diurnal variability of pharmaceutical, personal care product, estrogen and alkylphenol concentrations in effluent from a tertiary wastewater treatment facility. Environ. Sci. Technol. 45 (4), 1228–1234.

Oldenkamp, R., Beusen, A.H.W., Huijbregts, M.A.J., 2019. Aquatic risks from human pharmaceuticals—modelling temporal trends of carbamazepine and ciprofloxacin at the global scale. Environ. Res. Lett. 14 (3), 034003 https://doi.org/10.1088/1748-9326/ab0071.

Oropesa, A.L., Floro, A.M., Palma, P., 2016. Assessment of the effects of the carbamazepine on the endogenous endocrine system of Daphnia magna. Environ. Sci. Pollut. Res. 23, 17311–17321.

Osorio, V., Marcé, R., Pérez, S., Ginebreda, A., Cortina, J.L., Barceló, D., 2012. Occurrence and modeling of pharmaceuticals on a sewage-impacted Mediterranean river and their dynamics under different hydrological conditions. Sci. Total Environ. 440, 3–13. https://doi.org/10.1016/j.scitotenv.2012.08.040.

Palma, P., Fialho, S., Lima, A., Novais, M.H., Costa, M.J., Montemurro, N., Pérez, S., de Alda, M.L., 2020. Pharmaceuticals in a Mediterranean Basin: the influence of temporal and hydrological patterns in environmental risk assessment. Sci. Total Environ. 709, 136205 https://doi.org/10.1016/j.scitotenv.2019.136205.

Patel, M., Kumar, R., Kishor, K., Mlsna, T.E., Pittman, C.U., Mohan, D., 2019. Pharmaceuticals of emerging concern in aquatic systems: chemistry, occurrence, effects, and removal methods. Chem. Rev. 119 (6), 3510–3673. https://doi.org/10.1021/a.

Pereira, A.M.P.T., Silva, L.J.G., Laranjeiro, C.S.M., Meisel, L.M., Lino, C.M., Pena, A., 2017. Human pharmaceuticals in Portuguese rivers: the impact of water scarcity in the environmental risk. Sci. Total Environ. 609, 1182–1191. https://doi.org/10.1016/j.scitotenv.2017.07.200.

Petrovic, M., Ginebreda, A., Acuña, V., Batalla, R., Elosegi, A., Guasch, H., de Alda, M.L., Marcé, R., Muñoz, I., Navarro-Ortega, A., Navarro, E., Vericat, D., Sabater, S., Barceló, D., 2011. Combined scenarios of chemical and ecological quality under water scarcity in Mediterranean rivers. TrAC Trends Anal. Chem. 30 (8), 1269–1278. https://doi.org/10.1016/j.trac.2011.04.012.

Pfeiffer, M., Ionita, M., 2017. Assessment of hydrologic alterations in Elbe and Rhine Rivers, Germany. Water 9 (9), 684.

Prudhomme, C., Giuntoli, I., Robinson, E.L., Clark, D.B., Arnell, N.W., Dankers, R., Fekete, B.M., Franssen, W., Gerten, D., Gosling, S.N., Hagemann, S., Hannah, D.M., Kim, H., Masaki, Y., Satoh, Y., Stacke, T., Wada, Y., Wisser, D., 2013. Hydrological droughts in the 21st century, hotspots and uncertainties from a global multimodel ensemble experiment. Proc. Natl. Acad. Sci. 111 (9), 3262–3267. https://doi.org/10.1073/pnas.1222473110.

Rapp-Wright, H., Regan, F., White, B., Barron, L.P., 2023. A year-long study of the occurrence and risk of over 140 contaminants of emerging concern in wastewater influent, effluent and receiving waters in the Republic of Ireland. Sci. Total Environ. 860, 160379.

Sacher, F., Ehmann, M., Gabriel, S., Graf, C., Brauch, H.J., 2008. Pharmaceutical residues in the river Rhine—results of a one-decade monitoring programme. J. Environ. Monit. 10 (5), 664. https://doi.org/10.1039/b800701b.

Sathishkumar, P., Meena, R.A.A., Palanisami, T., Ashokkumar, V., Palvannan, T., Gu, F. L., 2020. Occurrence, interactive effects and ecological risk of diclofenac in environmental compartments and biota - a review. Sci. Total Environ. 698, 134057 https://doi.org/10.1016/j.scitotenv.2019.134057.

da Silva Santos, N., Oliveira, R., Lisboa, C.A., Mona E Pinto, J., Sousa-Moura, D., Camargo, N.S., Perillo, V., Oliveira, M., Grisolia, C.K., Domingues, I., 2018. Chronic effects of carbamazepine on zebrafish: behavioral, reproductive and biochemical endpoints. Ecotoxicol. Environ. Saf. 164, 297–304. https://doi.org/10.1016/j.ecoenv.2018.08.015.

Sjerps, R.M., ter Laak, T.L., Zwolsman, G.J., 2017. Projected impact of climate change and chemical emissions on the water quality of the European rivers Rhine and Meuse: a drinking water perspective. Sci. Total Environ. 601–602, 1682–1694. https://doi.org/10.1016/j.scitotenv.2017.05.250.

Sluijter, R., Plieger, M., van Oldenborgh, G.J., Beersma, J., de Vries, H., 2018. De droogte van 2018.

Tang, J., Sun, J., Wang, W., Yang, L., Xu, Y., 2021. Pharmaceuticals in two watersheds in Eastern China and their ecological risks. Environ. Pollut. 277, 116773 https://doi.org/10.1016/j.envpol.2021.116773.

Trenberth, K.E., Dai, A., van der Schrier, G., Jones, P.D., Barichivich, J., Briffa, K.R., Sheffield, J., 2013. Global warming and changes in drought. Nat. Clim. Chang. 4 (1), 17–22. https://doi.org/10.1038/nclimate2067.

Uehlinger, U.F., Wantzen, K.M., Leuven, R.S., Arndt, H., 2009. The Rhine River Basin.

van Vliet, M.T.H., Thorslund, J., Strokal, M., Hofstra, N., Flörke, M., Ehalt Macedo, H., Nkwasa, A., Tang, T., Kaushal, S.S., Kumar, R., van Griensven, A., Bouwman, L., Mosley, L.M., 2023. Global river water quality under climate change and hydroclimatic extremes. Nat. Rev. Earth Environ. 1–16.

Wang, Z., Walker, G.W., Muir, D.C.G., Nagatani-Yoshida, K., 2020. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. Environ. Sci. Technol. 54 (5), 2575–2584. https://doi.org/10.1021/acs.est.9b06379.

Wiegel, S., Aulinger, A., Brockmeyer, R., Harms, H., Löffler, J., Reincke, H., Schmidt, R., Stachel, B., von Tümpling, W., Wanke, A., 2004. Pharmaceuticals in the river Elbe and its tributaries. Chemosphere 57 (2), 107–126. https://doi.org/10.1016/j.chemosphere.2004.05.017.

van der Weijden, C.H., Middelburg, J.J., 1989. Hydrogeochemistry of the River Rhine: long term and seasonal variability, elemental budgets, base levels and pollution. Water Res. 23, 1247–1266. https://doi.org/10.1016/0043-1354(89)90187-5.

van der Wiel, K., Lenderink, G., de Vries, H., 2021. Physical storylines of future European drought events like 2018 based on ensemble climate modelling. Weather Clim. Extr. 33, 100350 https://doi.org/10.1016/j.wace.2021.100350.

Wolff, E., van Vliet, M.T.H., 2021. Impact of the 2018 drought on pharmaceutical concentrations and general water quality of the Rhine and Meuse rivers. Sci. Total Environ. 778, 146182 https://doi.org/10.1016/j.scitotenv.2021.146182.

Wright, B., Stanford, B.D., Reinert, A., Routt, J.C., Khan, S.J., Debroux, J.F., 2014. Managing water quality impacts from drought on drinking water supplies. J. Water Supply Res. Technol. AQUA 63, 179–188. https://doi.org/10.2166/aqua.2013.123.

Yuan, X., Li, S., Hu, J., Yu, M., Li, Y., Wang, Z., 2019. Experiments and numerical simulation on the degradation processes of carbamazepine and triclosan in surface water: A case study for the Shahe Stream, South China. Sci. Total Environ. 655, 1125–1138. https://doi.org/10.1016/j.scitotenv.2018.11.290.

Zhou, J., Zhang, Z., Banks, E., Grover, D., Jiang, J., 2009. Pharmaceutical residues in wastewater treatment works effluents and their impact on receiving river water. J. Hazard. Mater. 166 (2–3), 655–661. https://doi.org/10.1016/j.jhazmat.2008.11.070.

Zind, H., Mondamert, L., Remaury, Q.B., Cleon, A., Leitner, N.K.V., Labanowski, J., 2021. Occurrence of carbamazepine, diclofenac, and their related metabolites and transformation products in a French aquatic environment and preliminary risk assessment. Water Res. 196, 117052 https://doi.org/10.1016/j.watres.2021.117052.