Drought impact on pharmaceuticals in surface waters of major river basins in Europe

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Abstract

Hydrological droughts are one of the most devastating natural disasters worldwide, which are expected to increase in magnitude, frequency and severity due to climate change, resulting in higher air temperatures and longer dry spells. In the last 20 years several drought occurred in North-western Europe, like the 2018 drought, which was one of the most extreme in the last decade. The 2018 drought had a severe impacts on environmental and ecological aspects of the affected regions on both water quantity and quality perspectives. As the impact of droughts on water quantity are well studied, there is still a lot unknown of the impact on water quality. Especially, little understanding exists on the responses in pharmaceutical concentrations in surface water under drought. As measured concentrations in surface water are overall small, the potential ecotoxicological effects that those low concentrations can have on the environment are of major concern. Therefore, this study investigates the impact of the 2018 drought on four selected pharmaceuticals (i.e. carbamazepine, sulfamethoxazole, diclofenac and metoprolol) in the Elbe and Rhine river. Twelve monitoring stations six alongside each river, located in the German part of the river basins were analysed for the study period 2010-2020. The first part of the analysis focusses on the spatial and temporal patterns to get a better understanding on the seasonal dynamics. The second part compares the 2018 drought, to four selected reference years (2014,2016,2017 and 2020 Elbe) and (2014,2016,2017 and 2019 Rhine) for the period June-October and will be placed in a broader context. The results show an overall, deterioration of the water quality for both the Elbe and Rhine river, this can be attributed to the extreme low flow and higher water temperatures (~+1.5 °C and ~+2.0 °C) for the Elbe and Rhine, respectively. Furthermore, while our findings show in general increased concentrations for the pharmaceutical's carbamazepine, sulfamethoxazole, and metoprolol, overall decreased concentrations were observed for diclofenac during the 2018 drought compared to the reference years. Although, these changes were overall statistically insignificant, for carbamazepine at 3 out of 6 monitoring stations (Schmilka, Zehren and Dommitzsch) alongside the Elbe statistically significant increases were found (~+45%). The increased pharmaceutical concentrations are mainly caused by limited dilution of chemical loads from wastewater treatment plants, while the decreased diclofenac concentrations can be attributed to increased degradation processes due to higher water temperatures. Additionally, the rain dominated Elbe showed a stronger water quality deterioration compared to the snowmelt dominated Rhine river, as the reduction in dilution capacity for the Elbe was larger.

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1. Introduction

Hydrological droughts are one of the most devastating natural disasters, which impose severe impacts on ecological and environmental aspects of the affected region on both water quantity and quality perspectives (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 predicted to show large increases in frequency and severity of hydrological drought conditions due to climate change (Hirabayashi et al., 2008; Mosley, 2015; Prudhomme et al., 2013). The drought of 2018 was in north-western Europe one of most severe droughts in this century, with long periods of high temperatures (July-August) in Germany and the Netherlands (van der Wiel et al., 2021) and extreme low flow conditions in the Elbe and Rhine rivers (Buras et al., 2020; Mallast et al., 2020).

The presence of pharmaceutical active compounds (PhACs) in surface water (i.e. streams, rivers, lakes and reservoirs) is a growing concern because, some of these substances have shown adverse effects on ecosystems and drinking water quality, when concentrations are exceeding water quality standards for aquatic ecosystem health and drinking water production (Deo, 2017). The high production and extensive use of pharmaceuticals result in the continuous release of pharmaceuticals into surface waters (Tang et al., 2021). More than 3000 different pharmaceuticals belonging to different therapeutic classes are used for human application in the European Union (Osorio et al., 2016). Additionally, over 200 different PhAC's have been identified in groundwater, surface water, and drinking water (Osorio et al., 2012; Osorio et al., 2016). The overall concentrations in surface waters are small (in the low $\mu g.L^{-1}$) and sometimes below the detection limit. However, the potential ecotoxicological effects that these low concentrations can have on the environment and potential drinking water are of major concern (Sjerps et al., 2017). As some pharmaceuticals can 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, it can deteriorate the water quality. The most abundant pharmaceutical therapeutic classes in surface waters are painkillers (e.g. ibuprofen and diclofenac), Anti-epileptic (e.g. carbamazepine), Anti-biotics (e.g. sulfamethoxazole) and beta-blockers (e.g. metoprolol) (Chauveheid and Scholdis, 2019; Deo, 2014; Kunkel and Radke., 2012; Ngqwala and Muchesa, 2020).

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), whereby, households, old people homes, and healthcare services are the most important sources of pharmaceuticals (Mackuľak & Brandeburová, 2019). Injected, ingested, and inhaled pharmaceuticals are secreted by the body and flushed down the toilet, while expired and unwanted leftover pharmaceuticals are disposed into the sewage (Deo, 2014). 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 either discharged into surface waters or used for land irrigation and farming, which may also enter surface water via leaching or surface runoff (Tang et al., 2021). Moreover, veterinary pharmaceuticals consumed by livestock (e.g. anti-biotics and painkillers), can enter the aquatic environment via runoff of agricultural areas. As these pharmaceuticals are partly excreted via urine and faeces and then later used for fertilizing the land (ter Laak et al., 2010).

During droughts, emissions from point sources are less diluted and thus concentrations of pharmaceutical compounds in surface water will probably increase (Mosley, 2015; Osorio et al., 2012; Wolff and van Vliet, 2021). Pharmaceutical concentrations can be removed out of the system by biotic and abiotic natural degradation processes (Osorio et al., 2012). The reduced discharge can lead to an increase in residence times due to lower flow velocity. Reduced water volumes and higher air temperatures often lead to higher water temperatures, which may change processes such as decay of organic matter, respiration, and dissolved oxygen levels (Mosley et al., 2012). Droughts may also change the delivery patterns of pollutants. During dry periods pollutants can be temporary retained in catchments and subsequently released during wet conditions (Mosley, 2015).

Over the past decades PhACs have emerged as a major group of environmental contaminants, resulting in a rapid increase of published papers from 2003 onwards (Hughes et al., 2012). Whereby, most studies have investigated the removal efficiency in WWTPs (e.g. Khasawneh and Palaniandy, 2021), environmental risk assessment regarding the occurrence of PhAC's in the aquatic environment (e.g. Meyer et al., 2016; Zhou et al., 2019) and processes effecting 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., 2012; Petrovic et al., 2012) in the aquatic environment. Those processes are all influenced by seasonal variation of environment factors (i.e. temperature, precipitation, and sunlight) and are all drought sensitive (Osorio et al., 2012). Additionally, most studies on the impact of stream flow droughts on river water quality focused on physical-chemical parameters, such as, temperature, salinity (Jones and van Vliet, 2018), nutrients and inorganic micropollutants (Mortazavi-Naeini et al., 2019; Mosley, 2015), these studies show for most physical-chemical parameters an overall water quality deterioration. However, research on pharmaceutical concentrations in surface waters under hydrological droughts is scarce (Palma et al 2020; Sjerps et al., 2017; Wolff and van Vliet, 2021). As flow changes can either correlate negatively or positively with pharmaceutical concentrations (Osorio et al., 2012), little understanding exists on the impact of droughts on the pharmaceutical concentrations across multiple river basins.

Objective, research questions and approach

The main objective of this research is to estimate the impact of the 2018 drought on concentrations of a selection of pharmaceuticals in two major river basins in Europe. The research questions assigned to accomplish this objective are:

1) RQ1: What are the temporal and spatial patterns in pharmaceutical concentrations at available monitoring stations?

2) RQ2: To what extent are pharmaceutical concentrations statistically significant different under droughts compared to reference hydrological situations? And to what extent do the water quality standards exceed the target values under droughts?

3) RQ3: To what extent are the responses in pharmaceuticals during drought and non-drought periods seemingly similar for different river basins?

4) RQ4: How do external factors that are impacted during droughts such as; river flow changes (e.g. dilution and residence times) and water temperature, influence the pharmaceutical concentrations?

The focus of this study will be on a selected group of monitoring stations with sufficient monitoring data availability of pharmaceutical concentrations, discharge, and water temperature. The study area is the river basins of the Elbe and Rhine in the German part of the river catchment. The main processes that occur during drought events compared to water quality under common hydrological regimes will be studied. Four pharmaceuticals form four therapeutic classes are included in the data analyses: Anti-epileptic (carbamazepine), antibiotics (sulfamethoxazole), painkillers (diclofenac), and ß-blockers (metoprolol). The study is organized as follows; chapter 2 provides an introduction of the study area and the severity of the 2018 drought that occurred in that area, furthermore the selected pharmaceuticals will be briefly discussed. Chapter 3 provides the methodology of data collection and processing and the approaches used per research question, which are presented in chapter 4 the results. Finally, in chapter 5 the results will be discussed within a broader context and the limitations of the research will be evaluated.

2. Literature study

2.1 Study area

The Elbe and Rhine are two major rivers located in Central and Western Europe (Fig. 1). The Elbe river rises high in the “Riesengebirge” (Giant Mountains) in the Czech Republic and enters the North Sea near Cuxhaven in Germany (Amman et al., 2012; Wiegel et al., 2014). The Elbe flows over a distance of 1090 km and has a drainage basin of 148.268 km^2, of which two-third (~100.000 km^2) is located in Germany and one-third in 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, of which two- third (120.000 km^2) in Germany (Huang, 2012). Additionally, the catchment covers large parts of Switzerland and the Netherlands and parts of France, Luxemburg, and Belgium (Weijden & Middelburg 1989). The climate for the Elbe basin can be described as humid and temperate, while the Rhine basin has more a temperate and marine climate. With an annual precipitation of 700 and 592 mm and an average temperature of 10.0 and 9.0 °C for the Rhine and Elbe, respectively (Babarowski and Einax, 2016; EEA 2020). Two hydrological regimes dominate the discharge of both rivers. The headwaters of the Elbe and the largest tributary (Vltava) in Czech Republic are a snowmelt dominated regime, while the largest tributary in Germany (Saale) has a rain dominated regime (Huang, 2012). Other major tributaries are the Mulde and Schwarze Elster (Babarowski and Einax, 2016). After the Elbe enters Germany, it flows through the major city of Dresden which has a population density of 1700 people per km^2. Downstream Dresden the Saale joins the Elbe near Magdeburg. Before the Elbe enters the North-Sea it flows through the large industrial city of Hamburg.

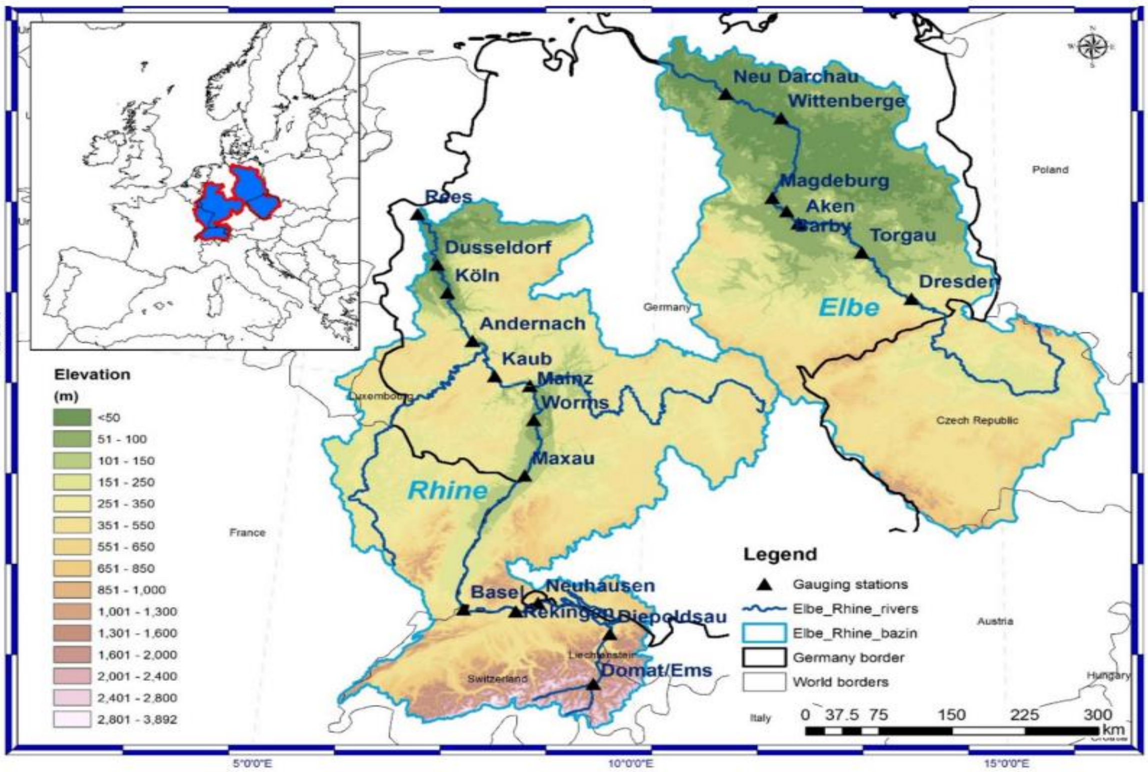


Fig. 1. Location of the study areas of the rivers Elbe and Rhine in Germany (Ionita and Nagavciuc, 2020).

From May until November most of the discharge of the Rhine is meltwater originated from the Swiss part of the river catchment. From December till May the river is, however, mainly rainfall dominated (e.g. runoff and groundwater) as most of the precipitation in the Alps is retained as snow. After Lake Constance the river Aare joins the Rhine and flow westwards over approximately 142 km until Basel. After Basel the Rhine flows through the Upper Rhine graben, near the city of Mainz the tributary river Main joins the Rhine. From there the Rhine flows to Koblenz where the Mosel joins. After flowing through Bonn and Cologne (Rurh area) the Rhine enters the Netherlands near Bimmen/Lobith (Kempe et al., 2005). Furthermore, the water quality is exposed to deterioration due to a high population density, emissions from wastewater treatment plants, large industrial areas, and extensive agriculture around both rivers (Houtman et al., 2013; Wiegel et al., 2004). For the Elbe the largest input of treated wastewater originates in the Hamburg region, but also around Dresden, Leipzig, and Magdeburg. Thereby, is the Saale River characterized by a high density of sewer treatment plants that attributes to the wastewater into the Elbe (Wiegel et al., 2004). While, for the Rhine, the largest input of treated wastewater is from the Ruhr area and Koblenz.

2.2 Background drought 2018

In the last 20 years four major droughts can be distinguished in Central Europe, the drought of 2003, 2015, 2018 and 2019 (Boergens et al., 2020; Buras et al., 2020; Mallast et al., 2020; Laaha et al., 2017; Sluijter et al., 2018). The mean recurrence time of the 2018 drought was approximately 30 years (Sluijters et al., 2018), with varying return periods of 10-100 years throughout Europe. In comparison the mean recurrence time of the droughts of 2003 and 2015 were estimated on 10 years and 20 years, respectively (Laaha et al., 2017). The drought of 2003 and 2019 had a larger spatial extend throughout central Europe, while the drought of 2015 affected mainly parts of Czech Republic (return period 100 years) and to a lesser extend south-western Germany (return period 10 years) (Laaha et al., 2017). However, the drought of 2018 was overall the most severe drought in western Europe in this century, with long periods of high temperatures (July-August) in Germany and the Netherlands (van der Wiel et al., 2021). This resulted in the hottest year recorded in Germany since the beginning of the weather recordings in 1881 (Mallast et al., 2020). With all time low water levels recorded in the Elbe River, at gauge station Magdeburg, the water level dropped to an all-time low 45 cm, which is 47 cm lower than the mean annual low water level (Mallast et al., 2020). Early spring 2018, a persistent high-pressure system established above Northern (Scandinavia) and Central Europe (Buras et al., 2020; Sluijter et al., 2018). This high-pressure systems prevented low depression areas entering Europe from the Atlantic Ocean and so blocking westerly winds, which normally brings moist and colder air (Moravec et al., 2021; Sluijter et al., 2018). This high-pressure system in combination with a positive phase of the North Atlantic oscillation and global warming resulted in this long-lasting drought spell (Buras et al., 2020; van der Wiel et al., 2021).

The number of summer days in 2018 was 74 days (air temperature > 25 °C), which is significantly more than the 62 days in 2003. Very high temperatures, often above 30 °C, were recorded during the period from end-July to mid-August 2018 (DWD annual report 2018, accessed 2022). Furthermore, next to the high temperatures, there was a precipitation deficit in the Elbe and Rhine basin. Precipitation deficit is defined as the cumulative difference between the potential evapotranspiration and precipitation (van der Wiel et al., 2021). The precipitation deficit started in April and increased quickly early June in the Rhine basin (Fig. 2a). The peak of the precipitation deficit occurred for the Rhine in October (275 mm) with even higher deficits in the Elbe basin in the period August-October (Fig. 2b) (van der Wiel et al., 2021). 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.

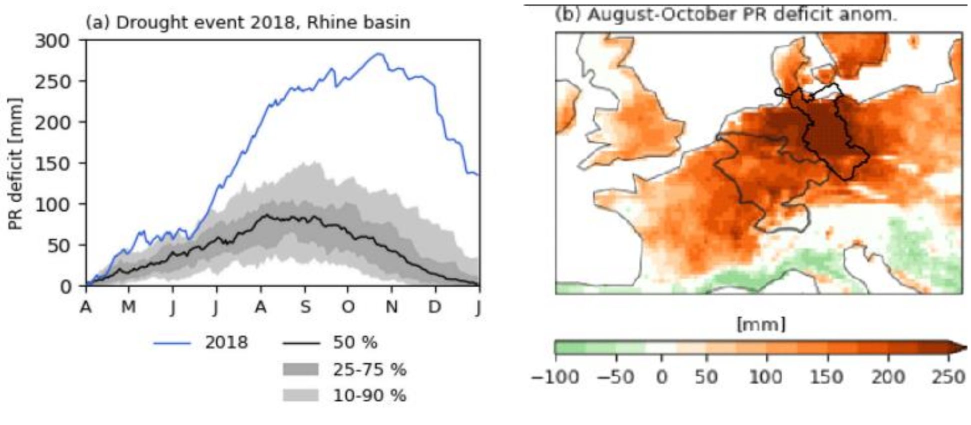


Fig. 2. (a) Precipitation deficit in [mm] during the 2018 drought for the Rhine basin. (Blue line)mean time series 2018 and (Black line) average (with corresponding percentiles). (b) Map of mean precipitation deficit [mm] for the August–October period. Included Rhine and Elbe basin (van der Wiel et al., 2021, modified).

2.3 Pharmaceutical background

The analysis of this study will focus on four selected pharmaceuticals from four different therapeutic classes; Anti-epileptic (carbamazepine), antibiotics (sulfamethoxazole), painkillers (diclofenac),and ß-blockers (metoprolol).

Carbamazepine (CBZ) (5H-dibenz(b,f)azepine-5-carboxamide, CAS number: 298-46-4) (Fig. 3) is an important anti-epileptic medicine, which is additionally used for bipolar depression, trigeminal neuralgia, excited psychosis and was also introduced as treatment against schizophrenia because of its mood stabilizing characteristics (Cunningham et al., 2010). CBZ is a small molecule which was first put on the marketed in 1962 (Shorvon et al., 2015). Due to the wide use of CBZ it is one of the most frequently detected pharmaceutical in surface waters in Europe (Yuan et al., 2019). Therefore, it is used as indicator for measuring the overall pharmaceutical contamination of river waters (Yuan et al., 2019). The total amount of CBZ prescribed in Germany was estimated on 77.000 kg in 2001 and decreased to approximately 51.000 kg in 2011 (Bahlmann et al., 2014). After ingested CBZ is heavily metabolized, more than 30 metabolites have been identified, whereby (10,11- dihydro-trans-10,11-dihydroxy-CBZ and 1/2/3-hydroxy-CBZ) are the two most abundant (Cunningham et al., 2010; Bahlmann et al., 2014). Approximately, 70% of the consumed CBZ is excreted via urine and 30% via faeces. Whereby, 1% and 13% of the total dose is excreted as parent compound via urine and faeces, respectively (Bahlmann et al., 2014). Due to the strong heterocyclic structure and weak acids CBZ is a stable pharmaceutical and therefore difficult to remove by artificial processes in WWTP's and natural degradation processes (e.g. photolysis, hydrolysis, and biodegradation) in the aquatic environment (Yuan et al., 2019). Moreover, the combination of low removal rates and the continual release of CBZ into the aquatic environments, it can cause negative effects in aquatic ecosystems and can even results in a variety of physiological effect in aquatic organisms (Zhou et al., 2010; Yuan et al., 2019)

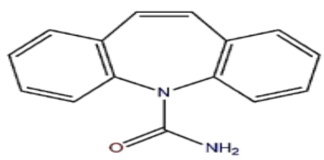


Fig. 3. Chemical structure Carbamazepine, with chemical formula $C_{15}H_{12}N_2O$ (Yazdanbakhsh et al., 2019).

Sulfamethoxazole (SMX) (4-amino-N-[5-methyl-1,2-oxazol-3-yl] benzene-1-sulfonamide; CAS number: 723–46–6) (Fig. 4), is a sulfonamide antibiotic, given in combination with trimethoprim, is used to treat infections of the respiration system, urinary tract, and gastrointestinal tract, which is used for human and veterinary applications. It is a common prescribed and consumed antibiotic in Europe, leading to its occurrence in river water via wastewater discharge and runoff from agricultural areas (Larcher et al., 2012; Straub., 2015). SMX is a small-molecular active pharmaceutical ingredient, which was first put on the market in 1969 (Straub, 2015). The estimated total human use in Europe was around 260.000 kg in 1995 and decreased to approximately 160.000 kg in 2013 (Straub, 2015). Moreover, during the period 2013-2017 most European countries showed no significant increase, among whom Germany and the Netherlands (Kovalakova et al., 2020). SMX is excreted from the body, which can reach up to 45-70% of the initial consumed dose. However, only 15-25% is present as parent compound, while 30-45% is present as metabolites (N_4-acetyl-sulfamethoxazole or sulfamethoxazole-N_1-glucuronide) (Radke et al., 2009).

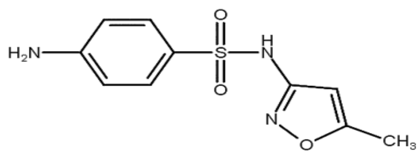


Fig. 4. Chemical structure sulfamethoxazole with chemical formula $C_{10}H_{11}N_3O_3S$ (Straub, 2015).

After SMX is released from WWTPs and enters the river water, the largest part will remain as dissolved SMX in the aquatic environment, which can be up to 60-80% and can therefore be easily transported (Straub, 2015). The fate of SMX is the aquatic environment is determined by the rate of photo- and biodegradation influenced by the availability of degrading micro-organisms and sunlight. Finally, substantial amount of SMX may have a negative effect on non-target organisms in the aquatic ecosystems including Zooplankton, macrophytes, microphytes, freshwater algae, and fishes. (Kovalakova et al., 2020). Whereby, the greatest concerns are that their presence will lead to antibiotic resistance in bacteria (Larcher and Yargeau, 2012).

Diclofenac (DCF) (2-[2-(2,6-dichloroanilino)phenyl]acetic acid; CAS number: 15307-86-5) (Fig. 5) is a nonsteroidal anti-inflammatory drug used as painkiller and inflammatory diseases (Sathishkumar et al., 2020; Stülten et al., 2008). In 2015, DCF was added on the Watch List of EU Decision 2015/495, this to gather sufficient monitoring data on surface waters (Lonappan et al., 2016; Sathishkumar et al., 2020). DCF is a widely used pharmaceutical for both human as domestic livestock since the 1970's. The total global consumption was estimated on 1442.000 ± 58.000 kg of DCF in 2015 (without the use for livestock), whereby 28.7% is consumed in Europe (Lonappan et al., 2016). Germany is the largest contributor in Europe, with a total consumption of 86.000 kg in 2001 (Lonappan et al., 2016). After consumption DCF is heavily metabolized, more than 28 metabolites have been identified (major metabolites; 4-hydroxy-diclofenac and 4,5-dihydroxy-diclofenac) (Stülten et al., 2008). Orally consumed DCF is excreted from the body, which can reach up to 65-70% via urine and 20-30% via faeces mostly in the form of the metabolites (Sathishkumar et al., 2020; Schmidt et al., 2018). Excessive consumption and incomplete removal in WWTPs (20-40%) results in up to 75% of the used DCF entering the aquatic environment (Schmidt et al., 2018). Furthermore, due to its hydrophilicity and stability DCF is more likely to persist in surface water. This can result in an increased ecological risk for aquatic organisms (Sathishkumar et al., 2020).

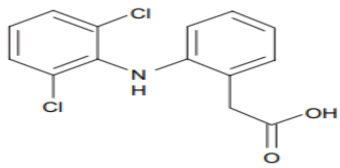


Fig. 5. Chemical structure Diclofenac with chemical formula $C_{14}H_{11}CL_2NO_2$ (Johnson et al., 2007).

Metoprolol (MET) (1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino)propan-2-ol; CAS number: 51384-51-1) (Fig. 6) is a cardiovascular ß-blocker and is used to treat hypertension and angina pectoris (Barclay et al., 2012; Oosterhuis et al., 2013). MET was first produced in 1969 and approved for medical use in 1982. The total consumption in Germany was in 2011 estimated on 135.000 kg per year (Oosterhuis et al., 2013). After ingestion 11% of the original dose is excreted via urine (Oosterhuis et al., 2013), however MET is extensively metabolized into three main metabolites (α-hydroxy-metoprolol, deaminated-metoprolol and (4-(2-hydroxy-3-isopropylaminopropoxy)-phenylacetic acid)), which make up for 85% of the excretion via urine (Barclay et al., 2012). Furthermore, MET cannot completely be removed WWTPs, in combination with the high prescription and consumption, MET is widely measured in the aquatic environment (Filipe et al., 2017). This can have a potential impact on aquatic organisms as MET acts by competitive inhibition of β-adrenergic receptors, which also exists in fish and other vertebrates (Felipe et al., 2017; Gröner et al., 2015).

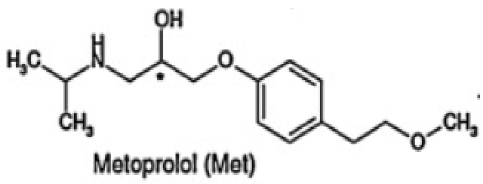


Fig. 6. Chemical structure metoprolol with chemical formula $C_{15}H_{25}NO_3$ (Bervlay et al., 2012).

3. Method

In this section, the methodological approaches adopted to complete this research are presented (Fig. 7). This chapter is structured as follows. First, the method used to identify the 2018 drought period is described in section 3.1. Then the method of data collection and processing will be elaborated in section 3.2, this to demarcate the different river basins and the available monitoring stations. Finally, when the river basins and water quality monitoring stations are established, the analyses of responses in pharmaceutical concentrations during the drought will be elaborated in section 3.3. This will be structured in accordance with the four Research Questions (Fig. 7).

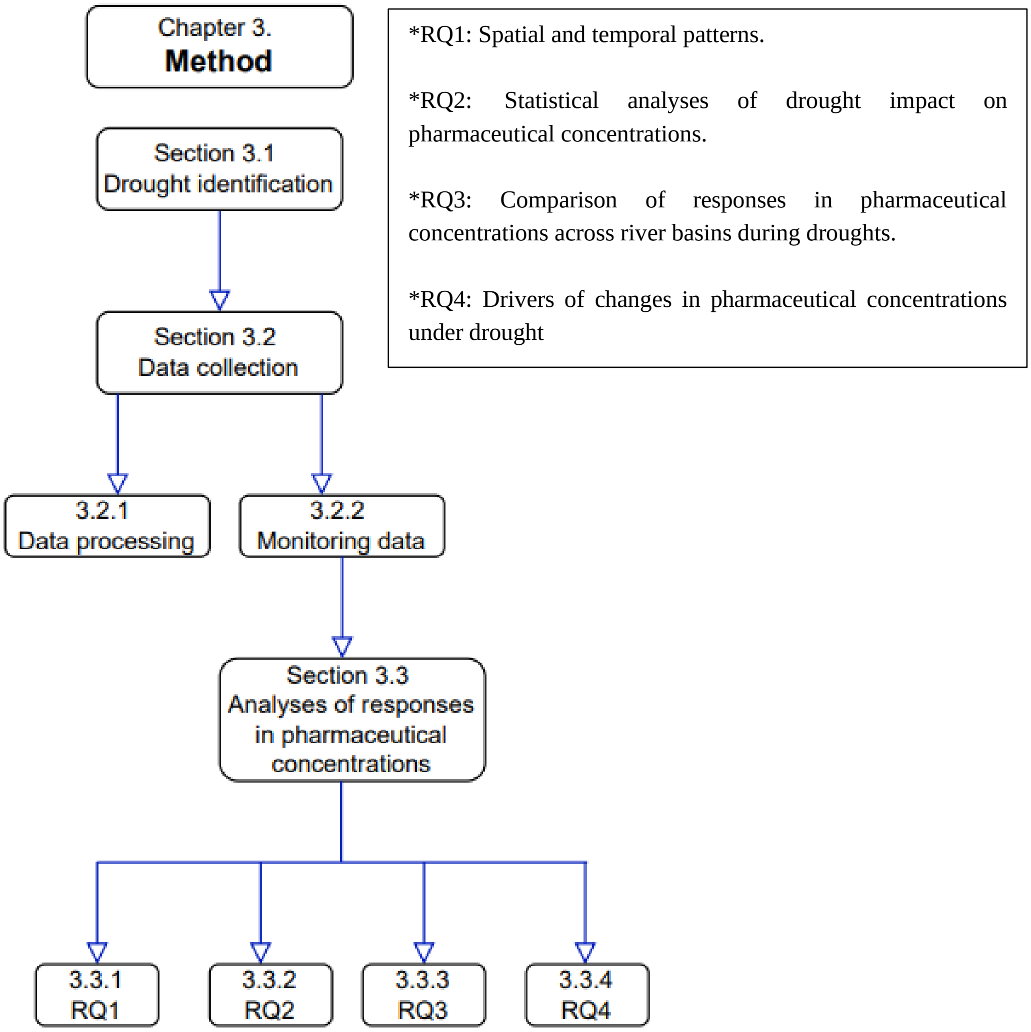


Fig. 7. Flow-chart of the method section.

3.1 Drought Identification

Streamflow droughts can be defined based on different indices such as, magnitude and timing of the low flow discharges, or a characterization of the drought event when the discharge is below a given threshold (Laaha et al., 2017). This study focusses on the flow period when discharge is below a certain threshold value, this value can be seasonally varying or constant throughout the year. A seasonal varying threshold gives a view on seasonal anomalies, while a constant threshold identifies the absolute stream flow drought. Hence, for his 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; Wolff and van Vliet, 2021), which can be calculated over a period of approximately 9-10 years. The threshold is calculated per monitoring station over the period 2012-2020 and 2011–2019 for the river Elbe and Rhine, respectively.

To compare the 2018 drought with common hydrological regimes, four reference years where selected as they overall represent common hydrological conditions and similar pharmaceutical concentrations. The drought of 2018 started in the first week of June and continued till the end of autumn. Therefore, this research will focus on the June-October period for the 2018 drought and compared 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 2014, 2016, 2017 and 2019. The median discharges and the total amount of days that the discharge is below the 20-percentile threshold will be 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 will be compared to the individual reference years. As the European River Memorandum (ERM) target value for water temperature is set at 25 degrees Celsius. This threshold of 25 °C must not be exceeded to prevent harming natural self-cleaning processes, such as bank infiltrations, sand filtration and artificial groundwater recharge (IAWR et al., 2020). The ERM is a covenant in which 170 European drinking water companies in the major European river basins (eg. Rhine, Elbe, Meuse, and Danube) have set minimum quality target values for river water (IAWR et al., 2020).

To test whether the discharge and water temperature deviate significant from the reference years the Mann-Whitney U test was conducted with a 95% significance level. The Mann-Whitney U test was used as the discharge and water temperature are normally distributed. The discharge and water temperature will be plotted versus time for the respective drought compared to the reference years.

3.2 Data collection

The selection of pharmaceuticals is based on a literature study and availability of sufficient monitoring data. To determine suitable river basins for this study some data requirements where set. Monitoring stations had to have at least monthly measured pharmaceutical concentrations over multiple years. The first assessment looked for general databases per river basin (e.g. Elbe, Rhine, Danube etc..). The second assessment looked for general databases per country.

Table 1 lists the sources of all pharmaceutical databases that are used for this research and the direct link to the site where the data can be downloaded. Each database has a different time period and frequency that the pharmaceuticals are measured, however all databases display the instantaneous measurements per pharmaceutical (in $\mu g.L^{-1}$). Initially, five pharmaceuticals were selected (carbamazepine, sulfamethoxazole, diclofenac, metoprolol, and ibuprofen). However, for Ibuprofen there were not sufficient measurements above limit of detection (LOD). The LOD is the lowest corresponding concentrations that can be determined with a sufficient degree of confidence (99%), this LOD value can differ per pharmaceutical, but also per water quality monitoring station and is therefore a bit arbitrary. Hence, ibuprofen is excluded for this research and the analysis will focus on the four pharmaceuticals: carbamazepine, sulfamethoxazole, diclofenac, and metoprolol. All publicly available data for each pharmaceutical over the last 20 years (2000-2020) is downloaded and stored in excel files.

Where available, daily mean discharge ($m^3.s^{-1}$) and water temperature (°C) data was downloaded at each of the selected monitoring sites. Table 2. lists the databases that are accessed for the discharge and water temperature data.

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

Database	Links	Time period	Frequency
Norman Empodat database	https://www.norman-network.com/nds/empodat/chemicalSearch.php?s=update	2000-2020	-
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-1	2000-2020	Monthly/yearly
IPCR – IKSR database	https://iksr.bafg.de/iksr/dl_auswahl.asp?S=3&JA=2019	2008-2019	Monthly/bi-weekly

Table 2. Discharge and water temperature databases used for this research, with corresponding links, time periods and frequency of measurements.

Database	Links	River	Time period	Frequency
Elbe-data portal (Fis Fgg Elbe)	https://www.elbe-datenportal.de/FisFggElbe/content/start/BesucherUnbekannt.action	Elbe	2008-2020	Daily
Service-portal Hamburg	https://serviceportal.hamburg.de/HamburgGateway/FVP/FV/BSU/wasserguete/wfWassergueteAnfrageKarte.aspx?sid=37#	Elbe	2008-2020	Daily
Umwelt Sachsen	https://www.wasser.sachsen.de/daten-und-berichte-archiv-9541.html	Elbe	2008-2020	Daily
Federal Institude of hydrology	https://www.bafg.de/EN/06_Info_Service/02_WaterQuality/waterQuality	Rhine	2008-2020	Daily
IPCR – IKSR database	https://iksr.bafg.de/iksr/dl_auswahl.asp?S=3&JA=2019	Rhine	2008-2019	Bi-weekly
Rijkswaterstaat water data	https://www.rijkswaterstaat.nl/water/waterdata-en-waterberichtgeving/waterdata	Rhine	2008-2019	Daily

3.2.1 Data processing

Fig. 8 displays all water quality monitoring stations and the number of measurements for the pharmaceuticals; carbamazepine, sulfamethoxazole, diclofenac and metoprolol for the past 20 years (period 2000-2020). Multiple river basins can be distinguished (e.g. Rhine, Elbe, Danube, Meuse, and Seine). The maps are produced with the program ArcGIS, each map visualises the publicly available pharmaceutical data. Only the data where the concentrations are above LOD are used. This is done to get a better overview of the available data which can be used for answering the research questions. First, all measurements are arranged to their station name using the pivot table tool in Excel, with this function the total number of measurements, average, minimum and maximum concentrations, variance, and standard deviation are easily calculated. Second, the longitude and latitude coordinates were added. The longitude and latitude coordinates of the monitoring stations are put in decimals or in degrees minutes seconds which is required when using the Coordinate system GCS_WGS_1984 in ArcGIS. After all coordinates are attributed to the monitoring stations, and are downloaded from Excel into ArcGIS.

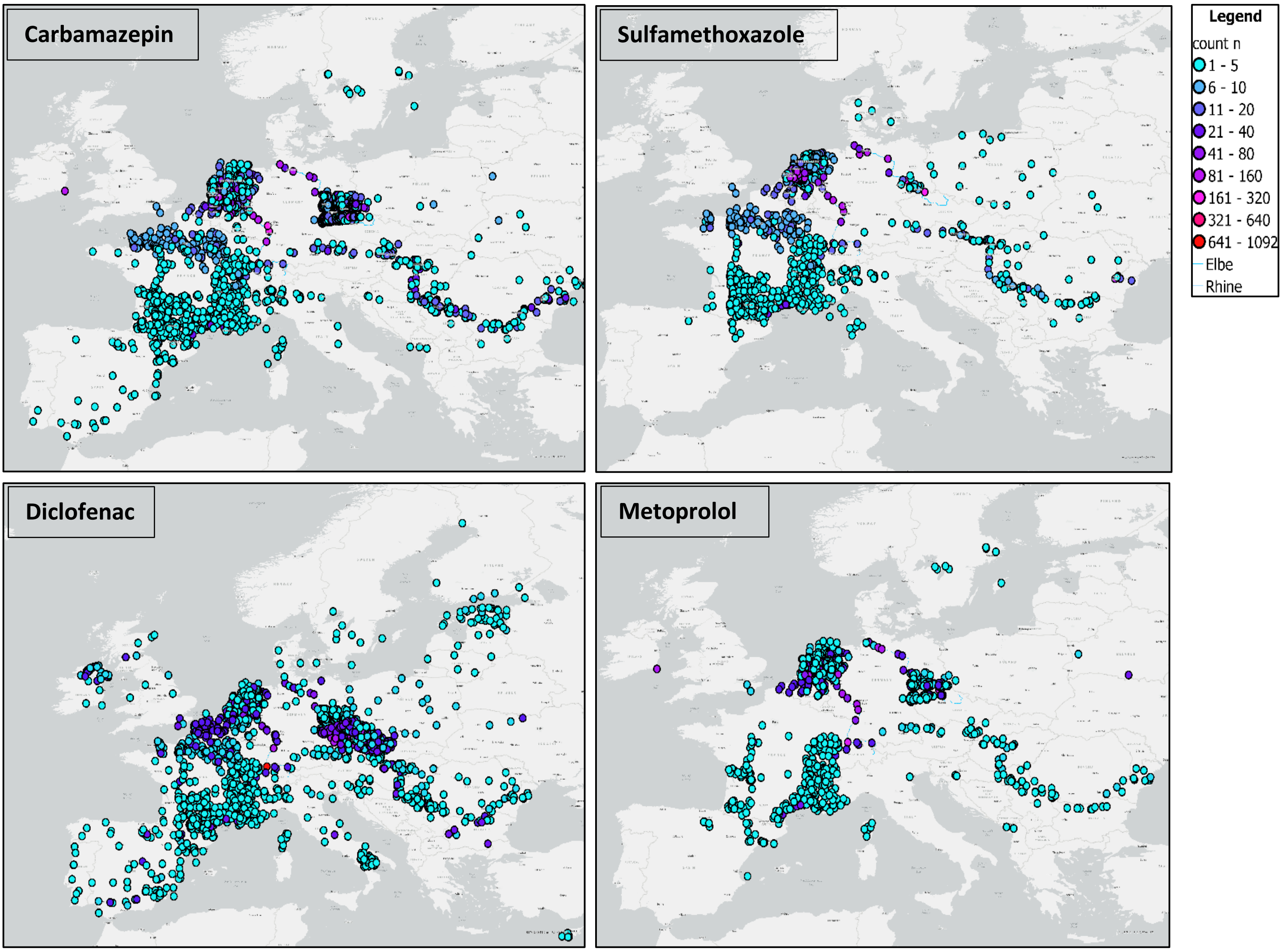


Fig. 8. Map of all monitoring stations and the number of measurements for carbamazepine (top left), sulfamethoxazole (top right), diclofenac (bottom left) and metoprolol (bottom right) for the period 2000-2020. Major rivers with data are the Rhine, Elbe, Danube, Seine and Meuse.

With the tool Geoprocessing and the function XY Table to point, the stations with their corresponding longitude and latitude coordinates are converted to point symbols. The Graduated Colours tool from the primary symbology is used to quantify the sub-groups of the total number of measurements.

To get a better overview on the useful data for this research, four additional maps are created, one for each pharmaceutical. Fig. 9 shows the maps of the selected pharmaceuticals and the data availability for the 2018 drought period June-October, which clearly demonstrates that only for the Elbe and Rhine there are sufficient measurements for the 2018 drought for all four pharmaceuticals over multiple monitoring stations.

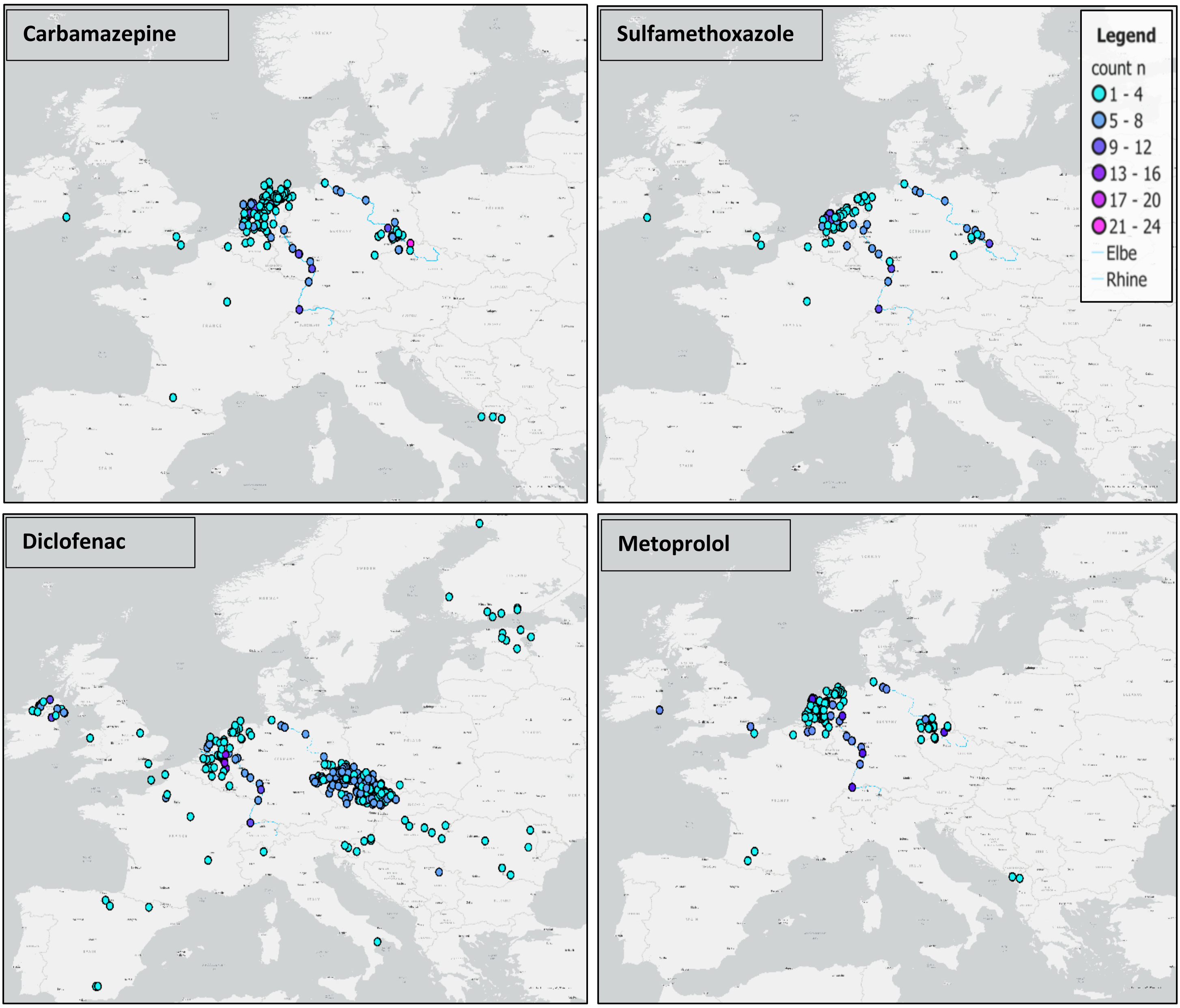


Fig. 9. Map of all monitoring stations and the number of measurements for carbamazepine (top left), sulfamethoxazole (top right), diclofenac (bottom left) and metoprolol (bottom right) for the drought period June-October 2018. Major rivers with data are the Rhine and Elbe. Note the different values in the legend for each pharmaceutical.

3.2.2 Monitoring data

This research will focus on the Elbe and Rhine river, for those river catchment sufficient data is available to answer the research questions (see Fig. 9). The study area will be in the German part of the river catchments. To determine a manageable and focused number of sites for data analysis, data requirements were set. The water quality monitoring site had to have at least monthly measurements for each pharmaceutical for the period June-October 2018. In total, 5 sites for the Elbe and 6 for the Rhine river were selected as having suitable data availability for the study (Fig. 10). The pharmaceutical parameters of the two rivers are investigated at the 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, and at the monitoring stations Weil am Rhine (km 165 from Lake Constance at the Swiss-German border), Worms (km 443), Mainz (km 498), Koblenz/Rhine (km 590), Bad Honnef (km 632) and Bimmen (km 858 at the Dutch-German border) alongside the Rhine (Fig. 10). Overall most stations have monthly measured pharmaceutical date available from 2010 onwards (Table 3 and 4). Hence, all data between 2010-2020 is downloaded and stored in excel files. One additional monitoring station alongside the Elbe is used (Zehren, left bank 89,6 km), this station has only weekly data for carbamazepine.

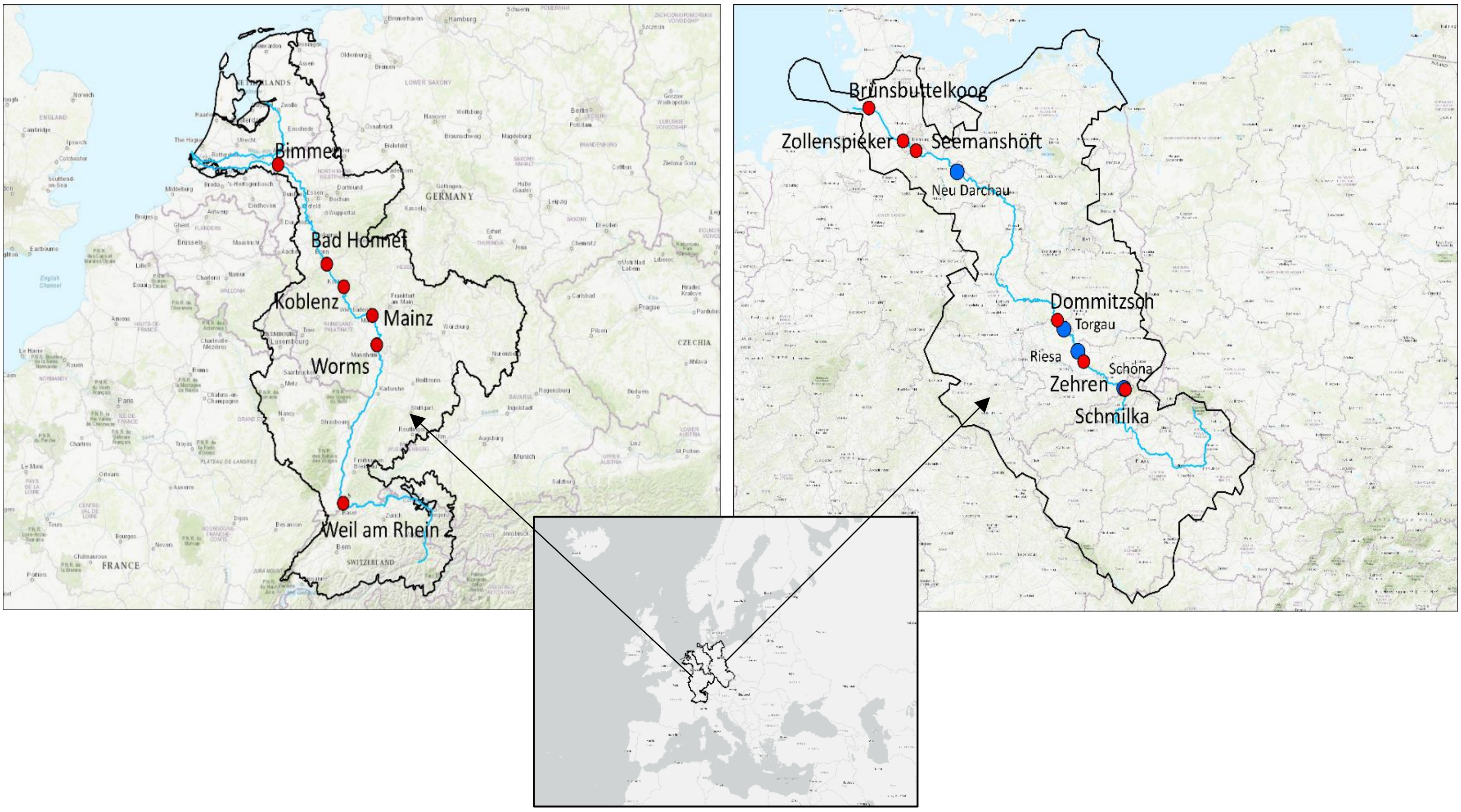


Fig. 10. Rhine (Left) and Elbe (Right) river catchment with the monitoring stations used for this research (Red dots). Blue dots represent the gauge stations, closest to the water quality stations.

Daily mean discharge ($m^3.s^{-1}$) and water temperature (°C) data was downloaded at each of the selected monitoring sites (Table 2). Out of the 6 sites from the Elbe where sufficient pharmaceutical data was available, only four (Schmilka, Zehren, Dommitzsch and Zollenspieker) had an appropriate amount of discharge measurements for the analysis. Since, the discharge is not measured directly at all water quality monitoring stations, discharge measurements from nearby gauge stations are used (Fig. 10) (blue dots are gauge stations). With Schmilka (Schöna), Zehren (Riesa), Dommitzsch (Torgau) and Zollenspieker (Neu Darchau), respectively. All gauge 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). Furthermore, daily mean discharge ($m^3.s^{-1}$) and water temperature (°C) data for the Rhine are directly measured at all 6 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 weekly. For the stations Weil am Rhine, Worms and Mainz along the Rhine pharmaceuticals are measured bi-weekly. While, at Koblenz, Bad Honnef and Bimmen they are measured monthly. 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 (Table 3 and 4).

Table 3. Monitoring stations alongside the Elbe with the data availability for the period 2010-2020.

	Schmilka	Zehren	Dommitzsch	Zollenspieker	Seemanshöft	Brunsbüttelkoog
Carbamazepine	525	523[1]	545	131	132	97
Sulfamethoxazole	133	-	155[2]	131	131	73[3]
Diclofenac	178	-	157	126	102	-
Metoprolol	166	-	119	124	96	78[3]
Water Temperature	X*	X*	X*	Bundshaus	X*	X*
Discharge	Schöna	Riesa	Torgua	Neu Darchau	Neu Darchau	-

[1]Zehren: reference year 2020 (April-August) carbamazepine missing

[2]Dommitzsch: reference year 2016 sulfamethoxazole missing

[3]Brunsbüttelkoog: reference year 2017 missing for sulfamethoxazole and metoprolol

X daily water temperature measured at location water quality monitoring stations*

Table 4. Monitoring stations alongside the Rhine with the data availability for the period 2010-2019.

	Weil Am Rhine	Worms	Mainz	Koblenz	Bad Honnef	Bimmen
Carbamazepine	259	143[1]	225	128	120	129
Sulfamethoxazole	257	129[1]	121[2]	179	104	147
Diclofenac	920	130[1]	225	126	102	123
Metoprolol	242	130[1]	122[2]	65[2]	103	125
Water Temperature	X[3*]	*X**	*X**	*X**	*X**	*X**
Discharge	X[3*]	*X**	*X**	*X**	*X**	*X**

[1] Worms: no data before 2015

[2] Mainz and Koblenz: no data before 2014

[3] Weil am Rhine: water temperature and discharge 2019 missing

X daily water temperature and discharge measured at water quality monitoring stations*

3.3Analysis of responses in pharmaceutical concentrations

In this section the method of analysis associated with each research question will be highlighted, in accordance with the research questions.

3.3.1 RQ1: Spatial and temporal patterns in pharmaceutical concentrations at available monitoring stations

To analyse the spatial and temporal patterns in pharmaceutical concentrations, the study period 2010-2020 is chosen as it represents overall constant pharmaceutical concentrations. Before 2010 pharmaceutical concentrations where much higher and are therefore not representative. As the pharmaceutical concentrations left out of the analysis, as these measurements cannot be compared with the drought period of 2018.

To analyse the spatial patterns of the four pharmaceuticals, all the available monitoring stations in Europe which have data for the 2018 drought will be represented. Four maps will be created in ArcGIS one for each pharmaceutical. Each map shows the average calculated concentration for the period 2010-2020. As this study focusses on the Elbe and Rhine river, the spatial patterns within this area will be further elaborated in detail. In the Appendix a table will be included that shows per monitoring station the average concentration with corresponding standard deviation.

The seasonal dynamics of the four pharmaceuticals will be discussed in accordance with the hydrological seasonal timescale. With season 1 (October-December), season 2 (January-March), season 3 (April-June) and season 4 (July-September). This seasonal timescale is used to get a better understanding of the relationship between drought conditions (low flow conditions) and pharmaceutical concentrations. To display the seasonal dynamics two stations per river basin are selected, one upstream and one downstream. Box and whisker plots will be made for each hydrological season which represent all measured data for the period 2010-2020. Boxplots show the 25^{th} (lower) , 50^{th} (median) and 75^{th} (upper) quantile and the extremes. However, for the analysis mainly the median concentrations are used to discuss the difference between the four hydrological seasons.

3.3.2 RQ 2: Statistical analyses of drought impact on pharmaceutical concentrations

The water quality is studied for the June–October period during the 2018 drought and will be compared to the selected reference periods. For the Elbe the reference years are 2014, 2016, 2017 and 2020 and for the Rhine 2014, 2016, 2017, 2019. In addition, for this part of the analysis the samples which had a pharmaceutical concentration lower than the detection limit were set at half of the individual detection limit (DL/2), which is in accordance with other studies (Sjerps et al., 2017; Wolff and van Vliet, 2021). This method can be used as a small amount (<15%) of the observed values are not detected, therefore those values can be replaced with the detection limit divided by two and the appropriate analysis can be proceeded (EPA, 2000; Haas and Sheff, 1990).

To test whether there are temporal changes in pharmaceutical concentrations during the drought which deviate significantly from the reference periods, descriptive statistics (e.g. mean, median, standard deviation) can be used. To test whether the concentration differences are statistically significant the Mann-Whitney U test or Unpaired T-test can be used. To determine which statistical test can be used, it must first be established if the data is normally distributed. To test if the pharmaceutical data is normally distributed the Shapiro-Wilk test can be used (as the sample size is < 5000). The normality test is executed on the timeseries (reference years + drought year for all months January-December). The results will be displayed in tables which are included in the Appendix, the tables will show the results of the Shapiro-Wilk test and descriptive statistics of the pharmaceuticals per monitoring station.

As the computed p-value is smaller than the significance level $\alpha=0.05$, the null hypothesis (H_0) can be rejected, hence the alternative hypothesis (H_a) is true. This means that the pharmaceutical data from which the samples were extracted follow a non-normal distribution, therefore the correlation between the variables can be quantified by the Mann-Whitney U test with a 95% significance level. If the computed p-value is greater than the significance level $\alpha=0.05$ the H_0 is accepted, and the pharmaceutical data follows a normal distribution, and an Unpaired t-Test can be used. The Mann-Whitney U or Unpaired t-Tests will be applied on each individual reference year in comparison with the drought period June-October 2018. When the computed p-values of the Mann-Whitney U test are lower than the significance level ($p < 0.05$) the H_0 can be rejected and the H_a is accepted, which indicates that the differences in average concentrations between the drought of 2018 compared to the reference years is statistically significant. When the p-value is higher than the significance level ($p > 0.05$) H_0 can be accepted and there is no significant difference between the drought and reference years.

Furthermore, to considering drinking water and ecotoxicological perspective, it is undesirable to exceed the target values for pharmaceutical concentrations in surface waters. This will be assessed by looking at the magnitude, frequency, and duration of exceedance target values. The ERM target values are set by the Internationale Arbeitsgemeinschaft der Wasserwerke im Rheineinzugsgebiet. The maximum ERM values for all four pharmaceuticals are set at $0.1\ \mu g.L^{-1}$ (the ERM target value will be added to the scatterplots as a horizonal line).

Finally, anomalies can be calculated to estimate the water quality impact under droughts. Anomalies are the percentage difference between the median drought concentrations and median long-term concentrations and can be calculated as follows:

$$\text{Change [\%]} = \frac{\text{observed}-\text{average}}{\text{average}} * 100 \qquad \text{Eq. (1)}$$

This will only be done for the pharmaceuticals where there is a statistically significant difference. This is done by calculating the long-term average pharmaceutical concentration based on the time series 2010-2020 at each station on a monthly basis.

3.3.3 RQ 3: Comparison of responses in pharmaceutical concentrations across river basins during droughts

To compare the responses in pharmaceutical concentrations across different river basins, the average concentrations of the 2018 drought (June-October) are compared with the average concentrations over the period 2010-2020 (June-October). First, a comparison is made by looking at the average concentration differences for all available monitoring stations, this to place it in a larger perspective. For a reliable and correct data analysis requirements were set, monitoring stations are included which have 30 measurements or more for the 2010-2020 (June-October) period and at least 3 measurements for the 2018 drought (June-October). This is visualised in 3 maps for each pharmaceutical made in ArcGIS. The first map displays the average concentration for the 2018 drought (June-October). The second map shows the average concentration for the period 2010-2020 (June-October). The third map visualizes the average percentage concentration differences between the two selected periods.

Second, a more comprehensive comparison between the monitoring station alongside the Elbe and Rhine river is done, to compare the responses of the pharmaceutical concentrations between the two major river basins. This is done by calculating the median percentage concentration differences between the 2018 drought and the selected reference years (2014, 2016, 2017 and 2020 Elbe) and (2014, 2016, 2017 and 2019 Rhine). This results in the fourth map, that illustrates the median concentration percentage differences between the 2018 drought and reference periods and is discussed per monitoring station.

3.3.4 RQ 4: Drivers of changes in pharmaceutical concentrations under drought

The focus will be on the comparison between the measured pharmaceutical concentrations and the corresponding measured discharge and water temperature. This is done for the drought year of 2018 (January-December) and corresponding reference years (January-December) per river basin. The measured pharmaceutical concentrations are compared with the corresponding measured discharge and water temperature. Using multiple linear regression analyses, the dependency between the pharmaceutical concentrations and water temperature will be assessed. The following parameters were determined: $R^{2.}$ and the p-value. R^2 is a measure for the proportion of the variance of a dependent variable (concentration) that is explained by the independent variable (water temperature). The p-value represents the probability that the gradient of the regression line deviates from zero. A 5% level of significance (α) was used to identify whether the gradient of the regression line is significant.

The effects of variability in discharge on water quality is estimated by fitting an empirical relations between water quality and discharge (Eq. (2)), this conceptual relation describing dilution is based on van der Weijden & Middelburg (1989).

$$C = \frac{a}{Q} + b \qquad \text{Eq. (2)}$$

Where C = concentration ($\mu g.L^{-1}$), a = chemical load ($\mu g.s^{-1}$), Q = discharge ($m^3\ s^{-1}$) and b = background concentration ($\mu g.L^{-1}$). The parameter R^2 which represents the goodness of fit will be used to determine the significant relationship. Parameter (b) will be estimated as the lowest measured value of the reference years and drought period. Parameter (a) for chemical load was derived from applying the equation a = (C_{pharma} - b)*Q. A single parameter value of (a) for each monitoring station and pharmaceutical was calculated based on the mean average of the derived (a) values. This equation describes a dilution-based model, the larger the discharge (Q) the smaller the modelled value.

4. Results

The results section is structured in accordance with the methodology. Section 4.1 describes the 2018 drought in the rivers Elbe and Rhine by looking at the discharge and water temperature. In Section 4.2 the spatial and temporal patterns at the available monitoring stations are discussed to get a better understanding on the seasonal dynamics of the four selected pharmaceuticals. Section 4.3 will then further elaborate the statistical analysis on the pharmaceutical concentrations under drought compared to the reference years. In section 4.4 a comparison between the two river basins is further studied by looking at the average percentage changes. Finally, the external factors (i.e. discharge and water temperature) that are impacted during droughts, are compared with the pharmaceutical concentrations in section 4.5. This chapter aims to summarise the most interesting findings for each research question and to present example results obtained at particularly interesting monitoring stations (Fig. 11). All other results will be displayed in the appendix.

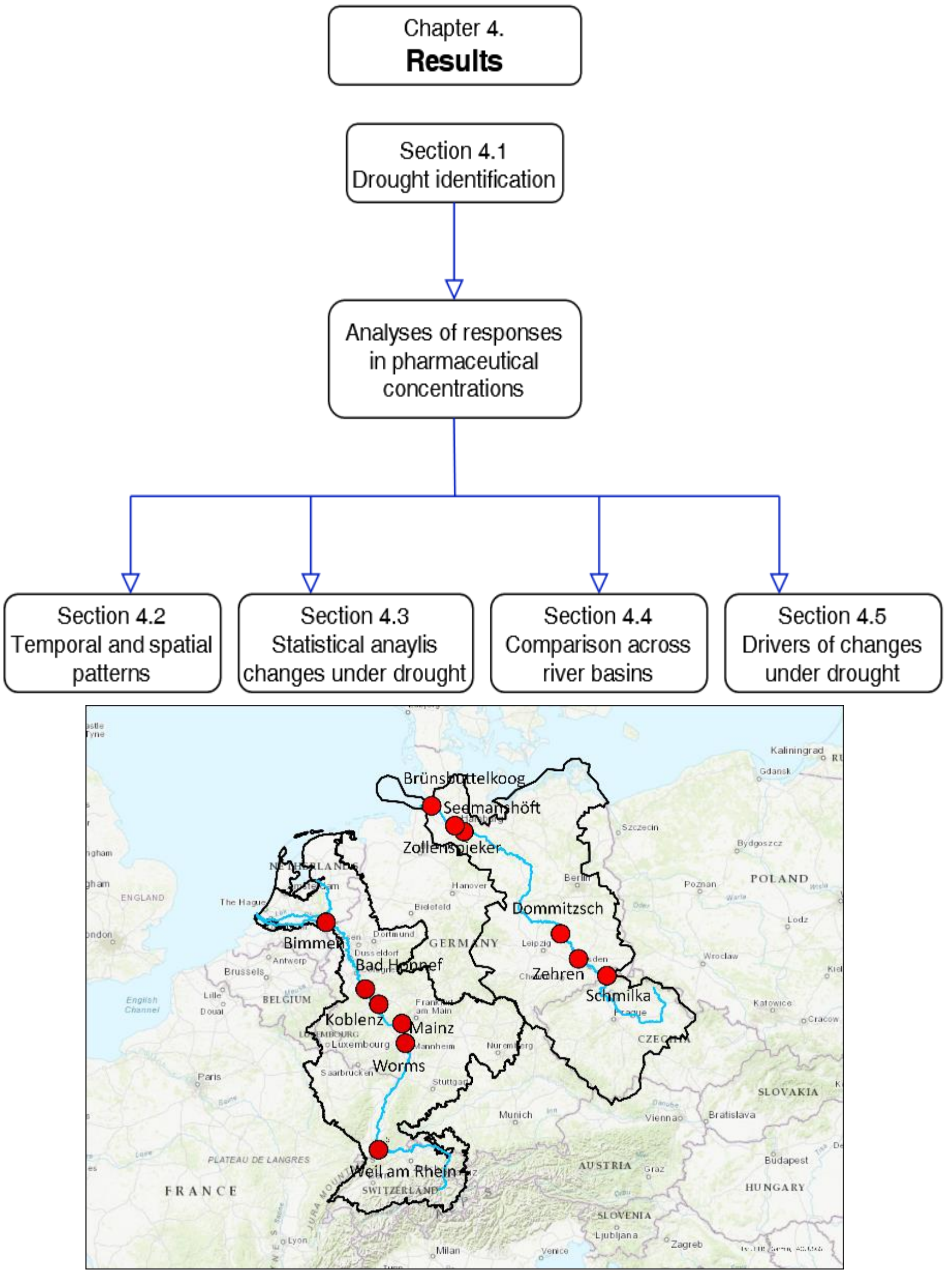


Fig. 11. Flow chart of the result section & study area with the locations of the water quality monitoring stations.

4.1 Drought Identification

4.1.1 Hydrometeorological conditions

Two-gauge stations, alongside the rivers Elbe (Schmilka-Schöna and Zollenspieker-Neu Darchau) and Rhine (Koblenz and Bimmen) were selected to display the hydrometeorological conditions (Fig. 12 a-d) (see Fig. 11 for location stations). Hydrological droughts can be defined based on the number of days when daily discharge is lower than the 20-percentile. This threshold value is calculated over the period 2012–2020 and 2011-2019 for the Elbe and Rhine, respectively. This resulted in the following threshold values for streamflow drought, 122 $m^3.s^{-1}$ for Schmilka, 290 $m^3.s^{-1}$ for Zollenspieker (Elbe), 1090 $m^3.s^{-1}$ Koblenz and 1316 $m^3.s^{-1}$ for Bimmen (Rhine). Table 5 shows the median discharge and days below threshold for the four-gauge stations for the period June-October. The median discharge values at all four stations were significantly lower ($P<0.01$) during the drought of 2018 compared to the reference years.

The discharge of the Elbe river was notably lower than the reference periods, with a median discharge of 94.2 $m^3.s^{-1}$ at Schmilka for the 2018 drought compared to the reference periods, 202 $m^3.s^{-1}$ (2014), 170 $m^3.s^{-1}$ (2016), 129 $m^3.s^{-1}$ (2017) and 194 $m^3.s^{-1}$ (2020) (median percentage difference -68% and an average percentage difference of -90%) (Table 5). For the drought of 2018 the discharge was 139 days lower than the 20-percentile discharge (122 $m^3.s^{-1}$) whereas this compared to 22 days, 41 days, 78 days, and 20 days for the same period (June-October) of the other reference years. Similar results were found downstream at gauge station Zollenspieker-Neu Darchau with a median percentage difference of -83% (Fig. 12b and Table 5). Mid-June 2018 onwards the discharge declined and stayed under the 20-percentile threshold until the first week of December, with the lowest discharge reached on August 23rd (70.6 $m^3.s^{-1}$) and September 4th (163 $m^3.s^{-1}$) (Fig. 12a-b) at Schmilka-Schöna and Zollenspieker-Neu Darchau, respectively. Furthermore, the June-October period of 2015 and 2019 was also characteristic with low discharges in the Elbe basin, with median discharges of 108 and 111 $m^3.s^{-1}$ at gauge stations Schmilka-Schöna and Zollenspieker- Neu Darchau. The droughts of 2015 and 2019 where not as extreme as the one of 2018, however, it is not appropriate to take those data as reference years as they do not represent common hydrological conditions, represented by the black solid line in Fig. 12a-b. The black solid line is the average discharge calculated over a 9-year period 2012-2020 (June-October). Moreover, the reference years represent overall common hydrological conditions.

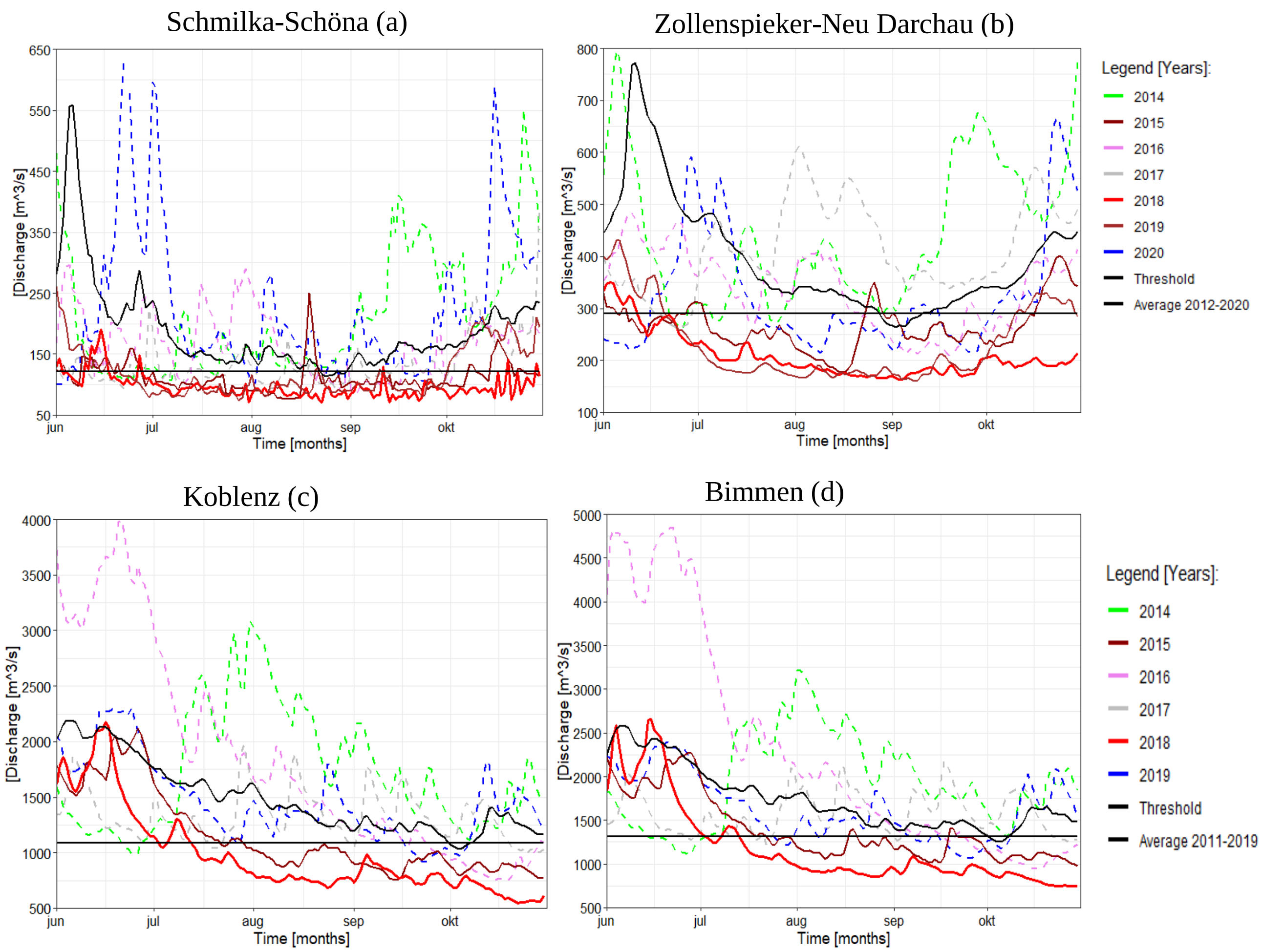


Fig. 12. Discharge at Gauge stations Schmilka-Schöna (a) and Zollenspieker-Neu Darchau (b) along the Elbe and Koblenz (c) and Bimmen (d) along the Rhine during the drought of 2018 and reference years and the average discharge of the period 2012–2020 (Elbe) and 2011-2019 (Rhine). The horizontal thresholds 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.

The drought of 2018 was also for the Rhine river associated with extremely low flow conditions, with 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) (median percentage difference -72%) (Fig. 12c and Table 5). For 114 days the discharge was lower than the 20-percentile threshold (1316 $m^3.s^{-1}$), compared to 6 days, 37 days, 18 days, and 21 days for the same period (June-October) of the reference years. Similar results were found upstream at Weil am Rhein (median percentage difference -63%) as downstream at station Bimmen (median percentage difference -72%) (Fig. 12d and Table 5). Mid-June the discharge started quickly to decline and went under the 20-percentile threshold line in the second week of July at Koblenz and Bimmen (Fig. 12c-d). This discharge deficit continued until late November with minimum values of 547 $m^3.s^{-1}$ (October 22nd) and 747 $m^3.s^{-1}$ (October 24th) at Koblenz and Bimmen, respectively.

The June-October period of 2015 was also characterised with a discharge shortage, especially in the German part of the catchment, with a median discharge of 1000 $m^3.s^{-1}$ and 1280 $m^3.s^{-1}$ at Koblenz and Bimmen (Table 5). Therefore, it is not appropriate to take 2015 as reference year as it does not represent a common hydrological year, represented by the black solid line in Fig. 12c-d, calculated over a 9-year period (2011-2019).

Table 5. Median discharge and days below Threshold for the period June-October at the gauge stations along the Elbe, Schmilka-Schöna (122 $m^3.s^{-1}$), Zollenspieker-Neu Darchau (290 $m^3.s^{-1}$), and along the Rhine Koblenz (1090 $m^3.s^{-1}$) and Bimmen (1316 $m^3.s^{-1}$).

Year	Median discharge [$m^3.s^{-1}$]				Days below Threshold [-]			
	Elbe		**Rhine**		**Elbe**		**Rhine**	
	Schmilka	Zollenspieker	Koblenz	Bimmen	Schmilka	Zollenspieker	Koblenz	Bimmen
2014	202	445	1580	1862	22	29	6	19
2015	108	270	1000	1240	120	115	98	97
2016	170	372	1530	1850	41	41	37	42
2017	129	429	1280	1520	78	73	18	19
2018	94,2	200	808	962	139	141	114	115
2019	111	219	1380	1545	102	104	21	38
2020	194	303	-	-	20	21	-	-

Red numbers represent drought periods. Black numbers represent reference years.

4.1.2 Water Temperature

During the 2018 drought water temperatures, in the period June-August were increased, compared to the reference period for both the Elbe and Rhine rivers (Fig. 13a-d). The median water temperatures were 22.7 °C and 22.4 °C (Fig. 13a-b) at the stations Schmilka and Zollenspieker (Elbe), respectively. The water temperatures were on average +1.9 °C and +1.2 °C warmer than the average of the reference years. Furthermore, the ERM target value of 25 °C were exceeded 13 (Schmilka) and 15 (Zollenspieker) times during the 2018 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.

During the 2018 drought the water temperatures of the Rhine where even higher than the Elbe for the period (June-August). With median water temperatures of 24.3 °C and 23.2 °C (Fig. 13c-d) at the stations Koblenz and Bimmen, respectively. This was on average +1.9 °C and +2.0 °C warmer than the average of the reference periods. The ERM target value of 25 °C were exceeded 34 (Koblenz) and 16 (Bimmen) times during this period. The longest uncontiguous period of exceedance occurred between July 15th and August 11th, with a total of 28 days and a maximum temperature of 28 °C at Koblenz. At Bimmen the exceedance occurred during one consecutive period from July 24th until August 8th, with a maximum water temperature of 26.6 °C.

Overall the reference years of both the Elbe and Rhine river represents common hydrological conditions. Despite the lower discharge conditions in 2017 at the Elbe and the higher water temperature at Schmilka, it is still suitable to investigate the impact of the 2018 drought on the pharmaceutical concentrations, this due to the extreme conditions during the 2018 drought.

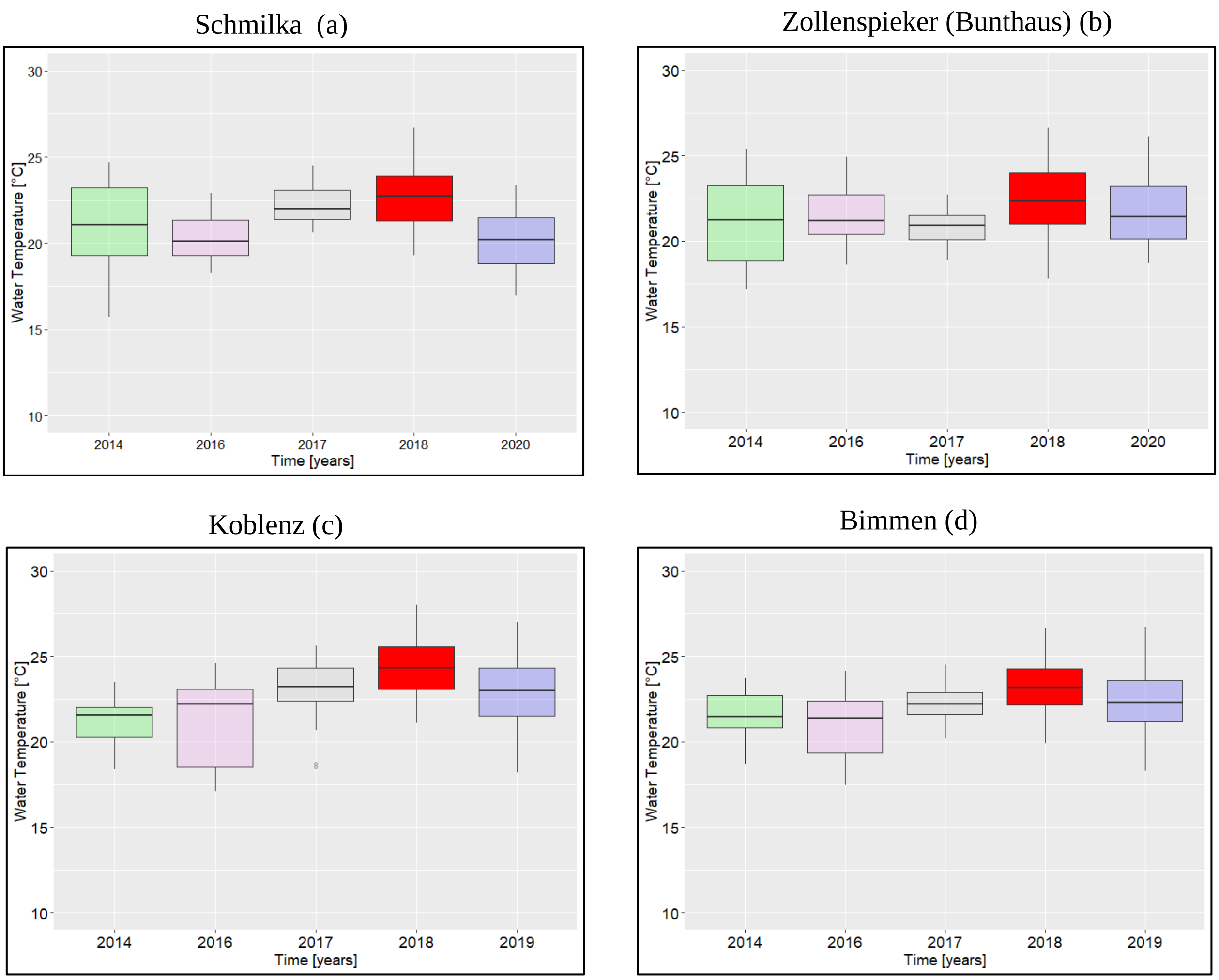


Fig. 13. Boxplots summarizing the distribution in water temperature for the June-August period for the 2018 drought and reference years. With two monitoring stations along the Elbe, Schmilka (a) and Zollenspieker-Bundshaus (b) and the two monitoring stations alongside the Rhine, Koblenz (c) and Bimmen (d).

4.2 RQ1: Analysis of spatial and temporal patterns in pharmaceutical concentrations at available monitoring stations

This section is structured as follows: First, the spatial patters of carbamazepine and sulfamethoxazole are discussed as they are both conservative like substances. Second, the spatial patterns of the substances diclofenac and metoprolol will be elaborated upon. This will be done for the period 2010-2020 for all available monitoring stations which have data for the 2018 drought. Finally, the temporal (seasonal) patterns of each pharmaceutical will be discussed in the same consecutive order as the section spatial patterns and for the same period. Four stations, two for each river (one upstream and one downstream) were selected to visualize the observed seasonal patterns for each pharmaceutical (see Fig. 11 for station locations).

4.2.1 Spatial patterns

The spatial patterns of the average carbamazepine and sulfamethoxazole concentrations are shown in Fig. 14. Most monitoring stations are in the river basins of the Elbe, Rhine, and Meuse, in Germany, France, Belgium and the Netherlands. For carbamazepine 23 out of the 212 monitoring stations and 12 out of the 82 monitoring stations for sulfamethoxazole are higher than the ERM target value of 0.1 µg.L^{-1}. Based upon the monthly available data for the 2018 drought and reference years, the next part of the analysis will focus on the rivers Elbe and Rhine and the selected monitoring stations in the German part of the river catchments (see Fig.11 for monitoring stations and location.

In general there are similar spatial concentration patterns for carbamazepine and sulfamethoxazole in both the Elbe and Rhine river. With an increasing trend in average concentrations when moving in downstream direction (Appendix 1 Table 1a), except for sulfamethoxazole, an opposite spatial distribution can be observed in the Elbe basin. For carbamazepine the lowest average concentrations are measured at monitoring station Schmilka (0.048 µg.L^{-1}) (Fig. 14 location (a)), with increasing concentrations until Seemanshöft (0.091 µg.L^{-1}) (Fig.14 location (b)). After Seemanshöft concentrations decrease, with an average concentration of 0.072 µg.L^{-1} at Brunsbüttelkoog (Appendix 1 Table 1a). Furthermore, carbamazepine shows similar patterns for the Rhine river, with low average concentration at Weil am Rhine (0.021 µg.L^{-1}) and high average concentrations at Bimmen (0.052 µg.L^{-1}) (Appendix 1 Table 1a).

Moreover, for sulfamethoxazole, an opposite spatial distribution can be observed. High concentrations are measured upstream at station Schmilka (0.055 µg.L^{-1}), a decline in concentration continues untill Brunsbüttelkoog (0.034 µg.L^{-1}) while moving in downstream direction (Appendix 1 Table 1b). Incontrast to the spatial distribution of sulfamethoxazole in the Elbe, the spatial distibution of this drug in the river Rhine shows low concentrations upstream at Weil am Rhine (0.015 µg.L^{-1}) and an overall increas in concentration when moving in dowstream direction untill Bimmen (0.037 µg.L^{-1}) (Appendix 1 Table 1b).

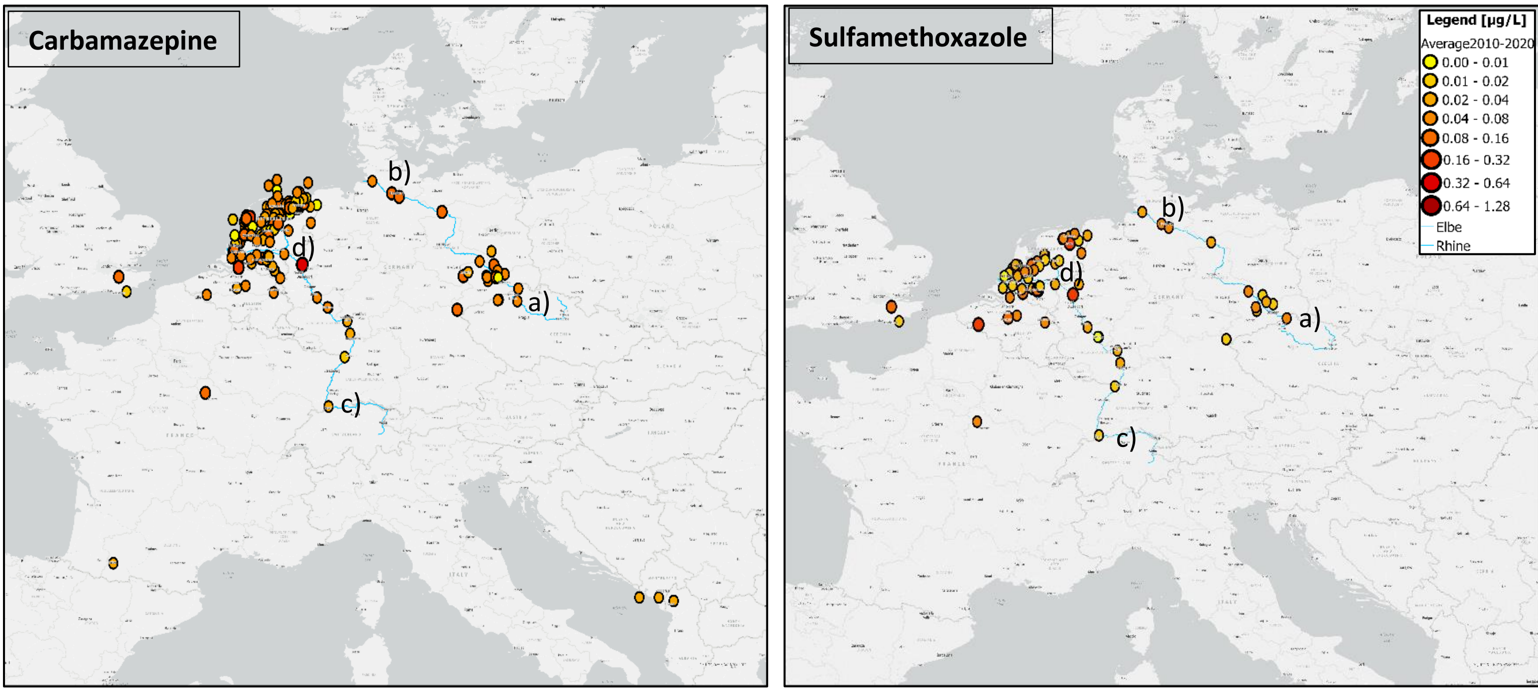


Fig. 14. Spatial patterns of the average concentrations of carbamazepine (left) and sulfamethoxazole (right) in (µg.L^{-1}) for the period 2010-2020. Station a): Schmilka, b): Seemanshöft (Elbe), c): Weil am Rhein and d): Bimmen (Rhine). Monitoring stations where the concentrations are above the ERM target value (0.1 µg.L^{-1}) are larger.

The spatial patterns of the average diclofenac and metoprolol concentrations are shown in Fig. 15. The maps show that for 83 out of 334 and 18 out of 126 monitoring stations the average concentrations are above the ERM target value of 0.1 μg.L^{-1} for diclofeanc and metorpolol, respectively. When looking more closely at the Elbe and Rhine rivers, the spatial patterns show a dynamic system, with both increasing and decreasing average concentrations between monitoring stations. For diclofenac there is a decrease in average concentrations of 35% between Dommitzsch (0.055 μg.L^{-1}) and Zollenspieker (0.036 μg.L^{-1}), while the average concentration increases again with 97% at Seemanshöft (0.071 μg.L^{-1}) (Appendix 1 Table 1c). The Rhine shows similar variations, with an increase in average concentration of 40% between monitoring station Weil am Rhein (0.035 μg.L^{-1}) and Mainz (0.049 μg.L^{-1}). Then the average concentration decreases with 27% at Koblenz (0.036 μg.L^{-1}), which then increases again with 78% at Bad Honnef (0.064 μg.L^{-1})(Appendix Table 1c).

For metoprolol at the Rhine river there is an increase in concentration between Weil am Rhein (0.012 μg.L^{-1}) and Worms (0.032 μg.L^{-1}) of 166%. Than a decreasing trend continues downstream till Koblenz (0.025 μg.L^{-1}), which is then again followed by an increase of 156% untill Bimmen (0.064 μg.L^{-1}) (Appendix 1 Table 1d).

Moreover, for the river Elbe there is an increasing trend when moving in downstream direction between Schmilka (0.043 μg.L^{-1}) and Zollenspieker (0.082 $^{-1}$) of 91%. This is followed by a decrease of 46% uptill Brunsbüttelkoog (0.044μg.L^{-1}) (see Fig.10 for locations monitoring stations).

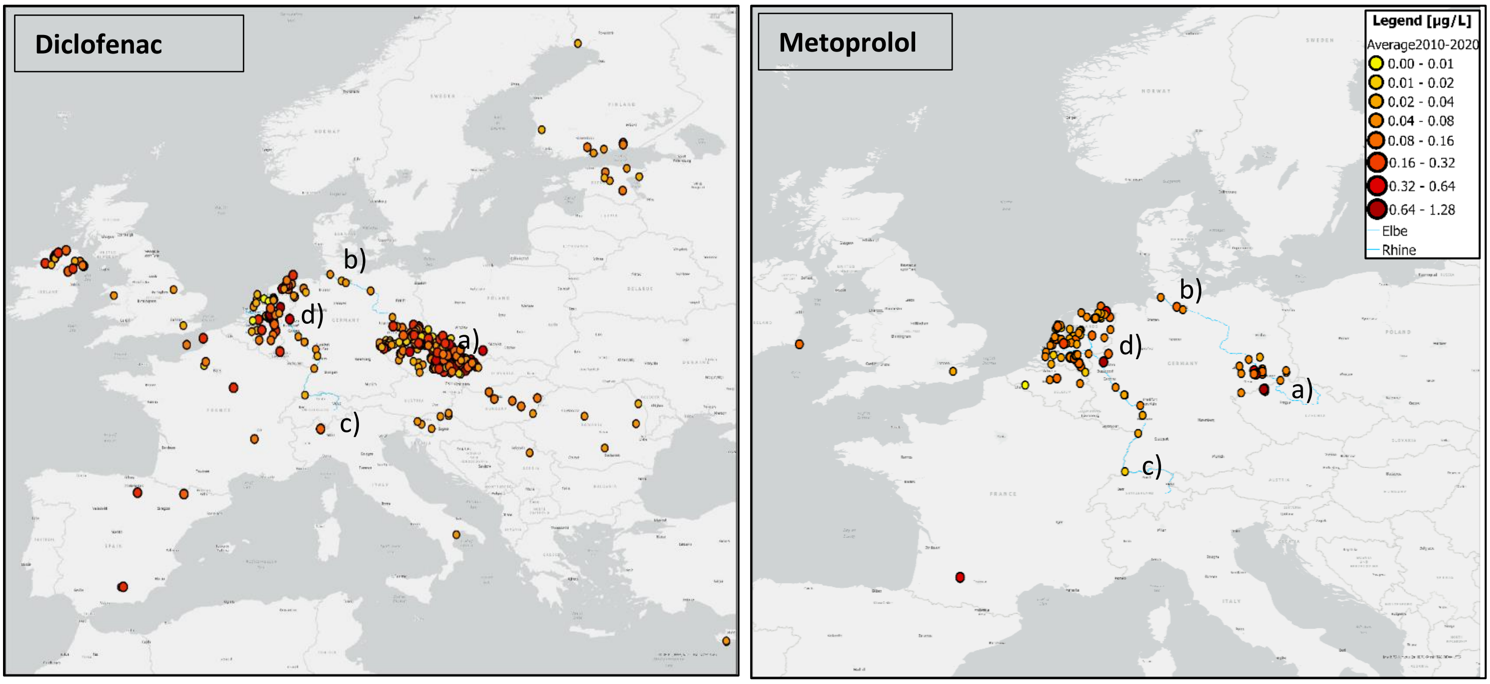


Fig. 15. Spatial patterns of the average concentrations of diclofenac and metoprolol for the period 2010-2020. Station a) Schmilka, b) Seemanshöft (Elbe), c) Weil am Rhein and d) Bimmen (Rhine). Monitoring stations where the concentrations are above the ERM target value (0.1 μg.L^{-1}) are enlarged.

4.2.2 Temporal patterns

Fig. 16a-d shows the seasonal patterns of the pharmaceutical carbamazepine for two selected monitoring stations alongside the Elbe (Schmilka and Seemanshöft) and Rhine (Weil am Rhine and Bimmen) rivers. For the Elbe, lowest concentrations are found in season 2 (January-March) with median concentration of 0.037 μg.L^{-1} and 0.071 μg.L^{-1} at Schmilka and Seemanshoft, respectively. After Season 2 the concentrations increase until season 4 (July-September) and season 1 (October-December) with highest concentrations in September and October for Schmilka (Fig. 16a) and Seemanshöft (Fig. 16b), respectively. The monitoring stations downstream show seemingly the same patterns for both the Eble and Rhine rivers. With the lowest median concentrations in season 2 (0.04 μg.L^{-1}) and highest concentrations in seasons 1 (0.058 μg.L^{-1}) at Bimmen (Fig. 16d). The concentrations at Weil am Rhine show different seasonal patterns, with high concentrations in season 2 (January-March) and low concentrations in season 3 (April-June) (Fig. 16c), however the differences between the seasons are minimal.

Fig. 17a-d displays the seasonal dynamics of sulfamethoxazole for the Elbe and Rhine rivers, with overall the same patterns for both rivers. With low concentrations in season 2 (January-March) with median concentrations of 0.044 μg.L^{-1} and 0.038 μg.L^{-1} at monitoring stations Schmilka en Seemanshöft, respectively. Concentrations start to increase after February untill October, and results in highest median concentrations of 0.06 μg.L^{-1} and 0.05 μg.L^{-1} during season 1 (October-December) for Schmilka and Seemanshöft, respectively.

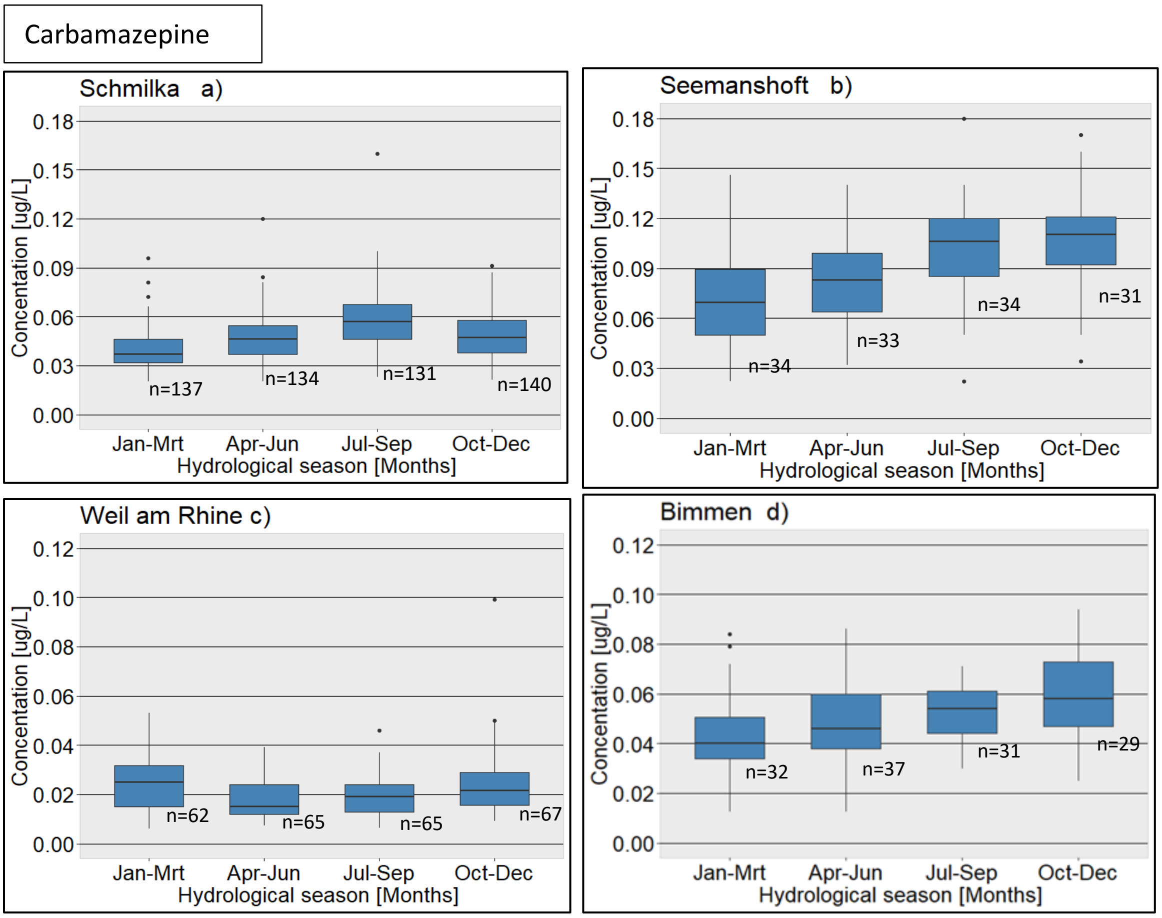


Fig. 16. Boxplots showing the seasonal distribution of carbamazepine concentrations for the four selected monitoring stations, Schmilka (a), Seemanshöft (b) (Elbe) and Weil am Rhine (c), Bimmen (d) (Rhine). The letters display the location of the monitoring stations in Fig. 14. (n) displays the number of measurements.

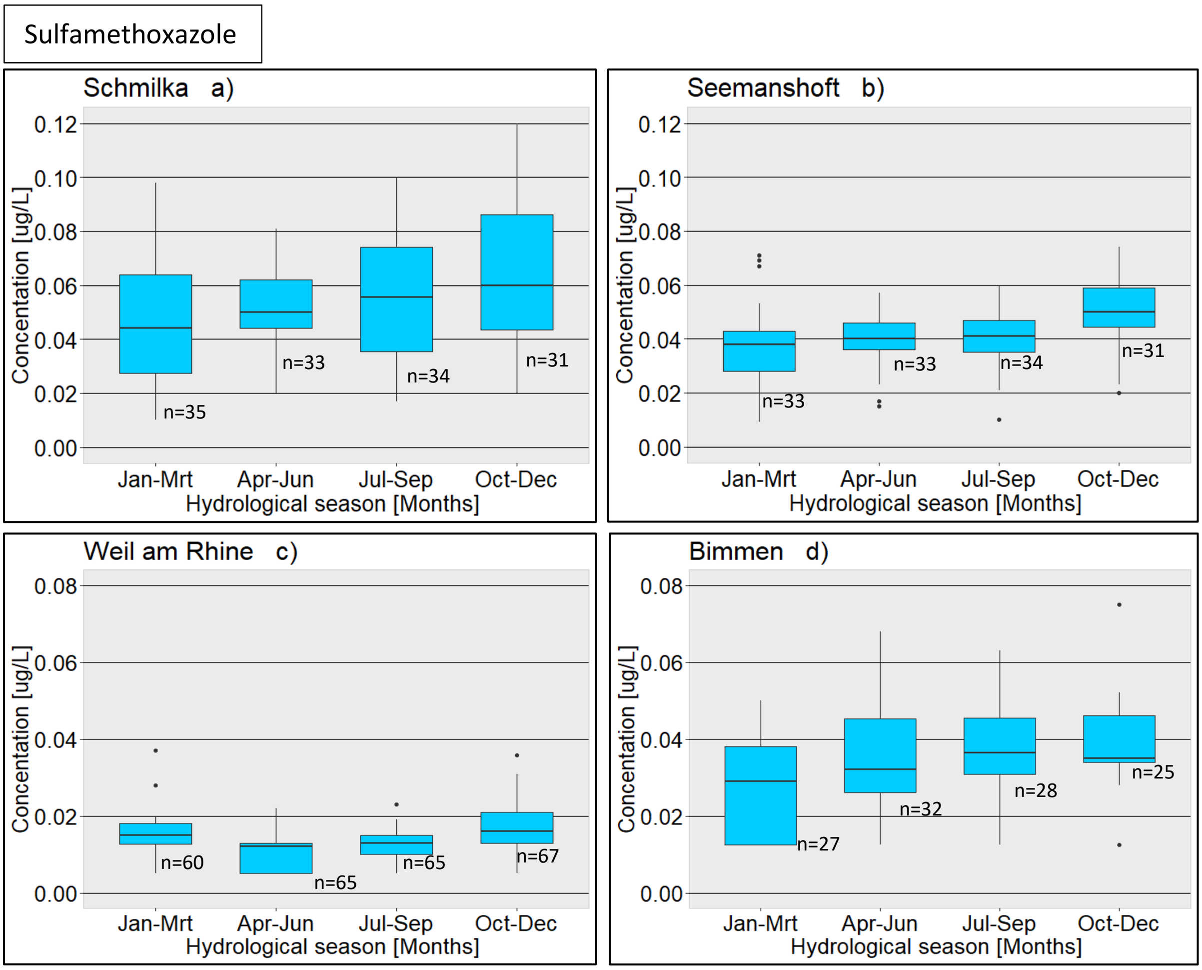


Fig. 17. Boxplots showing the seasonal distribution of sulfamethoxazole the four selected monitoring stations, Schmilka (a), Seemanshöft (b) (Elbe) and Weil am Rhine (c), Bimmen (d) (Rhine). The letters a-d display the location of the monitoring stations in Fig. 14. (n) displays the number of measurements.

Fig. 18 and 19 display the seasonal dynamics of diclofenac and metoprolol concentrations for four selected monitoring stations alongside the Elbe and Rhine river. The seasonal dynamics for both pharmaceuticals show in general the same patterns, with high concentrations in winter and autumn and low concentrations during spring and summer. At monitoring station Schmilka the differences in median concentrations for both diclofenac and metoprolol between the four seasons are minimal. With low concentrations in season 3 (April-June) (median 0.021 μg.L^{-1} and 0.031 μg.L^{-1}) and high concentrations in season 1 (October-December) (median 0.046 μg.L^{-1} and 0.050 μg.L^{-1}) for diclofenac and metoprolol, respectively. Downstream at monitoring station Seemanshöft the seasonal variantion for both diclofenac and metoprolol are more extreme. Highest maximum concentrations are measured in season 2 (January-March) for metoprolol (Fig. 19), while the median concentration is slighly higher in season 1 (0.119 μg.L^{-1}) (October-December). For diclofenac the highest concentrations occur in season 2 (January-March) with a median concentration of 0.095 μg.L^{-1}.

Furthermore, for both diclofenac and metoprolol the lowest minimum and median concentrations are observed in season 4 (July-September) for all four stations along the Rhine river (Fig. 18 c-d and Fig. 19 c-d). At monitoring station Bimmen the highest maximum and median concentrations are measured during season 2 (median 0.077 μg.L^{-1} and 0.076 μg.L^{-1}) for diclofenac and metoprolol, respectively. However, at Weil Am Rhine the highest maximum an median concentrations are measured in season 1 and 2 (median 0.054 μg.L^{-1} and 0.014 μg.L^{-1}) for diclofenac and metoprolol.

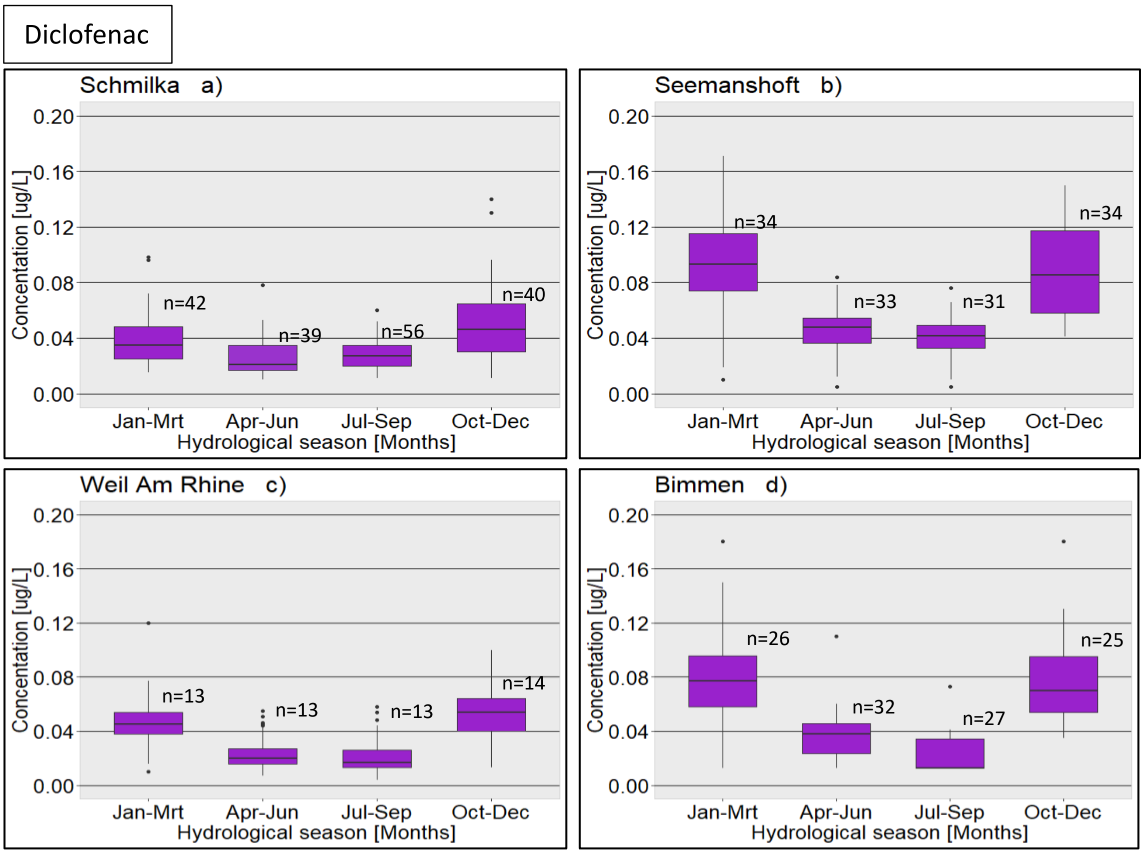


Fig. 18. Boxplots showing the seasonal distribution of diclofenac for the four selected monitoring stations, Schmilka a), Seemanshöft b) (Elbe) and Weil am Rhine c), Bimmen d) (Rhine). The letters a-d display the location of the monitoring stations in Fig. 15. (n) displays the number of measurements.

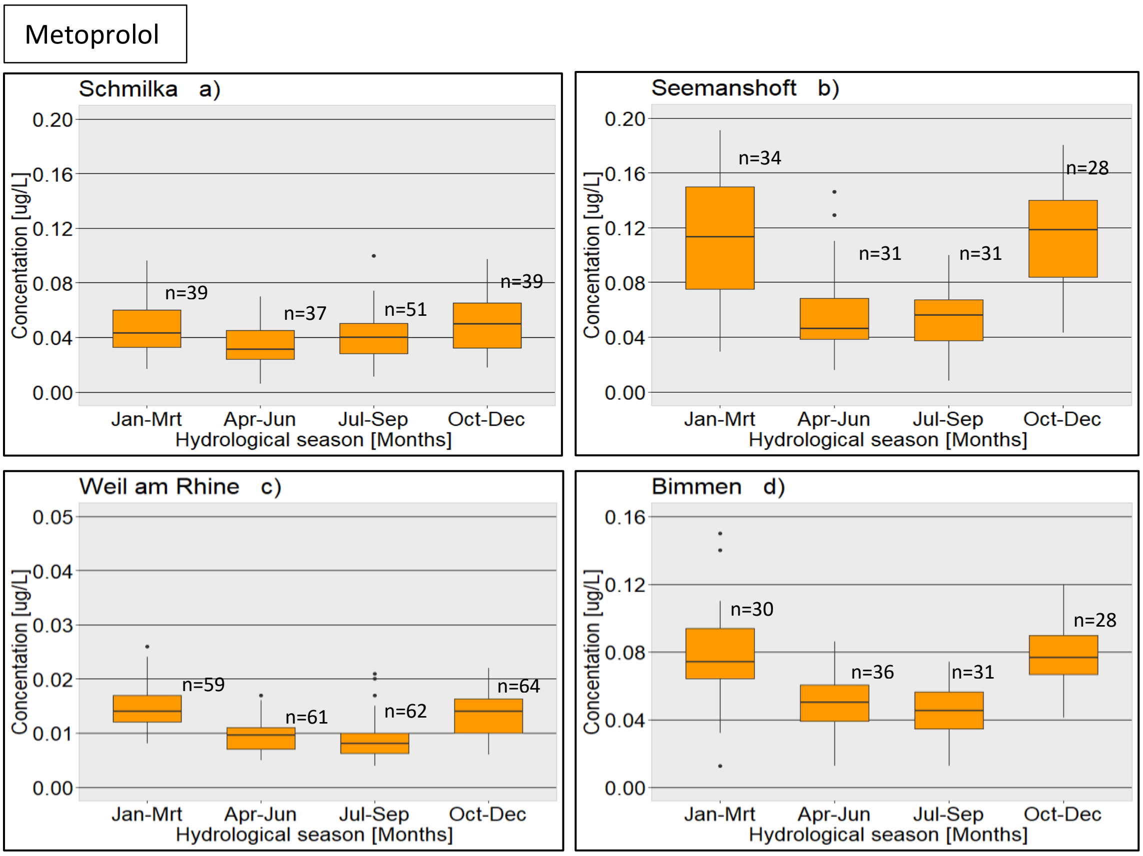


Fig. 19. Boxplots showing the seasonal distribution of metoprolol for the four selected monitoring stations, Schmilka a), Seemanshöft b) (Elbe) and Weil am Rhine c), Bimmen d) (Rhine). The letters a-d display the location of the monitoring stations in Fig. 15. (n) displays the number of measurements.

4.3RQ 2: Statistical analyses of pharmaceutical concentrations under drought

In this section, for both the river Elbe and Rhine, at least four monitoring stations were selected per pharmaceutical to display the difference in concentration under drought and non-drought conditions. The concentrations are plotted versus time for the respective drought compared to the June-October period of the reference years (2014, 2016, 2017 and 2020 Elbe and 2014, 2016, 2017 and 2019 Rhine). The complete statistical breakdown and plots per monitoring station has been added in Appendix 2 a-d.

4.3.1 Carbamazepine

The Shapiro-Wilk test is executed for carbamazepine concentrations for all monitoring stations along the Elbe and Rhine. As the computed p-value is lower than the significance level ($p < 0.05$) for almost all monitoring stations (Appendix 2a Table 2a), the concentrations from which the statistical analysis sample was extracted does not follow a normal distribution. Therefore, the Mann-Whitney U test will be conducted for all monitoring stations, except for Zollenspieker ($p = 0.144$) and Seemanshöft ($p = 0.695$) where the carbamazepine concentrations are normally distributed, hence an Unpaired T-test can be executed.

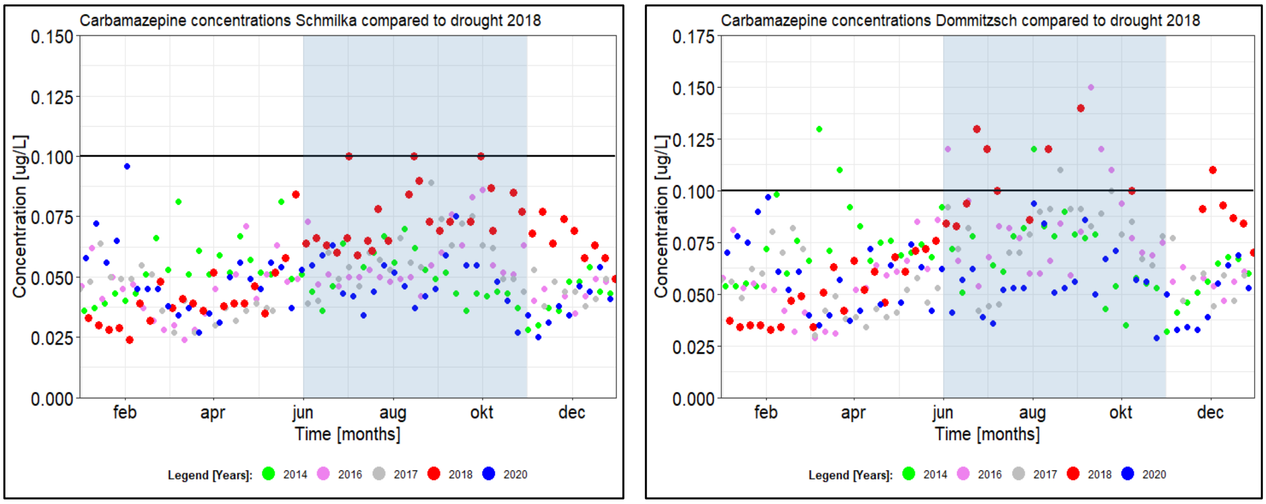


Fig. 20. Carbamazepine concentrations for the monitoring station Schmilka and Dommitzsch (Elbe) during the drought of 2018 and the reference years. Blue shade represents the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 $\mu g.L^{-1}$.

Fig. 20 shows a selection of monitoring stations (Schmilka and Dommitzsch that where selected to visualize the carbamazepine concentrations. With an average concentrations of 0.079 $\mu g.L^{-1}$ and 0.103 $\mu g.L^{-1}$ (June-October period 2018), compared to the average concentrations 0.053 $\mu g.L^{-1}$ and 0.073 $\mu g.L^{-1}$ for the reference years of Schmilka (+45%) and Dommitzsch (+36%), respectively. The computed p-values of the Mann-Whitney U test are lower than the significance level ($p < 0.001$) for 3 out of 6 monitoring stations; Schmilka, Zehren and Dommitzsch (Table 6, Appendix 2a Table 2A and Fig. 2a). This indicates that the differences in average concentrations of carbamazepine during the 2018 drought compared to all reference periods was statistically significant. The results of the unpaired T-test conducted for stations Zollenspieker and Seemanshöft show a statistically insignificant difference in carbamazepine concentrations ($p > 0.05$) (Appendix 2 Table 2a and Fig 2a). However, there are overall, increases in the carbamazepine concentrations found during the summer and fall of 2018 at these stations. With an average concentration increase of +20% for Zollenspieker and +13% for Seemanshöft.

Table 6. Descriptive statistics and Mann-Whitney U test compared to drought 2018 [Schmilka]

Variable	Observations	P-value	Average
Drought_18	24	-	0.079 ± 0.022
Ref_14	21	< 0.001	0.050 ± 0.010
Ref_16	22	< 0.001	0.057 ± 0.012
Ref_17	22	< 0.001	0.058 ± 0.012
Ref_20	20	< 0.001	0.049 ± 0.011

Average ± standard deviation

For the Rhine the differences in average carbamazepine concentrations during the drought of 2018 compared to most reference years and monitoring stations is statistically insignificant (**p** > 0.05) (Appendix 2a Table 2a and Fig. 2A). Overall, increased concentrations were found during the drought of 2018 for the June-October period at most monitoring stations (e.g. +21% Mainz and + 25% Bimmen) (Appendix Table 2a). Only at Weil am Rhine decreased concentrations where observed (-10%) for the drought compared to the reference years.

Moreover, the differences in concentrations at Koblenz during the drought of 2018 compared to the reference years 2016 and 2017 are statistically significant (p < 0.05) (Table 7). To elaborate further, the drought period is extended to November, which results in overall statistically significant difference. This is a direct result of the higher concentration in November for the 2018 drought compared to the reference years (Table 7).

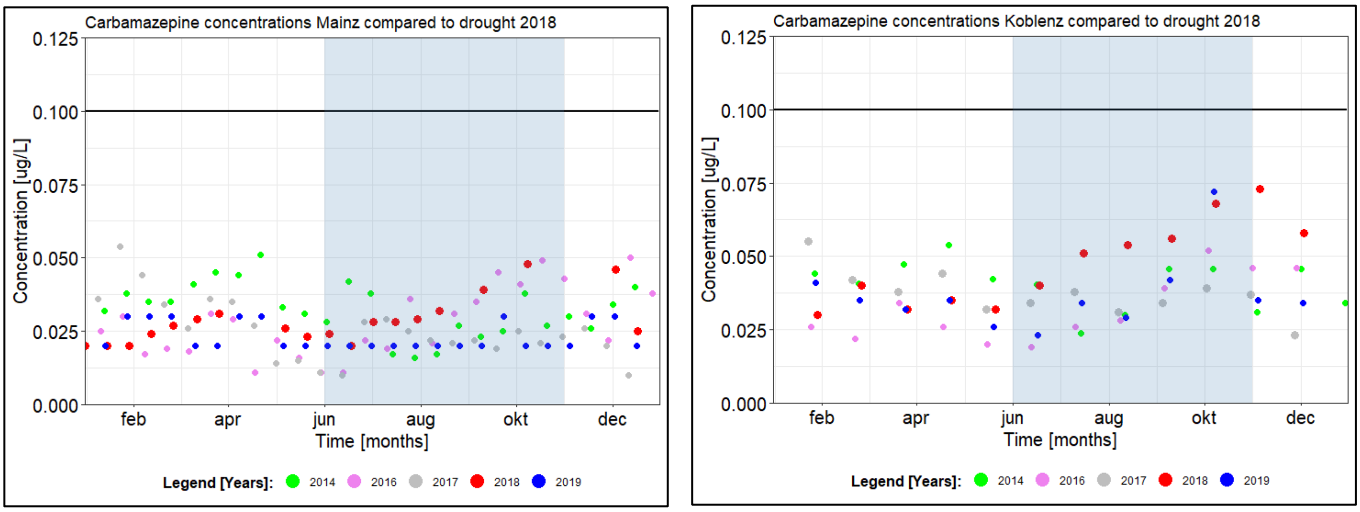


Fig. 21. Carbamazepine concentrations for the monitoring station Mainz and Koblenz (Rhine) during the drought of 2018 and the reference years. Blue shade represents the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 µg.L^{-1}.

Table 7. Mann-Whitney U test executed for carbamazepine concentrations at monitoring station Koblenz for the Jun-Oct (Top) and Jun-Nov period (Bottom)

Variable	Observations	P-value	Average
[Jun-Oct]			
Drought_18	5	-	0.054 ± 0.010
Ref_14	5	0.056	0.037 ± 0.010
Ref_16	5	0.032	0.033 ± 0.013
Ref_17	5	0.012	0.035 ± 0.003
Ref_19	5	0.222	0.040 ± 0.019
[Jun-Nov]			
Drought_18	6	-	0.057 ± 0.012
Ref_14	6	0.015	0.036 ± 0.009
Ref_16	6	0.015	0.035 ± 0.013
Ref_17	6	0.005	0.036 ± 0.003
Ref_19	6	0.065	0.039 ± 0.017

Average ± standard deviation

Upstream the Elbe at station Schmilka, carbamazepine concentrations are below or on the ERM target value of 0.1 $\mu g.L^{-1}$ (Fig. 20), however moving downstream to Zehren and Dommitzsch the concentrations increase, and late June the concentrations exceed the ERM target value at both stations (Fig. 21 and Appendix 2 Fig.2a). After June the concentrations fluctuate around the 0.1 $\mu g.L^{-1}$ untill mid-October with exceeding the target value 3 and 4 times, respectively. (Note that for station Dommitzsch the concentrations is not measured weekly in the August-October period). Downstream at the stations Zollenspieker and Seemanshöft the concentrations exceed the target value early June and fluctuate till august around 0.1 $\mu g.L^{-1}$. Early september the concentrations increase untill December (maximum 0.175 $\mu g.L^{-1}$ at Zollenspieker) (Appendix 2a Fig. 2a), which resulted in an exceedance period of 4 months (Note concentations stead above 0.1 $\mu g.L^{-1}$ until January 2019). Moreover, the carbamazepine concentrations do not exceed the ERM target value (0.1 $\mu g.L^{-1}$) for all monitoring stations alongside the Rhine.

4.3.2 Sulfamethoxazole

The Shapiro-Wilk test is executed for all monitoring stations. As the computed P-value is lower than the significance level ($p < 0.05$) (Appendix 2b Table 2b), the concentrations from which the sample was extracted does not follow a normal distribution. Therefore, the Mann-Whitney U test will be conducted for all monitoring stations along the Elbe and Rhine rivers, except for the monitoring stations Schmilka, Dommitzsch and Zollenspieker an unpaired T-test is used ($p>0.05$) (Appendix 2b Table 2b).

Fig. 22 shows a selection of scatterplots that were selected to visualize the responses in water quality of sulfamethoxazole concentrations for the Elbe and Rhine. The concentrations are plotted versus time for the respective drought compared to the reference years. The complete statistical breakdown and plots per monitoring station added to Appendix 2b. Overall, the P-value for most monitoring stations is larger than the significance level ($p>0.05$) (Appendix 2b Table 2B). This indicates that the differences in average concentrations of sulfamethoxazole during the drought of 2018 compared to most reference periods was statistically insignificant (Appendix 2a Table 2B). However, there are some exceptions, at Brunsbüttelkoog (Elbe) the average concentration of the 2018 drought (0.040 $\mu g.L^{-1}$) was significantly higher ($P<0.05$) than all reference years (average 0.026 $\mu g.L^{-1}$) (Fig. 22 and Appendix Table 2B.).

Furthermore, at monitoring station Schmilka the average concentrations of the drought of 2018 (0.080 µg.L^{-1}) is significantly higher ($p < 0.05$) than the reference years 2016 (0.049 µg.L^{-1}) and 2020 (0.051 µg.L^{-1}).

For the Rhine river the average concentrations, however, are noticeably higher for the drought of 2018 compared to the reference years but not statistically significant, accept at Mainz and Koblenz where concentrations are lower (Appendix 2b Table 2B and Fig.2B).

Overall, 2018 concentrations are below the ERM target value of 0.1 µg.L^{-1} for both river basins, except in December at Schmilka and Dommitzsch (Elbe) the concentrations exceed the target value (0.120 µg.L^{-1}). In the summer period of 2018 no target values were exceeded.

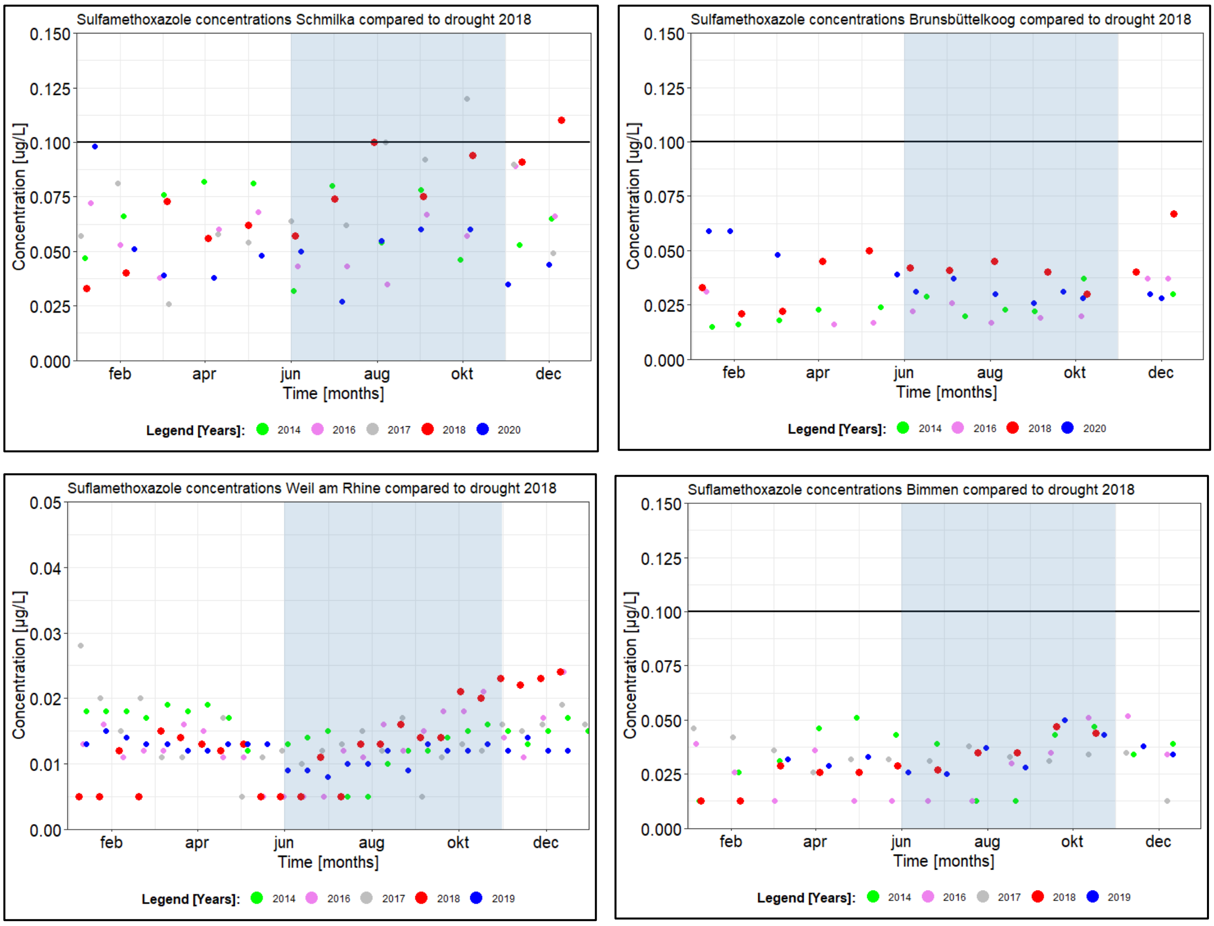


Fig. 22. Sulfamethoxazole concentrations for the monitoring station Schmilka and Brunsbüttelkoog (Elbe) and Weil am Rhein and Bimmen (Rhine) during the drought of 2018 and the reference years. Blue shade represents the drought period (Jun-Oct) and highlights the period of statistical analysis. The black solid line represents the ERM target value of 0.1 µg.L^{-1}. Note the different y-axis of the Weil am Rhein plot.

4.3.3 Diclofenac

The drought of 2018 is monitored for diclofenac at all monitoring stations at the Rhine and Elbe except at Brunsbüttelkoog (Elbe). The Shapiro-Wilk test is executed, as the computed p-value is lower than the significance level ($p < 0.05$) (Appendix 2c Table 2c), the diclofenac concentrations do not follow a normal distribution. Therefore, the Mann-Whitney U test will be conducted for all monitoring stations.

Four monitoring stations (Dommitzsch and Zollenspieker, Elbe) and (Weil am Rhein and Bimmen, Rhine) were selected to display the difference in diclofenac concentrations under drought and non-drought conditions (Fig. 23) (Appendix 2c Fig. 2c and 2C for other plots). The p-value obtained by the Mann-Whitney u-Test for all monitoring stations is larger than the significance level ($p > 0.05$) (Appendix 2c Table 2C). This indicates that the differences in average concentrations of diclofenac during the drought of 2018 compared to all reference years was statistically insignificant. Furthermore, the diclofenac concentrations at Mainz and Bimmen in the period June-October are below detection limit, therefore no statistical analysis is possible. Moreover, the diclofenac concentrations for the 2018 drought are overall lower than the reference years for almost all monitoring stations (Appendix 2c Table 2C).

Interesting to see is that at all monitoring stations and reference years there is the same parabola. However, for the drought of 2018 this is not the case. For almost all stations there is an increasing concentration in the period January-March. After March concentrations decrease until August, followed by a steep increase in concentration. This pattern is the same for the Elbe and Rhine rivers.

Diclofenac concentrations in the study period (June-October) are below ERM target value of 0.1 $\mu g.L^{-1}$ For both the Elbe and Rhine river. However, in winter period (Fig. 23) concentrations especially for the Elbe river are above the ERM target value. With maximum concentrations of 0.931 $\mu g.L^{-1}$ (September 9th 2018) and 0.480 $\mu g.L^{-1}$ (May 2th 2018) at Zollenspieker and Seemanshöft, respectively. This is almost 10 times and 5 times higher than the allowed target value. Finally, the diclofenac concentrations exceed the ERM target value 4 out of 12 measurments at Seemanshöft (Appendix 2c Fig. 2c), although this happened outside the drought period.

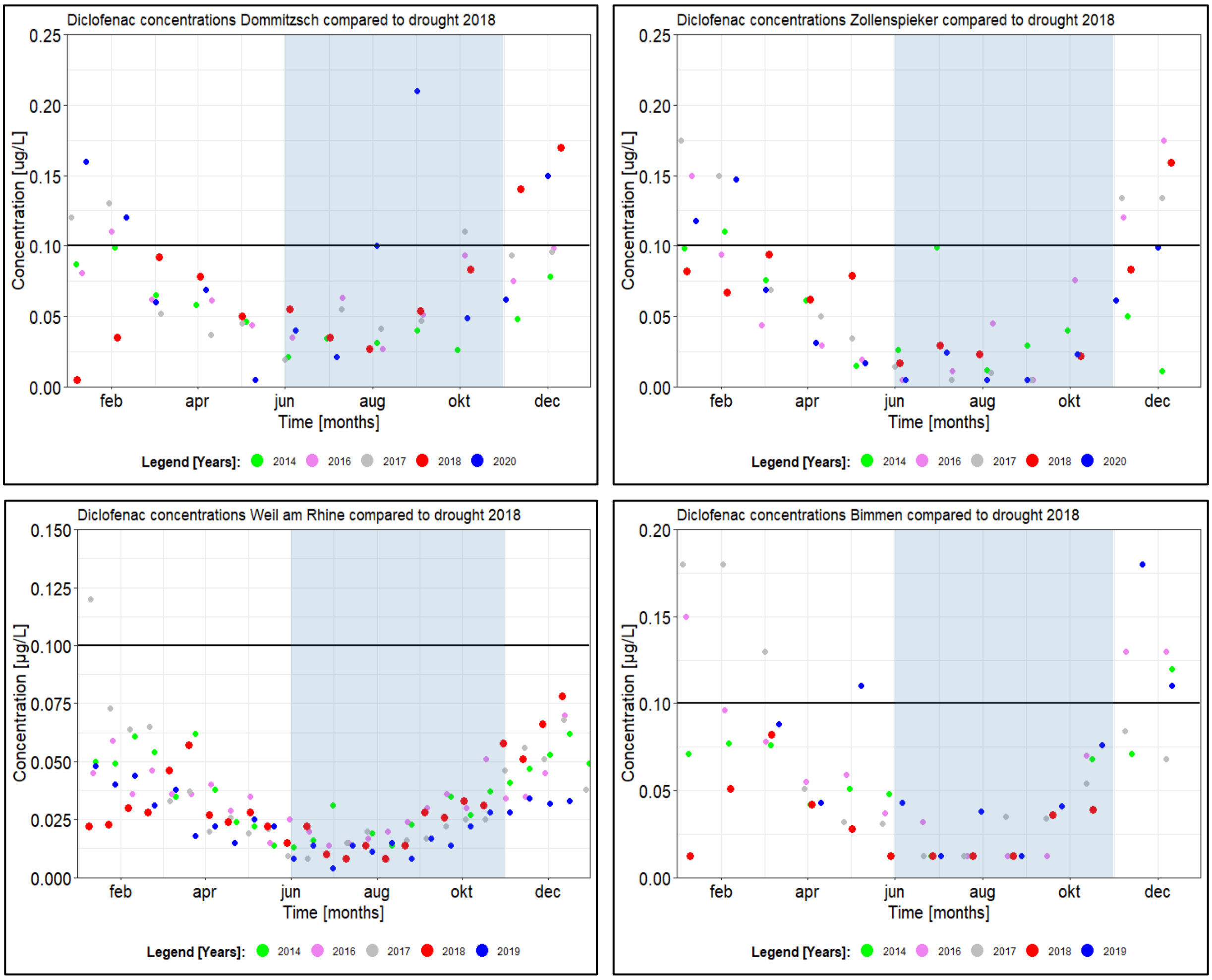


Fig. 23. Diclofenac concentrations for the monitoring station Schmilka and Zollenspieker (Elbe) and Weil am Rhein and Bimmen (Rhine) during the drought of 2018 and the reference years. Blue shade represents the drought period (Jun-Oct) and highlights the period of statistical analysis. The black solid line represents the ERM target value of 0.1 µg.L^{-1}.

4.3.4 Metoprolol

The Shapiro-Wilk test is executed for all monitoring stations. The computed P-value is lower than the significance level ($p < 0.05$) for all monitoring stations except Schmilka (Appendix 2d Table 2d). The concentrations do not follow a normal distribution, therefore the Mann-Whitney U test will be carried out. The data at Schmilka is normally distributed hence, an Unpaired T-test will be conducted.

Four monitoring stations (Schmilka and Seemanshöft) Elbe and (Worms and Koblenz) Rhine were selected to display the difference in metoprolol concentrations under drought and non-drought conditions (Fig. 24). The p-value for most monitoring stations is larger than the significance level ($p > 0.05$) (Appendix 2d Table 2D). This indicates that the differences in average concentrations of metoprolol during the drought of 2018 compared to all reference periods was statistically insignificant for both the Elbe and the Rhine river. However, at Worms and Koblenz (Rhine) the p-value is smaller than the significance level ($p < 0.05$) compared to some reference years (Appendix 2d Table 2D), especially when including the data of November (Fig. 24). With an average concentration of 0.035 $\mu g.L^{-1}$ and 0.038 μg.L-1 for the drought of 2018 compared to the average concentrations of the reference years 0.023 μg.L-1 and 0.017 μg.L-1 for Worms and Koblenz, respectively.

For most stations alongside the Elbe the concentrations do not exceed the ERM target value of 0.1 $\mu g.L^{-1}$, except at Seemanshöft and Brunsbüttelkoog where this threshold is exceeded ones during the 2018 drought. Moreover at Seemanshöft, between the period October and April the concentrations exceed the target value for most years. At Seemanshöft 5 out of 12 measurement exceed the target value, with a maximum concentration of 0.161 $\mu g.L^{-1}$ in April (Fig. 24).

For the Rhine river no measurements exceed the ERM target value during the 2018 drought, with the exception of the reference year 2017, where this target value is exceeded in the period January-March at monitoring stations Bad Honnef and Bimmen (Appendix 2d Fig. 2D).

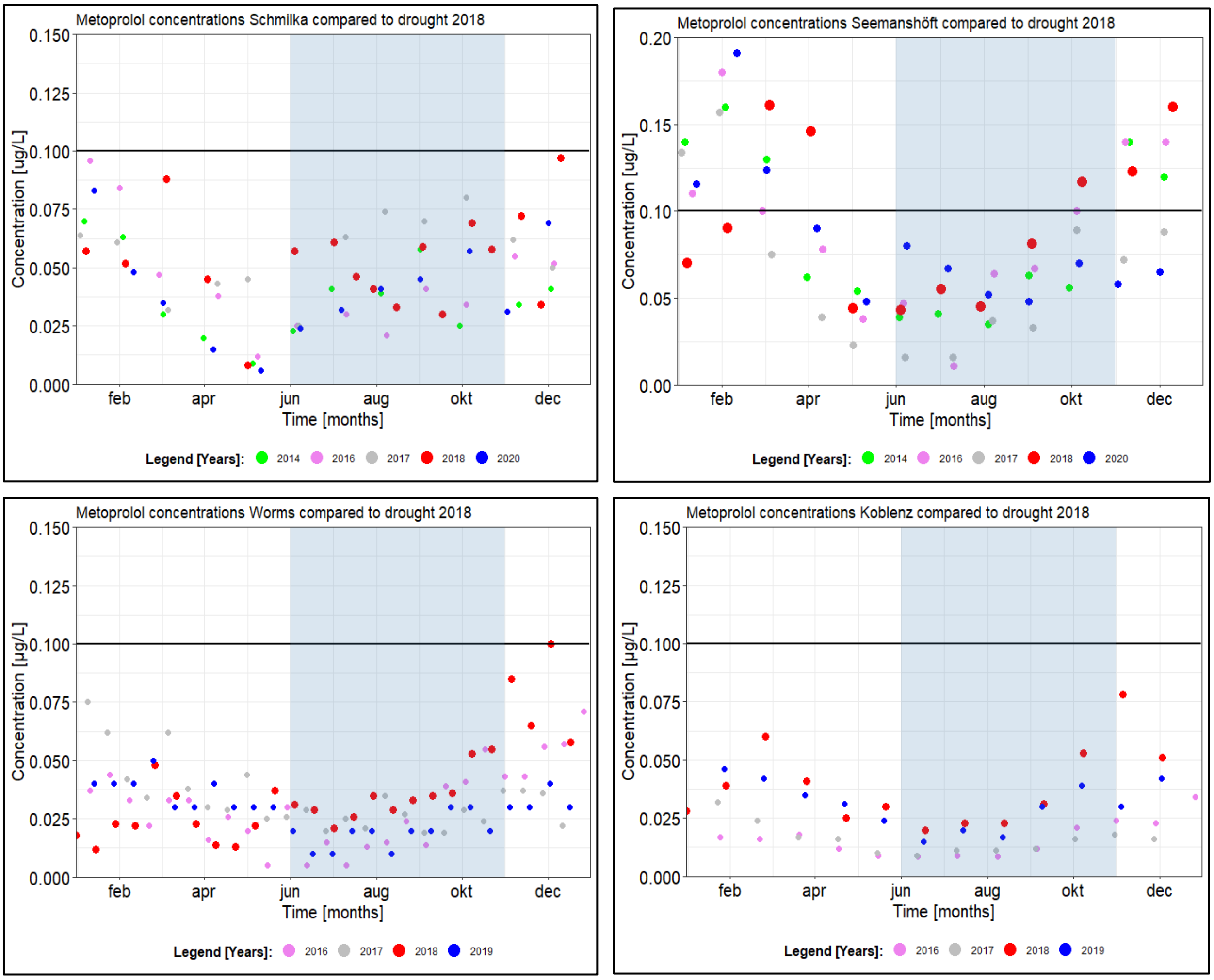
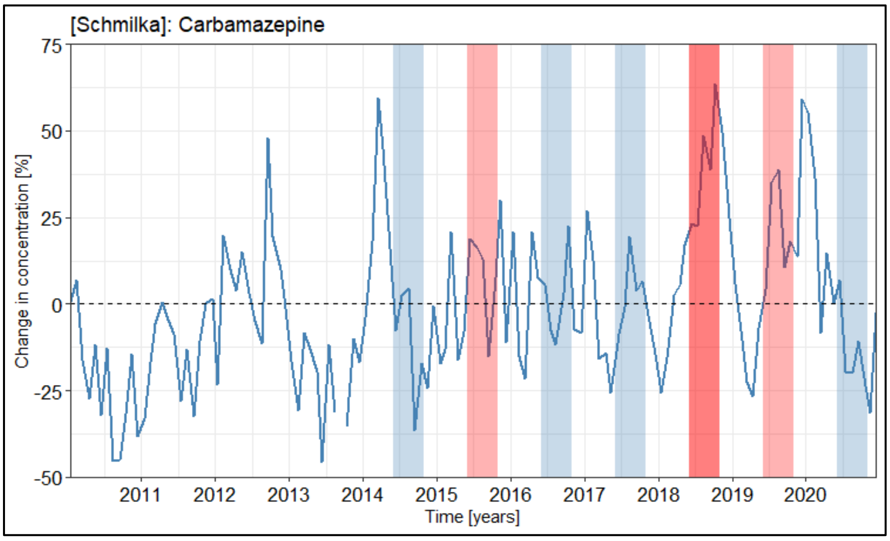


Fig. 24. Metoprolol concentrations for the monitoring station Schmilka and Seemanshöft (Elbe) and Worms and Koblenz (Rhine) during the drought of 2018 and the reference periods. Blue shade represents the drought period (Jun-Oct) and highlights the period of statistical analysis. The black solid line represents the ERM target value of 0.1 µg.L-1. (Note the missing reference year 2014 for Worms and Koblenz).

4.3.5 Anomalies

Anomalies can be calculated to estimate the water quality impact under droughts. Anomalies are the percentage difference between the median drought concentrations and median long-term concentrations and can be calculated as stated in (Eq. 1) (section 3.3.2).

Two monitoring stations (one for each river) were selected to visualize the anomalies in pharmaceutical concentrations under drought and non-drought conditions. The percentage difference between the median pharmaceutical drought concentration and non-drought concentrations was firstly calculated for the statistically significant monitoring stations. As the statistical analysis showed in section 4.3, only the changes in carbamazepine concentrations for the stations Schmilka, Zehren and Dommitzsch were statistically significant.



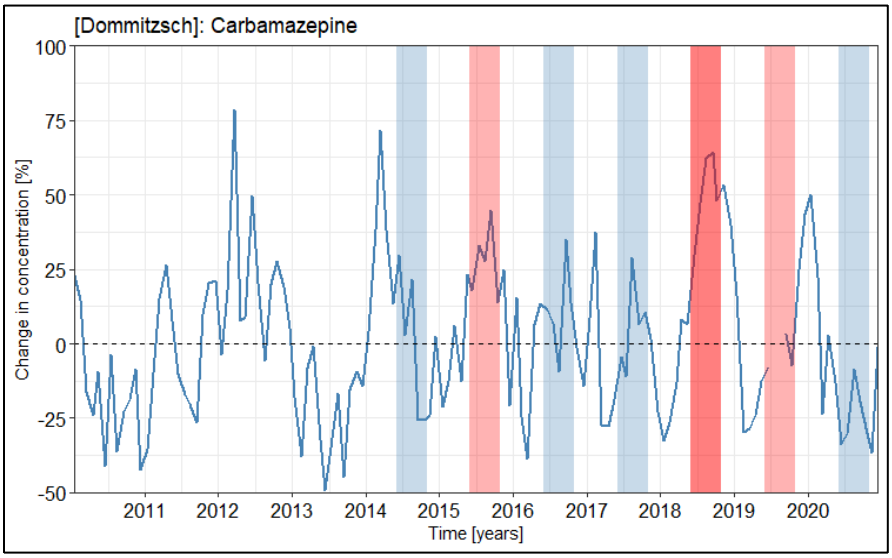


Fig. 25. Percentage change anomalies carbamazepine during drought conditions compared to the long-term monthly average (2010-2020) at four selected monitoring stations along the Elbe. Red shade represents the (Jun-Oct) droughts of 2015, 2018 and 2019, the blue shade is the (Jun-Oct) periods for the four reference years.

Fig. 25 shows the line graphs of the percentage change in carbamazepine concentrations under drought conditions in relation to the long-term average calculated over the period 2010-2020 for the monitoring stations Schmilka and Dommitzsch. The dark red and blue shades highlight the 2018 drought and the selected reference years for the period June-October, while the transparent red shade represents the droughts of 2015 and 2019. For Schmilka and Dommitzsch an average increase in carbamazepine of ~45% was found for the 2018 drought, with a maximum of 65%. Furthermore, the drought of 2015 and 2019 show increased concentrations compared to the reference years, however they are on average 20% lower than the 2018 drought. Additionally, the percentage change for the 2018 drought at monitoring stations Zollenspieker and Seemanshöft show especially for the months November and December increased values (Appendix 2e Fig. 2e)

Finally, to illustrate the increased (statistically insignificant) concentrations for carbamazepine (Rhine), sulfamethoxazole and metoprolol for the Elbe and Rhine rivers for the 2018 drought two additional plots per pharmaceutical are made, one for each river (Appendix 2e Fig. 2E).

4.4 RQ 3: Comparison of responses in pharmaceutical concentrations across river basins

This section shows the average concentration percentage differences of the four pharmaceuticals between the June-October period of the 2018 drought (Appendix 3 Fig. 3a-d) and the calculated long-term average concentrations of the June-October period of 2010-2020 (Appendix 3 Fig. 3a-d) for all monitoring stations in Europe. In Appendix 1 Table 1(a-d) the average concentrations (in numbers) for the monitoring stations alongside the Elbe and Rhine rivers for both periods are presented. Additional plots are made showing the median concentration percentage differences for the drought compared to the reference years.

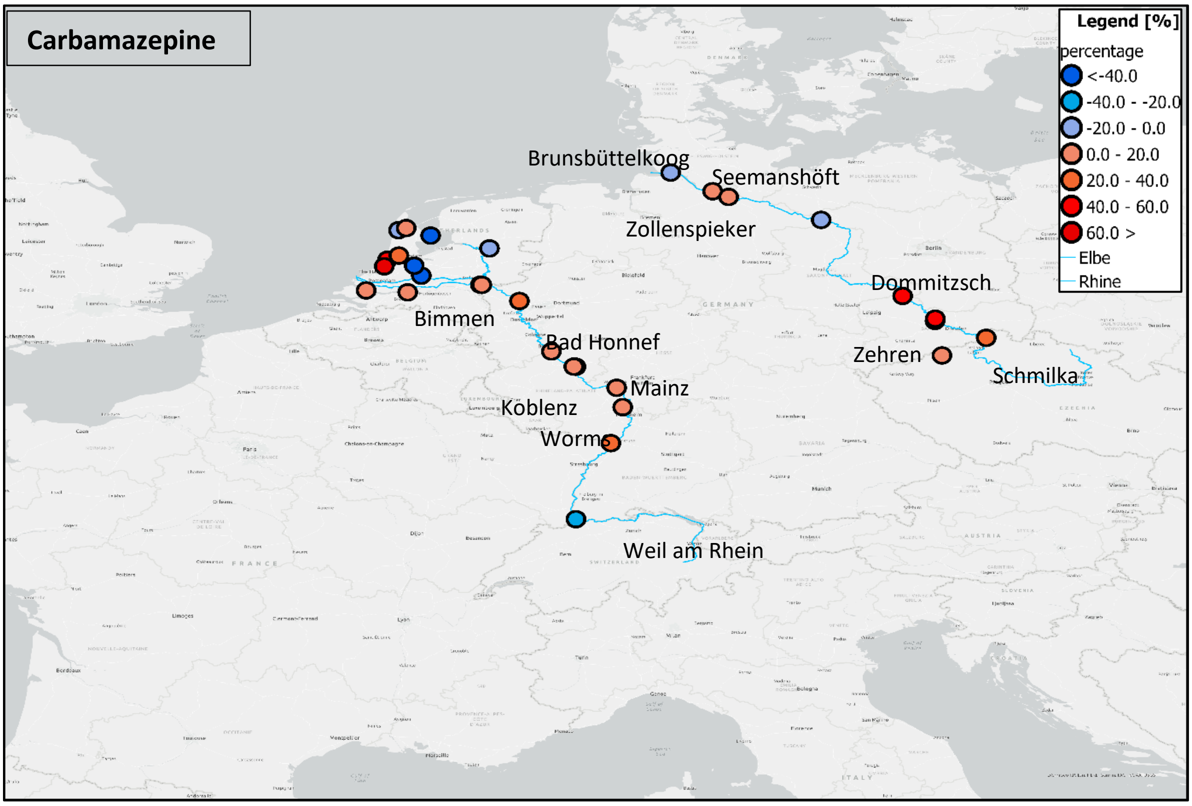


Fig. 26. Average percentage difference of carbamazepine between the average concentration 2018 drought (June-October) versus the average concentration 2010-2020 (June-October) period.

Fig. 26 shows the average percentage differences of the pharmaceutical carbamazepine, between the June-October period of the 2018 drought and the long-term average concentrations of the June-October period of 2010-2020 (Appendix 3 Fig. 3a). With 24 out of 34 stations where the concentration differences between the drought of 2018 and the 2010-2020 June-October period was positive. For the Rhine only at monitoring station Weil am Rhein there is a decrease of -28% in concentration for the 2018 drought compared to the average concentration of the June-October period of 2010-2020, while for all other monitoring stations there is an increase (~ +10%) in observed concentrations for the drought period.

For the stations upstream the Elbe (Schmilka: +39%, Zehren: + 36% and Dommitzsch: +46%) as downstream (Zollenspieker; +4% and Seemanshöft: +11%) increased concentration for the drought of 2018, except at Brunsbüttelkoog (-9%) where the concentrations for the drought period are lower compared to the average of 2010-2020 (June-October).

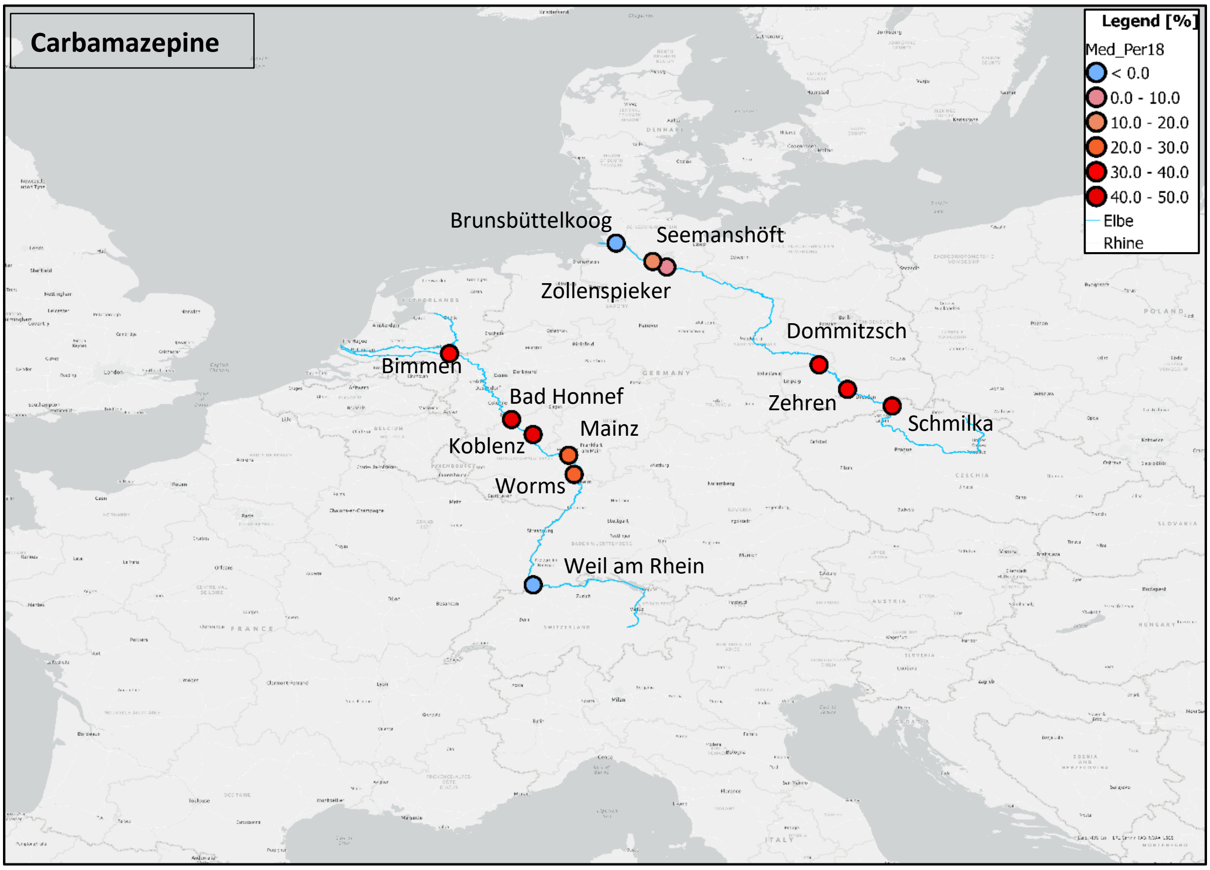


Fig. 27. Median percentage concentration differences of carbamazepine between the median concentration of the 2018 drought (June-October) versus the median concentrations of the reference period (June-October). Reference period Elbe: (2014, 2016, 2017, 2020) and Rhine: (2014, 2016, 2017 and 2019).

Fig. 27 shows the median percentage concentration changes of carbamazepine, between the June-October period of the 2018 drought and the June-October period of the reference years. Carbamazepine concentrations show an overall increase during the drought of 2018. For the Rhine only in the Upper part of the river at monitoring station Weil am Rhein there is a decrease (-13%) in concentrations for the drought of 2018 compared to the median concentration of the reference years. For the other monitoring stations there is a substantial increase of ~25% (Worms and Mainz), ~45% at (Koblenz and Bad Honnef) and 32% (Bimmen).

For the monitoring stations upstream the Elbe (Schmilka: +40%, Zehren: +35% and Dommitzsch: +38%) as downstream (Zollenspieker; +9% and Seemanshöft: +11%) there is an increase in the median concentration for the drought of 2018 compared to the reference years, except at Brunsbüttelkoog (-14%) where the concentrations for the drought period are lower. Moreover, the results show that the Rhine and Elbe behave in similar ways. However, highest median percentage changes for the Rhine were observed at the downstream stations, while for the Elbe these were observed at the upstream monitoring stations.

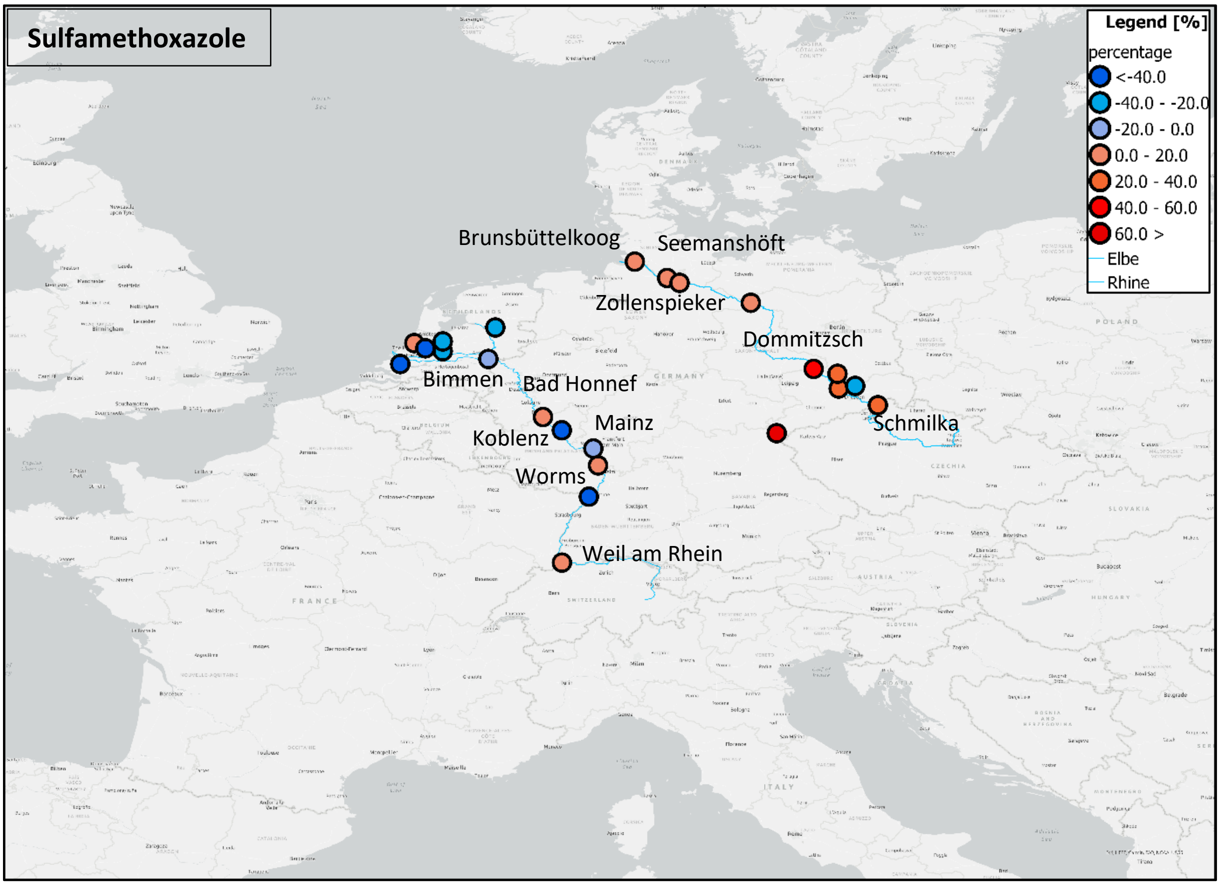


Fig. 28. Average percentage difference of sulfamethoxazole between the average concentration of the 2018 drought (June-October) versus the average concentration of the 2010-2020 (June-October) period.

The average percentage differences of sulfamethoxazole, between the June-October period of the 2018 drought and the long-term average concentrations of the June-October period of 2010-2020 are displays in Fig. 28 and (Appendix 3 Fig. 3b). Sulfamethoxazole concentrations show a combination of increased (13 stations) and decreased (12 stations) concentrations during the drought of 2018.

However, for all monitoring stations alongside the river Elbe there are increased sulfamethoxazole concentration, with an increase of ~45% at the stations Schmilka and Dommitzsch and ~15% for Zollenspieker, Seemanshöft and Brunsbüttelkoog. For the Rhine river, minor increases were found for the station Weil am Rhein, Worms and Bad Honnef of approximately 10%. While decreases of -60% and -3% where observed at Koblenz and Bimmen, respectively.

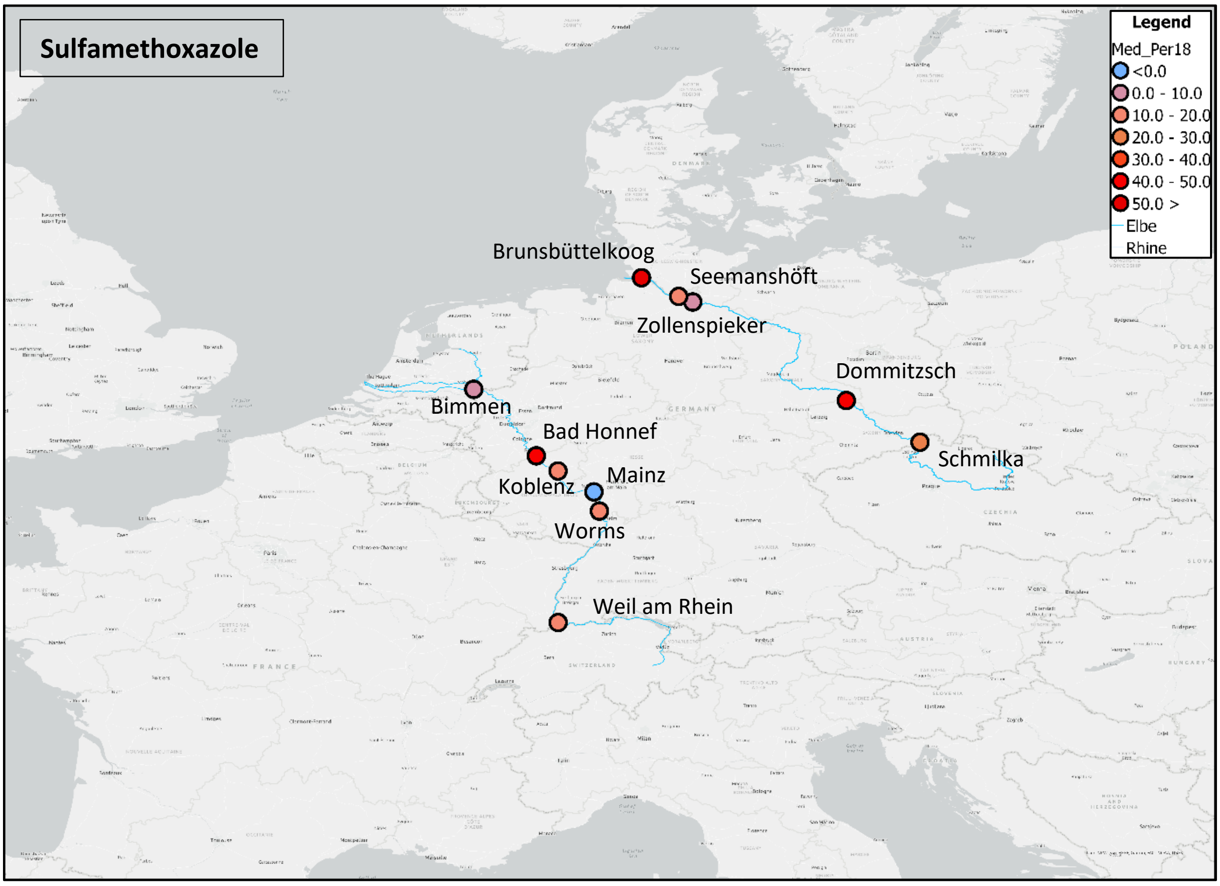


Fig. 29. Median percentage concentration differences of sulfamethoxazole between the median concentration of the 2018 drought (June-October) versus the median concentrations of the reference period (June-October). Reference period Elbe: (2014, 2016, 2017, 2020) and Rhine: (2014, 2016, 2017 and 2019).

Fig. 29 shows the median percentage concentration changes of sulfamethoxazole, between the June-October period of the 2018 drought and the June-October period of the reference years. Sulfamethoxazole concentrations show an overall increase during the drought of 2018. Those results are slightly different compared with Fig. 28. For the Rhine only at monitoring station Mainz there is a decrease (-5%) in concentrations for the drought of 2018 compared to the median concentration of the reference years. For the other monitoring stations there is a substantial increase of ~+15% (Weil am Rhine, Worms and Koblenz), while at bad Honnef there is an increase of +44%.

For the monitoring stations upstream the Elbe (Schmilka: +28% and Dommitzsch: +42%) as downstream (Zollenspieker; +3% and Seemanshöft: +12%) there is an increase in the median concentration for the drought of 2018, at Brunsbüttelkoog the largest increase is observed (+65%). Moreover, the results show that the Rhine and Elbe behave in similar ways, with overall increased sulfamethoxazole concentrations, however the magnitude of the deterioration of the water quality of the Elbe river is higher.

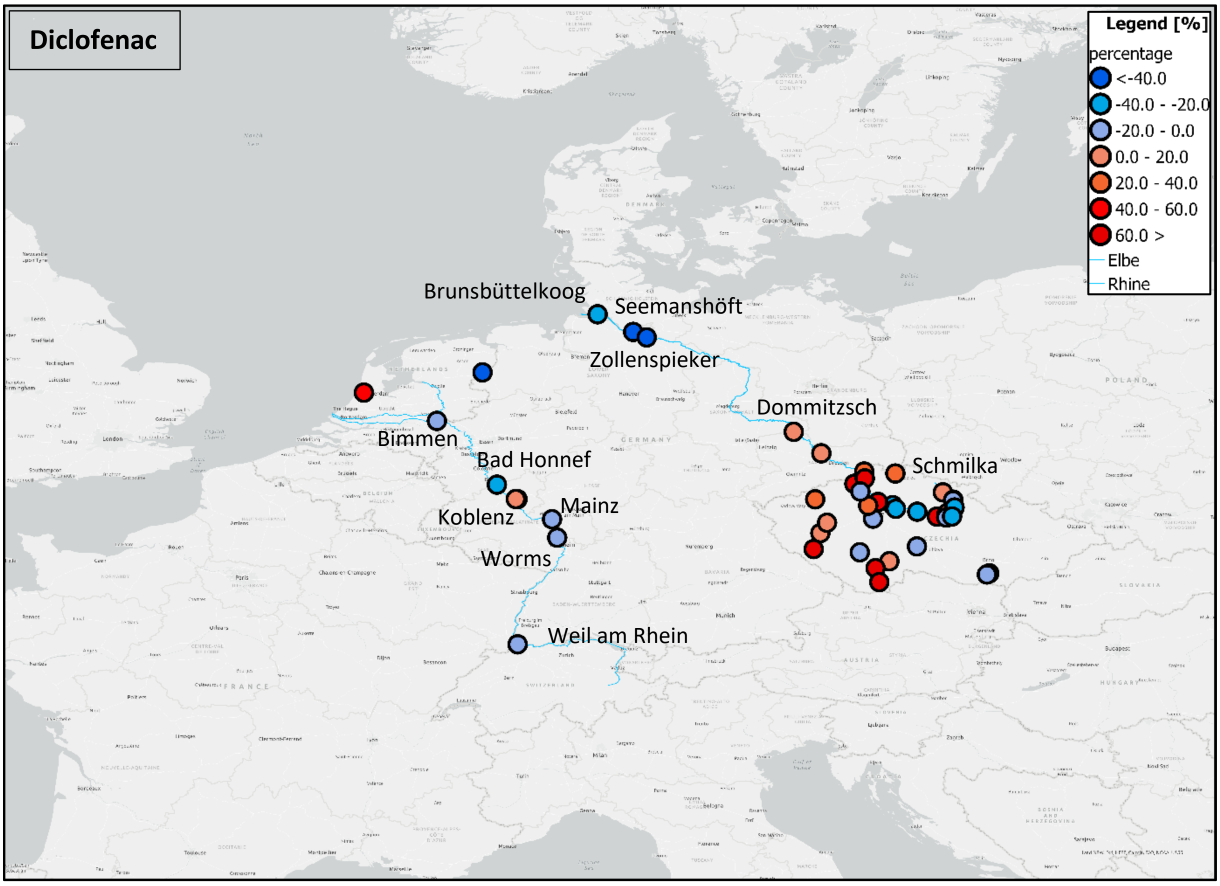


Fig. 30. Average percentage difference diclofenac between the average concentration of the 2018 drought (June-October) versus the average concentration of the 2010-2020 (June-October) period.

Fig. 30 displays the average concentrations differences of diclofenac, between the June-October period of the 2018 drought and the long-term average concentrations of the June-October period of 2010-2020 (Appendix 3 Fig. 3c). The monitoring stations show both an increase (22 stations) as decrease (30 stations) in concentration during the drought of 2018 compared to the average 2010-2020 period. When zooming in on the Elbe and Rhine rivers: both the upstream and downstream part of the Rhine, show a decrease of approximately -15% to -25% for all monitoring station. In contrary with the Rhine, the upstream monitoring stations of the Elbe show increased (+28% Schmilka and +13% Dommitzsch) concentrations for the 2018 drought, while the monitoring stations downstream the river show a decrease of -46% and -51% for Seemanshöft and Zollenspieker, respectively.

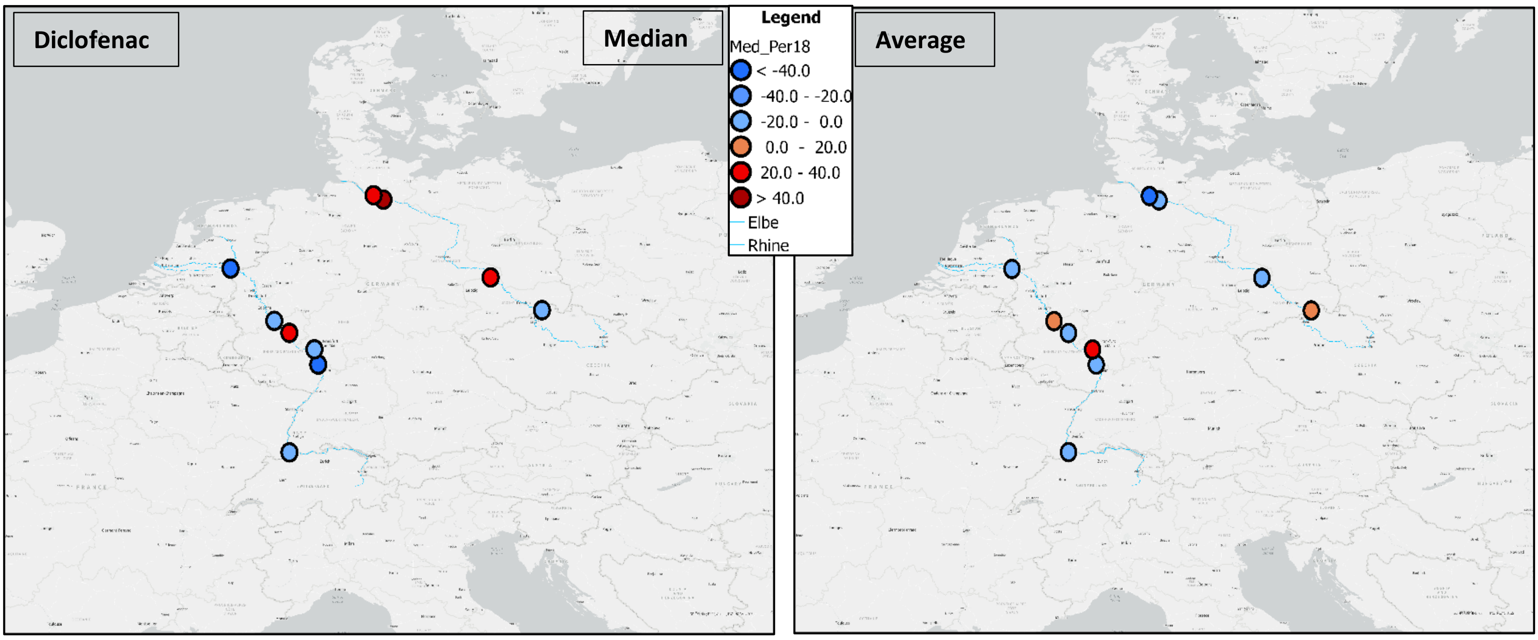


Fig. 31 Median (Left) and average (Right) percentage concentration differences of diclofenac between the median and average concentration of the 2018 drought (June-October) versus the median and average concentrations of the reference period (June-October). Reference period Elbe: (2014, 2016, 2017, 2020) and Rhine: (2014, 2016, 2017 and 2019).

Fig. 31 shows the median and average percentage concentration changes for diclofenac, between the 2018 drought and the reference years for the period June-October. As for most stations the concentrations are around or below LOD, which results in median percentage changes of zero or close to zero. Therefore, also the map of the average percentage changes is shown.

For the Rhine there are overall negative average percentage changes compared to the reference year. With ~ -12% for Weil am Rhein, Worms, and Koblenz and -3% at Bimmen, except at Mainz and Bad Honnef where a +26% and +10% change is observed. The results of the Elbe show minimal changes with a positive change of +4% at Schmilka and negative changes at Dommitzsch (-8%), Zollenspieker (-13%) and Seemanshöft (-49%).

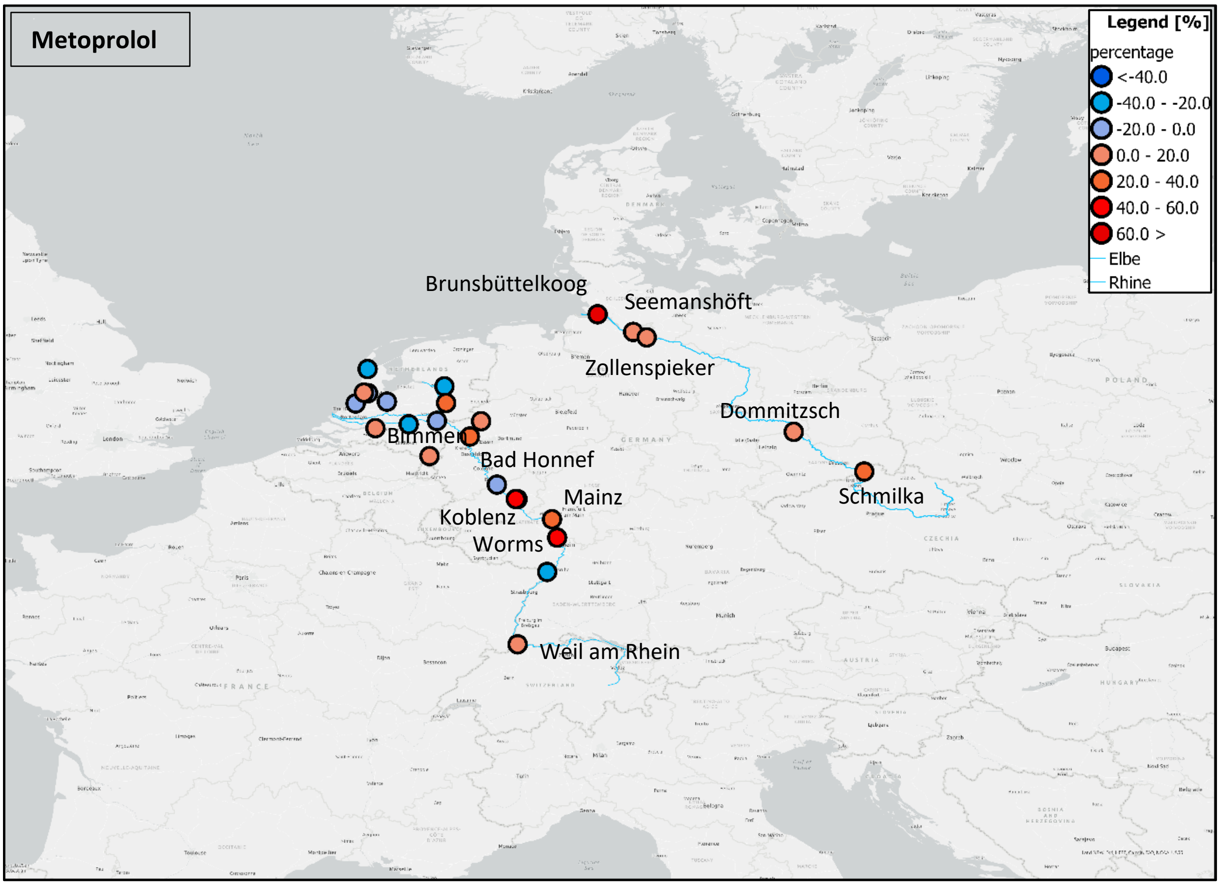


Fig. 32. Average percentage difference metoprolol between the average concentration of the 2018 drought (June-October) versus the average concentration of the 2010-2020 (June-October) period.

Fig. 32 displays the metoprolol concentrations which show a combination of increasing (17 stations) and decreasing (10 stations) concentrations during the 2018 drought (June-October) (Appendix 4 Fig. 4c) compared to the same period 2010-2020 (Appendix 4 Fig. 4c).

Moreover, for the Elbe and Rhine river there is an overall increase in concentration. With the highest increase in concentrations at the Rhine of +41% and +61%, for Worms and Koblenz, respectively. while for the lower part of the river there is a minor decrease of -6% and -14% for Bad Honnef and Bimmen during the 2018 drought. Furthermore, for all stations alongside the Elbe river there are increased concentration for the drought of 2018 compared to average 2010-2020. With ~+20% at stations Schmilka, Dommitzsch, Seemanshöft and Zollenspieker, and an increase of +98% at Brunsbüttelkoog. However, this +98% can be attributed to the 0.14 $\mu g.L^{-1}$ measured at june 3th, this concentration is 10 times higher than average during that same period.

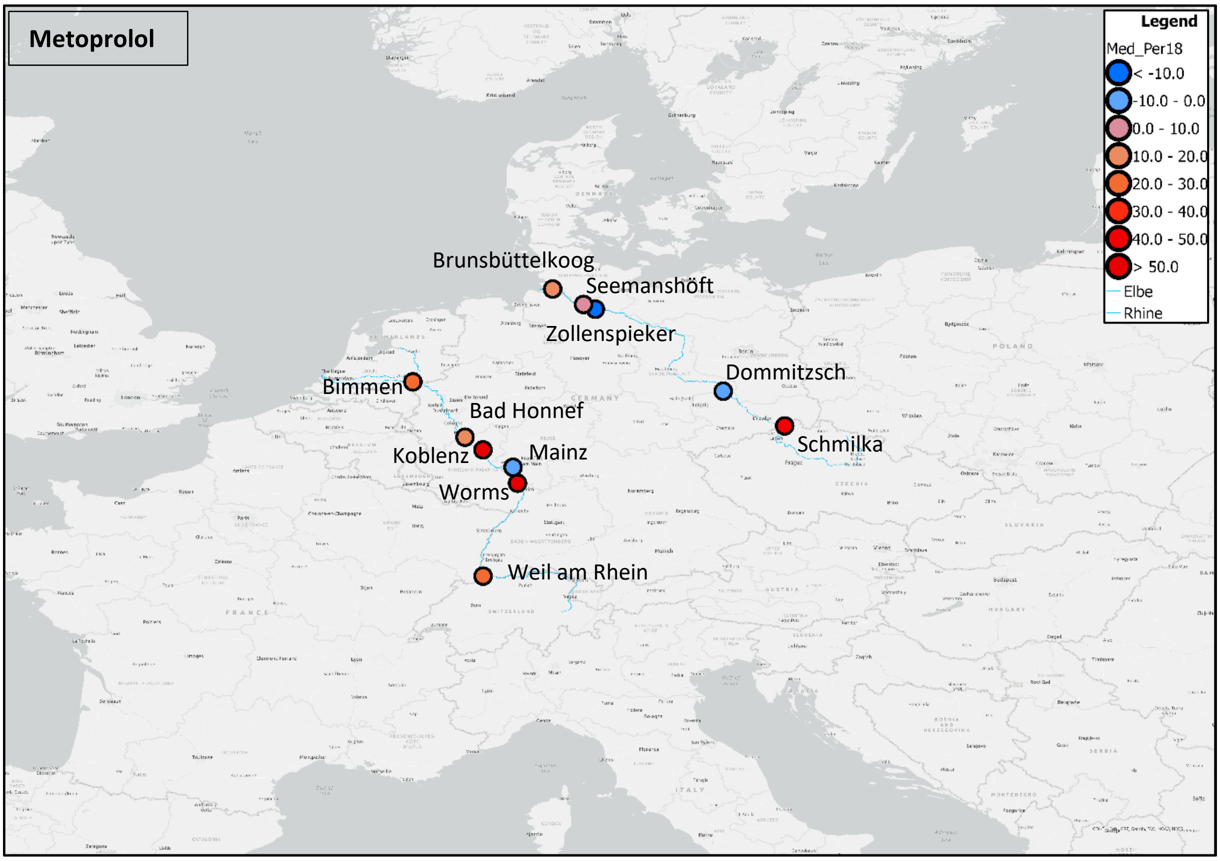


Fig. 33. Median percentage concentration differences of metoprolol between the median concentration of the 2018 drought (June-October) and the median concentrations of the reference period (June-October). Reference period Elbe: (2014, 2016, 2017, 2020) and Rhine: (2014, 2016, 2017 and 2019).

Fig. 33 shows the median percentage concentration changes of diclofenac, between the 2018 drought and the reference years for the period June-October. For the Rhine there are overall positive median percentage changes in the concentrations, accept at Mainz where the median percentage change is 0%, as most concentrations are below the LOD. The highest percentage changes are at Worms and Koblenz of +85% and +53%, respectively. While for the stations Weil am Rhein (+25%), Bimmen (+21%) and Bad Honnef (+13%) considerable increases were observed.

For the monitoring stations upstream the Elbe there is an increase of +43% at Schmilka and -12% at Dommitzsch, however it should be noted that at Dommitzsch the reference years of 2014 and 2016 are missing. Moreover, there is a slight increase of ~+10% at Seemanshöft and Brunsbüttelkoog, while at Zollenspieker there is a medial percentage change of -75%.

4.5 RQ 4: Drivers of changes in pharmaceutical concentrations under drought

This section is structured as follows: firstly the relationship between the discharge and pharmaceutical concentrations will be presented. Secondly, the relationship between the water temperature and pharmaceutical concentrations will be displayed and further elaborated upon for the 2018 drought and reference years for both river basins.

4.5.1 Discharge vs pharmaceuticals

Two scatterplots per river basin were selected to visualize the observed relationship between the discharge and pharmaceutical concentrations. The dilution-based relationship Eq. (1) of Van der Weijden and Middelburg (1989) was fitted, to display the relation. The measurements for the June-October period of the 2018 drought are highlighted in red. Fig. 34a-b and Fig. 35 displays the scatterplots of carbamazepine and sulfamethoxazole. They show a clear inverse discharge-concentration relation (Except for Sulfamethoxazole at Zollenspieker), which indicates that low pharmaceutical concentrations correspond with high discharges and vice versa. For the Elbe the relation between carbamazepine and sulfamethoxazole versus the discharge is stronger upstream at Schmilka (R^2=0.47 and R^2=0.30) compared to Zollenspieker downstream the river (R^2=0.35 and R^2=0.06). While for the Rhine the strongest carbamazepine relation is downstream at Bimmen (R^2=0.64) compared to the relation upstream at Weil am Rhein (R^2=0.27). Moreover, the relation between sulfamethoxazole and the discharge is for the Rhine the same upstream as downstream the river, with R^2=0.56 and R^2=0.53 for Weil am Rhein and Bimmen, respectively.

Finally, when comparing the fitted (a) values (emission loads) of the two pharmaceuticals, contained from the C-Q relation of Van der Weijden & Middelburg (1989) (Appendix 4, Table 4a and 4A), it can be concluded that there are substantial sources of emissions between the monitoring stations. With an increase in emission load of +458% for carbamazepine and +141% sulfamethoxazole between Schmilka and Zollenspieker (Elbe) and +410% and +288% between Weil am Rhein and Bimmen (Rhine) for carbamazepine and sulfamethoxazole, respectively.

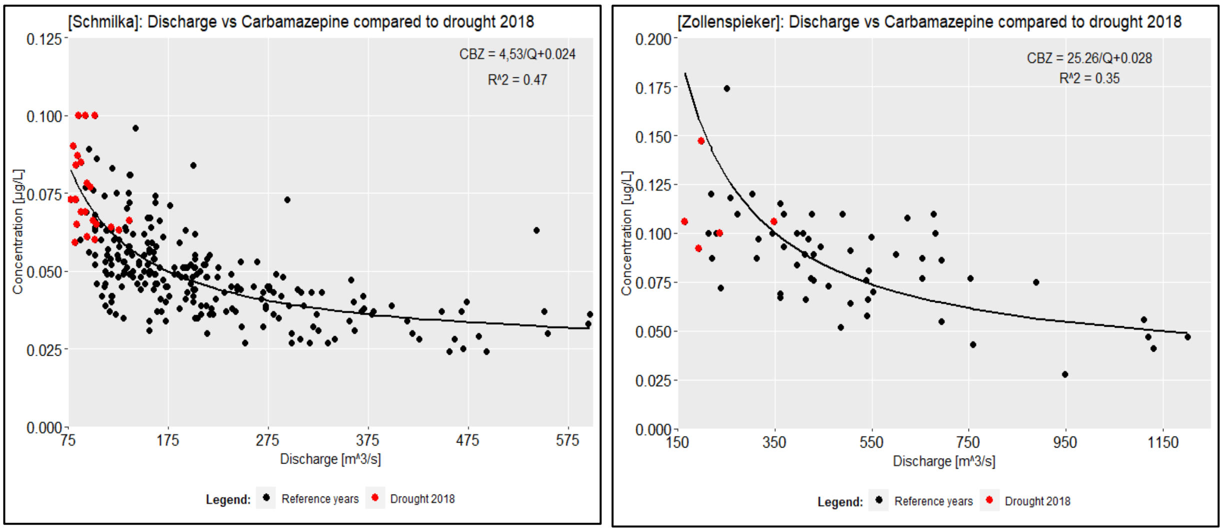


Fig. 34 a. The relation between the discharge and the carbamazepine concentrations for the stations Schmilka and Zollenspieker (Elbe) for the corresponding reference periods. The black line represents the C-Q relation by Eq. (2). The red dots represent the measurements of the 2018 drought (June–October).

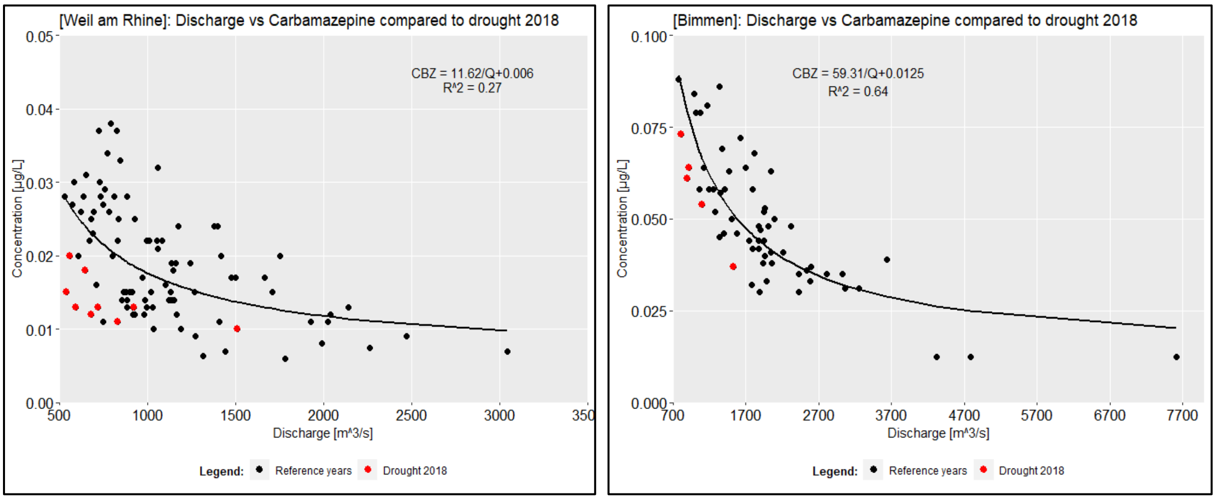


Fig. 34 b. The relation between the discharge and the carbamazepine concentrations for the monitoring stations Weil am Rhein and Bimmen (Rhine) for the corresponding reference periods. The black line represents the C-Q relation by Eq. (2). The red dots represent the measurements of the 2018 drought (June–October).

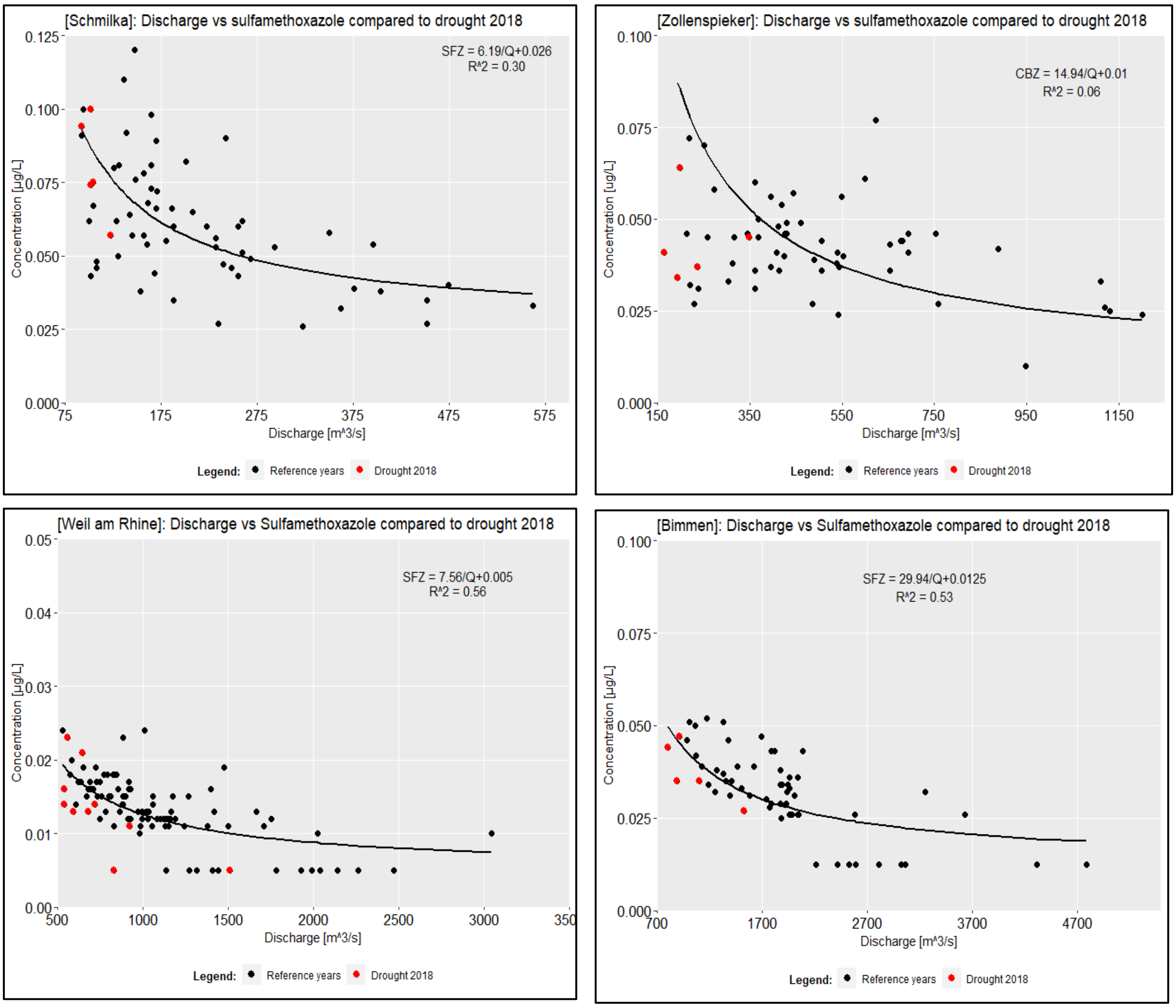


Fig. 34. The relation between the discharge and the Sulfamethoxazole concentrations for two stations alongside the Elbe (Schmilka and Zollenspieker) and the Rhine (Weil am Rhein and Bimmen) for the drought year and corresponding reference years. The black line represents the C-Q relation by Eq. (2). The red dots represent the measurements of the 2018 drought (June–October).

The C-Q relations of the pharmaceutical's diclofenac and metoprolol are shown in Fig. 36 and Appendix 4a Fig 4a. For the Elbe river scatterplots show no clear relation for all monitoring stations between discharge-diclofenac and discharge-metoprolol concentrations (R^2<0.1). For the Rhine e weak relations were found between discharge diclofenac (R^2=0.22 and R^2=0.14) and metoprolol (R^2=0.26 and R^2=0.22) concentrations at the monitoring stations Weil am Rhein and Koblenz, respectively. Moreover, for metoprolol a stronger relation with discharge is found at Worms (R^2=0.42). However, for all other monitoring stations there is no clear relation between discharge and diclofenac and metoprolol (R^2<0.01) (Appendix 4 Table 4a and 4A).

When comparing the fitted (a) values (emission loads) of the two pharmaceuticals (Appendix Table 4a), it can be concluded that there are substantial sources of emissions between the monitoring stations. With an increase in emission load of +286% for diclofenac and +381% metoprolol between Schmilka and Zollenspieker (Elbe) and +255% and +1293% between Weil am Rhein and Bimmen (Rhine) for diclofenac and metoprolol, respectively.

For diclofenac concentrations there is overall no clear relation with discharge, while for some stations there is a weak C-Q relation is found for metoprolol. Furthermore, in summer the concentrations are lower than in winter period, this indicates that other processes are involved that impact the behaviour of diclofenac and metoprolol. Consequently, the relation between water temperature and the pharmaceutical concentrations will be further analysed for both rivers.

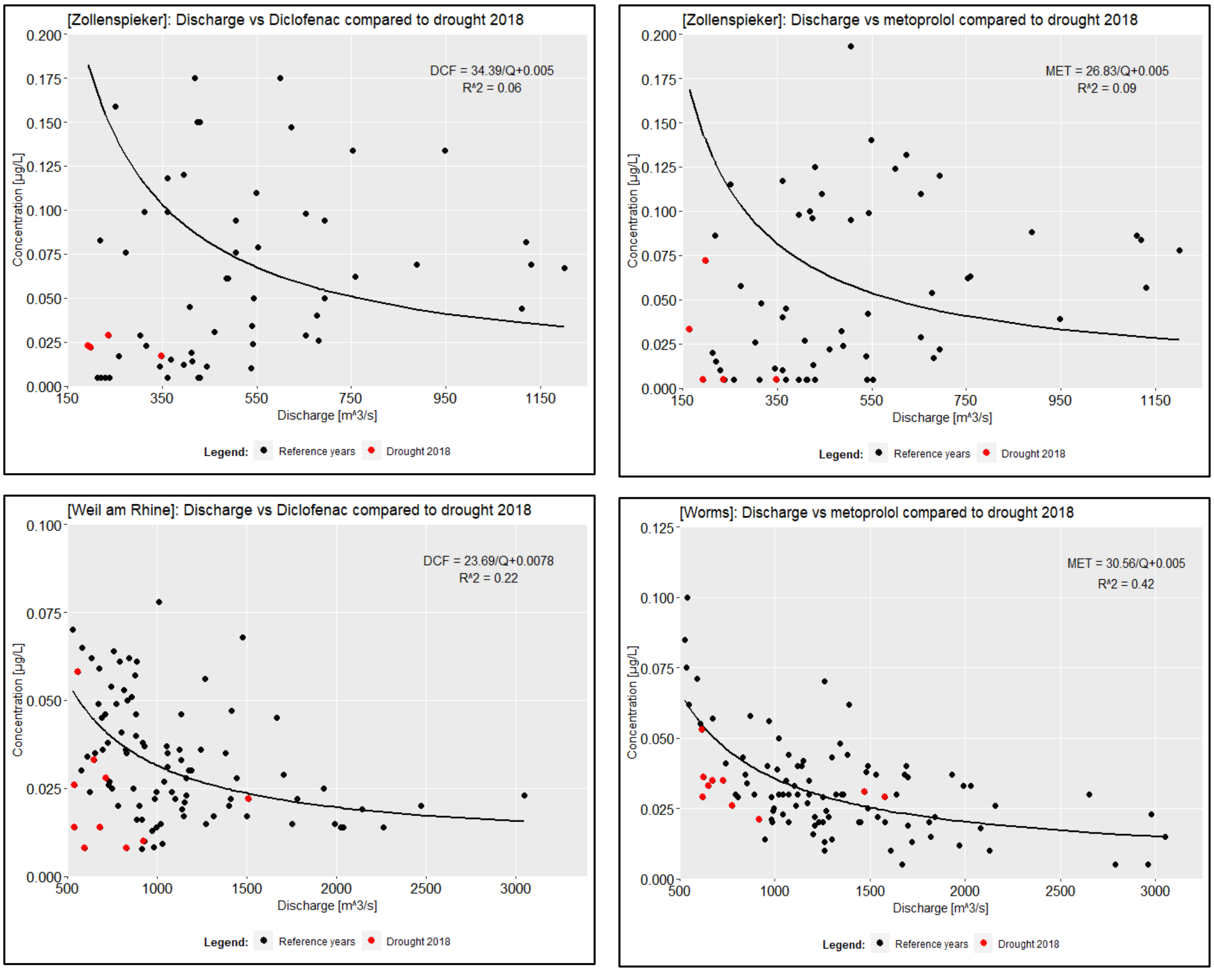


Fig. 35. The relation between the discharge and pharmaceuticals diclofenac and metoprolol concentrations for one stations alongside the Elbe (Zollenspieker) and the Rhine (Weil am Rhein) for the drought year and corresponding reference years. The black line represents the C-Q relation by Eq. (2). The red dots represent the measurements of the 2018 drought (June–October).

4.5.2 Water temperature vs pharmaceuticals

No relations were found between the water temperature and pharmaceuticals carbamazepine and sulfamethoxazole for both the Elbe and Rhine River, except at Schmilka for carbamazepine (Fig. 37 and Appendix 4b Fig. 4b and Fig. 4B). A weak positive relation (R^2=0.14) was found which was statistically significant ($p < 0.01$), this indicates that higher water temperatures result in higher concentrations.

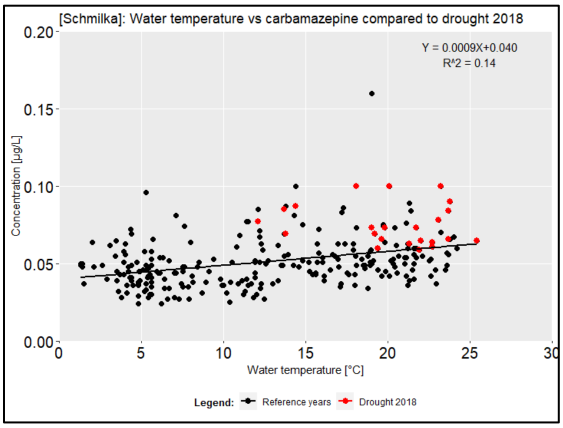


Fig. 36. The relation between the water temperature and carbamazepine concentrations at monitoring station Schmilka (Elbe) for the drought year and corresponding reference years. The black line represents the linear relation, and the red dots represent the measurements of the 2018 drought (June–October).

Clear negative relations were found between the water temperature and pharmaceuticals for diclofenac and metoprolol. Four scatterplots two for each river basin one upstream and one downstream were selected to display the observed relationship between the water temperature and the pharmaceuticals diclofenac (Fig. 37a-b) and metoprolol (Fig. 38). The scatterplots show a clear negative linear temperature-concentration relation. With high pharmaceutical concentrations corresponds with low water temperatures and vice versa. Additionally, stronger relations were found for both the Elbe and Rhine at stations that are more downstream the river. With a R^2 = 0.20 (Schmilka) versus R^2 =0.60 (Seemanshöft) and R^2 =0.13 (Schmilka) versus R^2 =0.68 (Zollenspieker) at the Elbe for diclofenac and metoprolol, respectively. And for the Rhine River, R^2 =0.50 (Weil am Rhein) versus R^2 =0.58 (Bimmen) and R^2 =0.35 (Weil am Rhein) versus R^2 =0.55 (Bimmen), for diclofenac and metoprolol, respectively. For all monitoring stations the relation is statistically significant ($p < 0.01$).

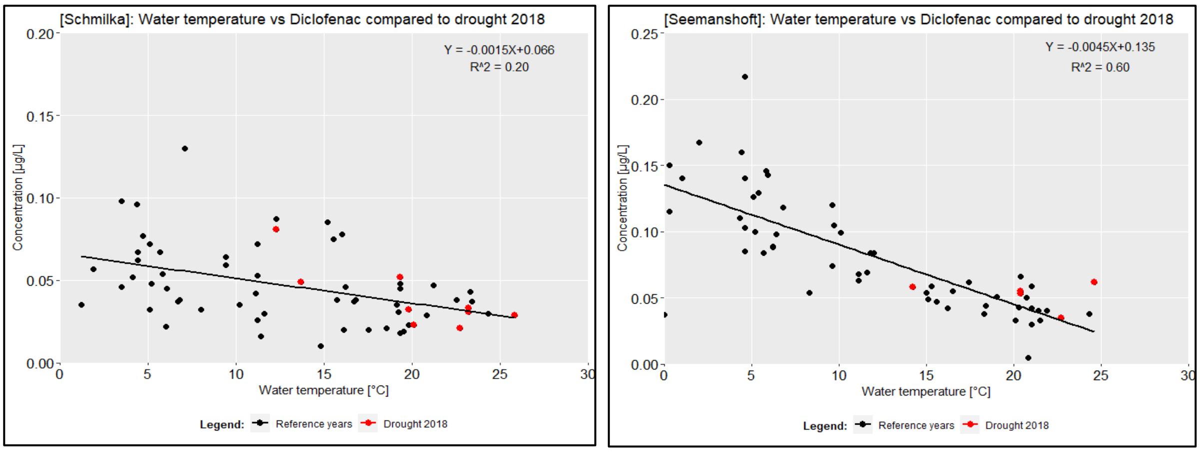


Fig. 37a. The relation between the water temperature and the diclofenac concentrations for two stations alongside the Elbe (Schmilka and Seemanshöft) for the drought year and corresponding reference years. The black line represents the linear relation, and the red dots represent the measurements of the 2018 drought (June–October).

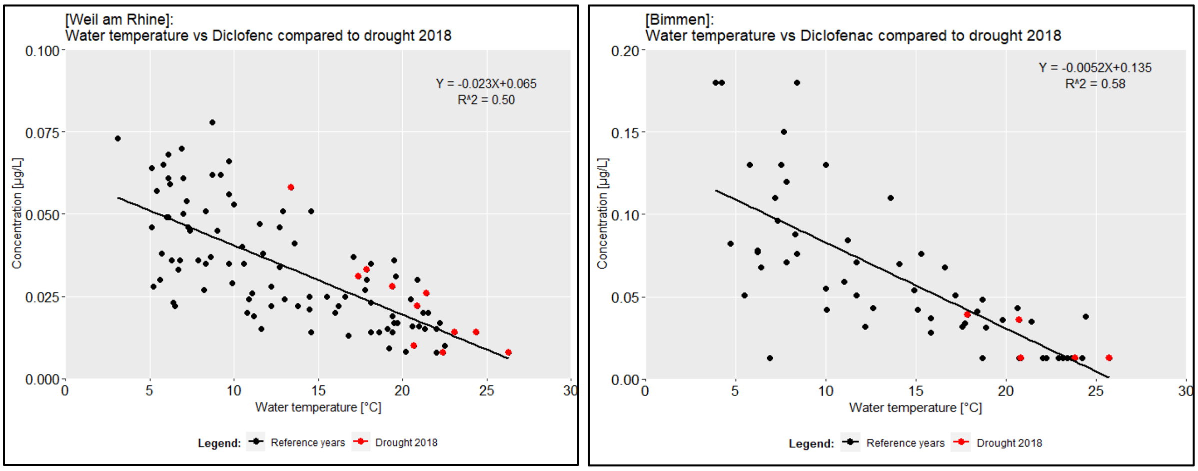


Fig. 38b. The relation between the water temperature and the diclofenac concentrations for two stations alongside the Rhine (Weil am Rhein and Bimmen) for the drought year and corresponding reference years. The black line represents the linear relation, and the red dots represent the measurements of the 2018 drought (June–October*)*.

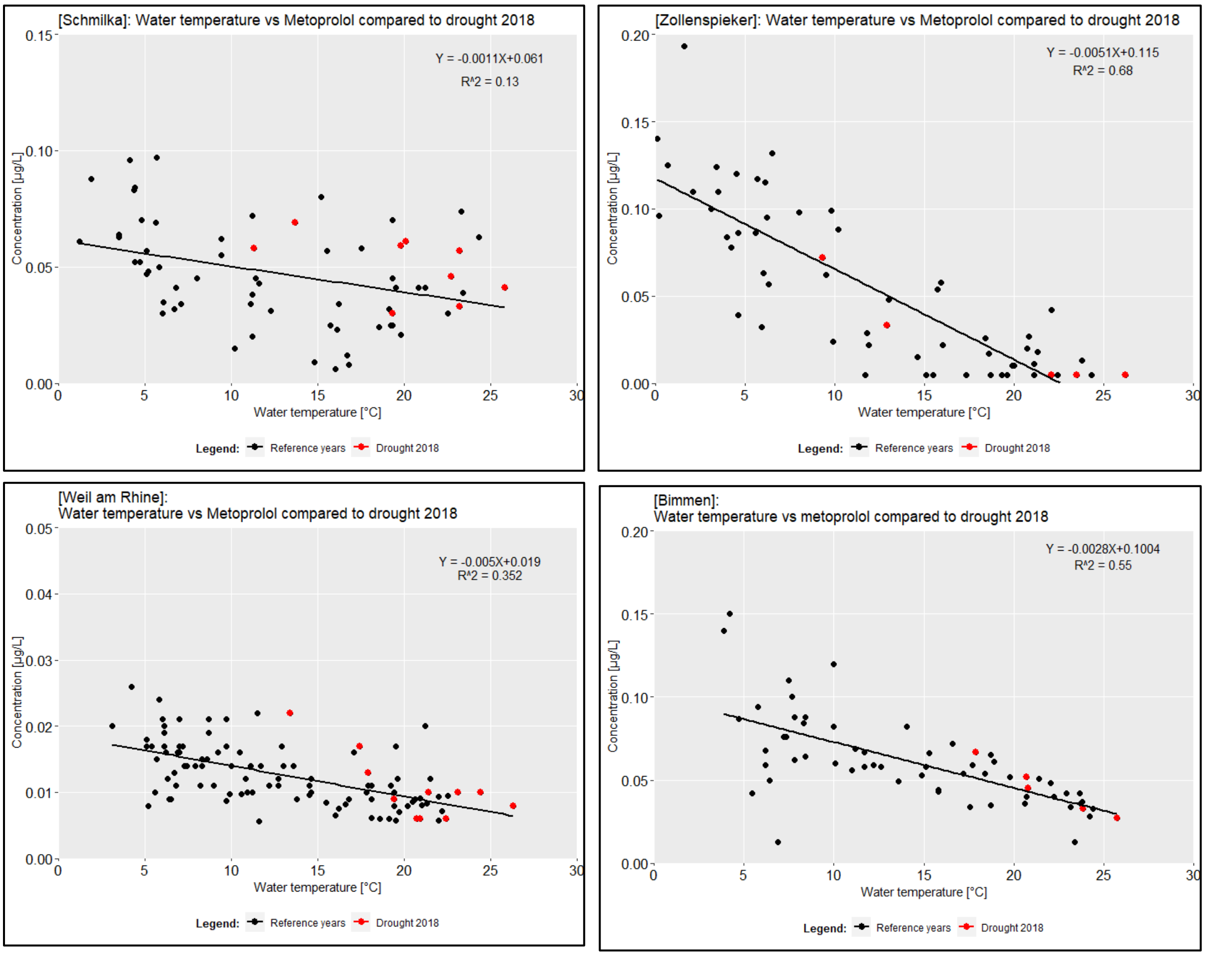


Fig. 39. The relation between the water temperature and the metoprolol concentrations for two stations alongside the Elbe (Schmilka and Zollenspieker) and the Rhine (Weil am Rhein and Bimmen) for the drought year and corresponding reference years. The black line represents the linear relation, and the red dots represent the measurements of the 2018 drought (June–October).

5 Discussion

5.1 Drought impact on pharmaceutical concentrations

During the drought of 2018 deterioration of the water quality and quantity, with extreme low flow conditions between the period June-December and increased water temperatures for both the Elbe (~+1.5 °C) and Rhine (~+2.0°C) rivers (June-August) was found. In this period, higher concentrations for the pharmaceutical's carbamazepine, sulfamethoxazole, and metoprolol were measured as 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 as compared to these reference years. The varied response of the four pharmaceutical's during the 2018 drought depends on their reactive or conservative characteristics. To understand these varied responses, the seasonal dynamics and their driving processes will be placed into a broader context in the next sections.

The higher concentrations found for carbamazepine and sulfamethoxazole during the 2018 drought compared to the reference years can be directly linked to the strong inverse C-Q relation (section 4.5.1) and 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 et al., 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 & 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; Sjerpa et al., 2017; Wiegel et al., 2013; Yuan et al., 2019). However, for metoprolol, no relations were found for the Elbe, while for the Rhine only weak relations with discharge were observed at monitoring stations upstream the river, in contrary to previous findings for the Rhine river by Sjerpa et al (2017) and Wolff and van Vliet (2021), which also found strong relations downstream at monitoring stations Bimmen/Lobith.

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 is from WWTPs (Wiegel et al., 2013) and there is a constant influx of these pharmaceuticals into both rivers, as human consumption, as prescription numbers are almost constant throughout the year (Sachers et al., 2008). During the extreme low flow conditions of the 2018 drought, wastewater gets less diluted and thus concentrations increase, this is also described in previous studies (Osorio et al., 2012, Osorio et al., 2016; Wolff and van Vliet, 2021).

Statistically significant increases during the 2018 drought were only observed for carbamazepine at 3 out of 6 monitoring stations upstream the Elbe (i.e. Schmilka, Zehren and Dommitzsch). As the elimination rate of carbamazepine is relatively lower compared to the elimination rates of sulfamethoxazole, metoprolol and diclofenac (Kinkel and Radke., 2012), it can explain the statistically significant increases found for carbamazepine concentrations compared to the reference years. Given that the responses in carbamazepine concentrations were not statistically significant at the downstream stations Zollenspieker and Seemanshöft, increased water travel time (longer residence time), which favour degradation processes (Mandaric et al., 2019) can explain the difference in response between the monitoring stations. As the upstream flow velocity is higher and so the residence time 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 affect the pharmaceutical concentrations. Therefore, the relation with water temperature is further investigated.

Significant relations were found between the diclofenac and metoprolol concentrations and the water temperature ($p < 0.01$), which could explain the seasonal variation (section 4.2.2) 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 (Sacher et al., 2008). Whereby, 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. As increased water travel time (longer residence times) and decreased river depth (low flow conditions), form a favourable environment for factors (i.e. temperature, solar irradiation, and turbidity) 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 4.5.2). As downstream conditions are more favourable (i.e longer residence time) for processes that are temperature depended. 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 depended on discharge (dilution) than on water temperature, which is also observed in other studies (Mandaric et al., 2019; Palma et al., 2020; Wolff and van Vliet., 2021).

In addition, as the main source of all pharmaceuticals (i.e. carbamazepine, sulfamethoxazole, metoprolol, and diclofenac) is from WWTPs, it can explain the higher concentrations found at downstream monitoring stations compared to monitoring stations upstream both rivers. As there is an increase in WWTPs which discharges into the river Elbe (Wiegel et al., 2004) and Rhine (Sachers et al., 2008). 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).

While overall the same pharmaceutical responses for both rivers where observed, a higher percental reduction in discharge (median discharge percentage change section 4.1.1) can account for the stronger water quality deterioration of the Elbe compared to the Rhine river. In summer and early autumn the Elbe is precipitation dominated (pluvial river system), while the Rhine river is snowmelt dominated (Nival-pluvial river system) (Kempe et al., 2005). During the 2018 drought the Elbe river had therefore a lower dilution capacity, which resulted in higher pharmaceutical (i.e. carbamazepine and sulfamethoxazole) concentrations.

5.2 Uncertainties

Even though, higher concentrations were found for the pharmaceuticals during the 2018 drought, the increases were in general non-significant. However, uncertainties arise in some of the assumptions that were made during this study regarding the pharmaceutical concentrations. First of all uncertainties in the pharmaceutical data required for this research must be considered. Pharmaceutical data was 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 moment 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. Furthermore, for this study it is assumed that during the years 2014-2020 for the Elbe and 2014-2019 for the Rhine the pharmaceutical concentrations were emitted to the surface water at a constant rate, with no increase or decrease in the human consumption. Fig. 39 illustrates the irregular concentration differences for carbamazepine during the years before 2010 and the more constant concentration fluctuations after 2010.

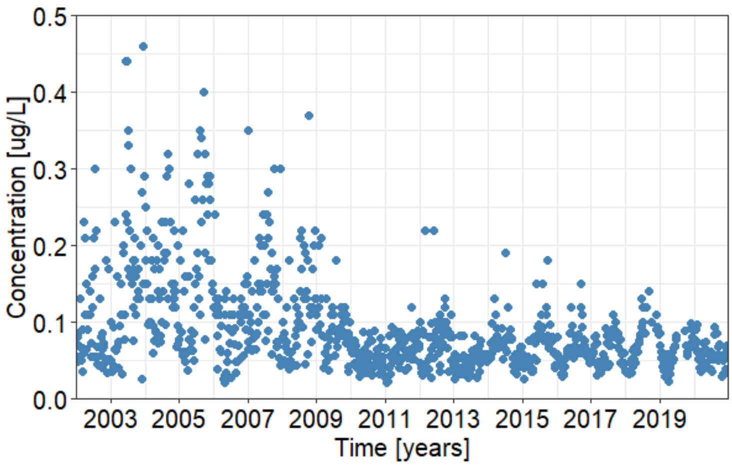


Fig. 40. Carbamazepine concentrations weekly measured at monitoring station Dommitzsch (Elbe) for the period 2002-2020. Showing the fluctuating concentrations before 2010 and the more constant concentrations after 2010.

Secondly, the artificially set values to half the limit of detection (LD/2) is assumed to be reliable, however, it makes the measurements during drought and non-drought conditions less representative. For example, the LOD can differ per pharmaceutical, monitoring station and year. At monitoring station Mainz alongside the Rhine, the LOD was set on 0.01 $\mu g.L^{-1}$ for carbamazepine during the reference years 2014, 2016, 2017 and 2019, however for the 2018 drought the LOD was set on 0.03 $\mu g.L^{-1}$. The artificially set value for the reference years was 0.005 $\mu g.L^{-1}$ and for the 2018 drought 0.015 $\mu g.L^{-1}$. This resulted in a statistically significant difference between the drought period June-October compared to the reference year 2019, which was, however not the case.

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. For instance, at monitoring station Weil am Rhein 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 has the bi-weekly measurements including the measured concentrations for the period 2015 and 2016 which corresponds to the EEA data. Fig. 40 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 an under representation of the maximum daily concentration of the EEA data of 30% (0.058 μg.L^{-1} versus 0.075 μg.L^{-1} , Februari 2015) and 27% (0.079 μg.L^{-1} versus 0.1 μg.L$^{-1,}$ December 2015), respectively. Especially for stations downstream where the concentration differences during the year are more fluctuating (differences minimum and maximum concentrations is larger) (section 4.4.2) this can give an under-representation of the maximum concentrations.

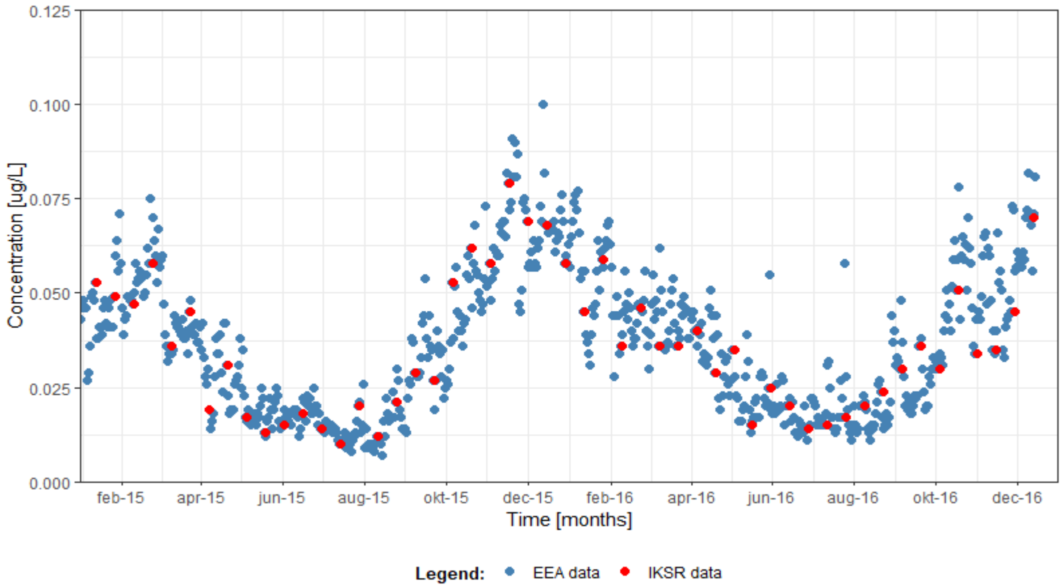


Fig. 41. Plot showing the uncertainties that arise when measuring the diclofenac concentrations for the period 2015-2016 with a different frequency at monitoring station Weil am Rhein (Rhine). EEA data (Blue) shows the daily measured concentrations, while the IKSR data (Red) shows the bi-weekly measurements.

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 Rhine 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, for example when comparing the pharmaceutical concentration with the discharge and water temperature. As the discharge and water temperature can fluctuate on daily basis, the reliability of the relation is questioned.

5.3 Outlook

Three out of four pharmaceuticals (carbamazepine, sulfamethoxazole, and metoprolol) showed increased concentrations during the 2018 drought for the Elbe and Rhine river. The ERM target value of 0.1 $\mu g.L^{-1}$ was not exceeded for carbamazepine, sulfamethoxazole, and metoprolol for the Rhine river during the June-October period 2018. However, the ERM target values for both metoprolol and especially for carbamazepine were exceeded during the 2018 drought in the Elbe river. The carbamazepine concentrations exceeded the ERM target value at four out of six monitoring stations. At Zollenspieker and Seemanshöft the concentrations exceeded 0.1 $\mu g.L^{-1}$ early June and remained above this threshold until January 2019 (only in august below 0.1 $\mu g.L^{-1}$). This resulted in a period of eight months during which the ERM target values where exceeded. For Dommitzsch and Zehren this was respectively shorter, late June the concentrations exceeded the 0.1 $\mu g.L^{-1}$ and fluctuated around this threshold until late November. Moreover, also for parts of the reference (non-drought) years the target values were exceeded, however, not in the same frequency and magnitude as the 2018 drought.

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).

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 (Sathiskumar et al., 2020). However, during the 2018 drought overall decreased diclofenac concentrations were observed to concentrations below the LOD, which reduces the risk of long-term exposure to high concentrations. Finally, and 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 WWTP's, resulting in a decrease in efficiency rate to remove other pollutants (Duarte et al., 2021; Larcher and Yargeau, 2020; Oldenkamp et al., 2019).

6 Conclusion

The main objective of this research was to estimate the impact of the 2018 drought on concentrations of four selected pharmaceuticals (carbamazepine, sulfamethoxazole, diclofenac, and metoprolol) in the Elbe and Rhine rivers. To investigate this objective, four research questions were addressed to improve understanding all the processes that influence the behaviour of the pharmaceuticals during droughts.

First of all, deterioration of the water quantity and quality for both rivers were found during the drought of 2018. With extreme low flow conditions between the period June-December and an increased water temperature for both the Elbe (~+1.5 °C) and Rhine (~+2.0°C) river during the June-August period compared to the reference years.

RQ1: Spatial and temporal patterns

The spatial patterns for all four pharmaceuticals; carbamazepine sulfamethoxazole, diclofenac and metoprolol showed overall the same patters, with low concentrations upstream and higher concentrations downstream the rivers. It can be concluded that as the main source of pharmaceuticals are from WWTP's, there is an important contribution of emission sources between the monitoring stations. (only sulfamethoxazole in the Elbe river showed relative decreasing concentrations in downstream direction which can be attributed to a higher dilution (increased discharge) rate compared to emission rates). Furthermore, the temporal patterns of carbamazepine and sulfamethoxazole where in direct relation with the discharge, as the discharge is lower in summer, the concentrations are higher due to less dilution. Moreover, the temporal patterns of diclofenac and metoprolol, showed seasonal patterns with low concentrations in summer and high in winter which can be accounted for by higher efficiency removal rates due to higher temperatures.

RQ2: Statistical analyses of pharmaceutical concentrations under drought

Substantial increases in the concentrations for the pharmaceutical's carbamazepine, sulfamethoxazole, and metoprolol were found during the 2018 drought compared to the reference years, while overall decreased concentrations were observed for diclofenac. However, those changes were overall statistically insignificant. Except for carbamazepine were the differences in average concentrations during the 2018 drought compared to all reference years were statistically significant ($p < 0.01$), for the upstream monitoring stations (i.e. Schmilka, Zehren and Dommitzsch) along the river Elbe. Furthermore looking at a toxicological perspective, the maximum ERM target value of 0.1 $\mu g.L^{-1}$ where overall not exceeded during the 2018 drought for all pharmaceuticals in the Rhine river. Though, for the Elbe the metoprolol and especially the carbamazepine concentrations exceeded the maximum ERM target value at four out of six monitoring stations. This resulted that at monitoring stations Zollenspieker and Seemanshöft between June 2018 and January 2019 the ERM target value of 0.1 $\mu g.L^{-1}$ were exceeded.

RQ3: Comparison of responses in pharmaceutical concentrations across river

While overall the same pharmaceutical patterns for both rivers where observed, stronger water quality responses were found for the Elbe river. Reduction in discharge due to the different hydrological regimes can account for the stronger water quality deterioration of the Elbe compared to the Rhine river. As the precipitation dominated Elbe river had a lower dilution capacity. Moreover, the higher water temperatures for the Rhine river can possibly explain the improved water quality regarding the diclofenac concentrations compare to the Elbe river.

RQ4: Drivers of changes in pharmaceutical concentrations under drought

RQ4 aimed to link the results obtained in RQ2 to specific hydro-metrological conditions. Strong inverse C-Q relations were found between carbamazepine and sulfamethoxazole (while weaker C-Q relations were observed for metoprolol in the Rhine river), as both substances are highly persistent in the environment they depend mainly on the discharge. During low flow conditions concentrations are less diluted and could therefore explain the higher concentrations during the 2018 drought. Furthermore, stronger negative relations with water temperature for diclofenac and metoprolol were found for downstream parts compared to upstream parts. Which can be attributed to longer residence time (e.g. lower flow velocities), since the conditions are more favourable for degradation processes and adsorption as the pharmaceuticals are less mobile.

Finally, considering, a perspective for the future, with increases in frequency and intensity of droughts resulting in higher air temperatures and longer dry spells due to climate change. Adding up 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. This could easily lead to the situation that the concentrations of certain pharmaceuticals may even further increase as measured to date. As a result, the concentrations may exceed the maximum ERM target values more often and with a higher magnitude in both the river Elbe and Rhine during future droughts, with all consequences for the aquatic environment. Consequently, it is important to closely monitor and most likely in the future aim to reduce the emissions of pharmaceuticals into the rivers in order to protect the water quality and aquatic life during future droughts.

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 Research*, *150*, 97–110. https://doi.org/10.1016/j.watres.2018.11.052

Bahlmann, A., Brack, W., Schneider, R. J., & Krauss, M. (2014). Carbamazepine and its metabolites in wastewater: Analytical pitfalls and occurrence in Germany and Portugal. *Water Research*, *57*, 104–114. https://doi.org/10.1016/j.watres.2014.03.022

Barclay, V. K., Tyrefors, N. L., Johansson, I. M., & Pettersson, C. E. (2012). Chiral analysis of metoprolol and two of its metabolites, α-hydroxymetoprolol and deaminated metoprolol, in wastewater using liquid chromatography–tandem mass spectrometry. *Journal of Chromatography A*, *1269*, 208–217. https://doi.org/10.1016/j.chroma.2012.09.090

Boergens, E., Güntner, A., Dobslaw, H., & Dahle, C. (2020). Quantifying the Central European Droughts in 2018 and 2019 With GRACE Follow-On. *Geophysical Research Letters*, *47*(14). https://doi.org/10.1029/2020gl087285

Brunsch, A. F., ter Laak, T. L., Rijnaarts, H., & Christoffels, E. (2018b). Pharmaceutical concentration variability at sewage treatment plant outlets dominated by hydrology and other factors. *Environmental Pollution*, *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

Cunningham, V. L., Perino, C., D'Aco, V. J., Hartmann, A., & Bechter, R. (2010). Human health risk assessment of carbamazepine in surface waters of North America and Europe. *Regulatory Toxicology and Pharmacology*, *56*(3), 343–351. https://doi.org/10.1016/j.yrtph.2009.10.006

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

Dai, A. (2012). Erratum: Drought under global warming: a review. *WIREs Climate Change*, *3*(6), 617. https://doi.org/10.1002/wcc.190

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

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. *Ecotoxicology and Environmental Safety*, *164*, 297–304. https://doi.org/10.1016/j.ecoenv.2018.08.015

Deo, R. P. (2014). Pharmaceuticals in the Surface Water of the USA: A Review. *Current Environmental Health Reports*, *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. (2021b). Ecological Risk Assessment of Pharmaceuticals in the Transboundary Vecht River (Germany and The Netherlands). *Environmental Toxicology and Chemistry*, *41*(3), 648–662. https://doi.org/10.1002/etc.5062

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. *Journal of Hazardous Materials*, *323*, 250–263. https://doi.org/10.1016/j.jhazmat.2016.05.072

Gröner, F., Ziková, A., & Kloas, W. (2015). Effects of the pharmaceutical's diclofenac and metoprolol on gene expression levels of enzymes of biotransformation, excretion pathways and estrogenicity in primary hepatocytes of Nile tilapia (Oreochromis niloticus). *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, *167*, 51–57. https://doi.org/10.1016/j.cbpc.2014.09.003

Guzel, E. Y., Cevik, F., & Daglioglu, N. (2018). Determination of pharmaceutical active compounds in Ceyhan River, Turkey: Seasonal, spatial variations and environmental risk assessment. *Human and Ecological Risk Assessment: An International Journal*, *25*(8), 1980–1995. https://doi.org/10.1080/10807039.2018.1479631

Haas, C. N., & Scheff, P. A. (1990). Estimation of averages in truncated samples. *Environmental Science & Technology*, *24*(6), 912–919. https://doi.org/10.1021/es00076a021

Hejcman, M., Dvorak, I. J., Kocianova, M., Pavlu, V., Nezerkova, P., Vitek, O., Rauch, O., & Jenik, J. (2006). Snow Depth and Vegetation Pattern in a Late-melting Snowbed Analyzed by GPS and GIS in the Giant Mountains, Czech Republic. *Arctic, Antarctic, and Alpine Research*, *38*(1), 90–98. https://doi.org/10.1657/1523-0430

HIRABAYASHI, Y., KANAE, S., EMORI, S., OKI, T., & KIMOTO, M. (2008). Global projections of changing risks of floods and droughts in a changing climate. *Hydrological Sciences Journal*, *53*(4), 754–772. https://doi.org/10.1623/hysj.53.4.754

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

Ionita, M., & Nagavciuc, V. (2020). Forecasting low flow conditions months in advance through teleconnection patterns, with a special focus on summer 2018. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-70060-8

Jarvis, A. L., Bernot, M. J., & Bernot, R. J. (2014). Relationships between the psychiatric drug carbamazepine and freshwater macroinvertebrate community structure. *Science of The Total Environment*, *496*, 499–509. https://doi.org/10.1016/j.scitotenv.2014.07.086

Johnson, A., Keller, V., Williams, R., & Young, A. (2007). A practical demonstration in modelling diclofenac and propranolol river water concentrations using a GIS hydrology model in a rural UK catchment. *Environmental Pollution*, *146*(1), 155–165. https://doi.org/10.1016/j.envpol.2006.05.037

Jones, E., & van Vliet, M. T. (2018). Drought impacts on river salinity in the southern US: Implications for water scarcity. *Science of The Total Environment*, *644*, 844–853. https://doi.org/10.1016/j.scitotenv.2018.06.373

Khasawneh, O. F. S., & Palaniandy, P. (2021). Occurrence and removal of pharmaceuticals in wastewater treatment plants. *Process Safety and Environmental Protection*, *150*, 532–556. https://doi.org/10.1016/j.psep.2021.04.045

Kolpin DW, Furlong ET, Meyer MT, Thruman EM, Zaugg SD, Barber LB, Buxton H (2000) PhACs, hormones and other wastewater contaminants in U.S. streams. Environ Sci Technol 32:2498–2506

Kondor, A. C., Jakab, G., Vancsik, A., Filep, T., Szeberényi, J., Szabó, L., Maász, G., Ferincz, R., Dobosy, P., & Szalai, Z. (2020). Occurrence of pharmaceuticals in the Danube and drinking water wells: Efficiency of riverbank filtration. *Environmental Pollution*, *265*, 114893. https://doi.org/10.1016/j.envpol.2020.114893

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. *Hydrology and Earth System Sciences*, *21*(6), 3001-3024

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

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

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. *Ecotoxicology and Environmental Safety*, *74*(3), 319–327. https://doi.org/10.1016/j.ecoenv.2010.09.008

Lonappan, L., Brar, S. K., Das, R. K., Verma, M., & Surampalli, R. Y. (2016). Diclofenac and its transformation products: Environmental occurrence and toxicity - A review. *Environment International*, *96*, 127–138. https://doi.org/10.1016/j.envint.2016.09.014

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. *Environmental Science: Processes & 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. *Environmental Monitoring and Assessment*, *188*(8). https://doi.org/10.1007/s10661-016-5481-2

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 Resources Management*, *26*(13), 3923–3946. https://doi.org/10.1007/s11269-012-0113-2

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

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

Moravec, V., Markonis, Y., Rakovec, O., Svoboda, M., Trnka, M., Kumar, R., & Hanel, M. (2021). Europe under multi-year droughts: how severe was the 2014–2018 drought period? *Environmental Research Letters*, *16*(3), 034062. https://doi.org/10.1088/1748-9326/abe828

Ngqwala, N. P., & Muchesa, P. (2020). Occurrence of pharmaceuticals in aquatic environments: A review and potential impacts in South Africa. *South African Journal of Science*, *116*(7/8). https://doi.org/10.17159/sajs.2020/5730

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. *Environmental Research Letters*, *14*(3), 034003. https://doi.org/10.1088/1748-9326/ab0071
.

Oosterhuis, M., Sacher, F., & ter Laak, T. L. (2013). Prediction of concentration levels of metformin and other high consumption pharmaceuticals in wastewater and regional surface water based on sales data. *Science of The Total Environment*, *442*, 380–388. https://doi.org/10.1016/j.scitotenv.2012.10.046

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. *Science of The Total Environment*, *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

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 in Analytical Chemistry*, *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. https://doi.org/10.3390/w9090684

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. *Proceedings of the National Academy of Sciences*, *111*(9), 3262–3267. https://doi.org/10.1073/pnas.1222473110

Radke, M., Lauwigi, C., Heinkele, G., Mürdter, T. E., & Letzel, M. (2009). Fate of the Antibiotic Sulfamethoxazole and Its Two Major Human Metabolites in a Water Sediment Test. *Environmental Science & Technology*, *43*(9), 3135–3141. https://doi.org/10.1021/es900300u

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. *Journal of Environmental Monitoring*, *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. *Science of The Total Environment*, *698*, 134057. https://doi.org/10.1016/j.scitotenv.2019.134057

Shorvon, S., Perucca, E., & Jr., E. J. (2015). *The Treatment of Epilepsy* (4th ed.). Wiley-Blackwell.

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. *Science of The Total Environment*, *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.

Skocovska, M., Ferencik, M., Svoboda, M., & Svobodova, Z. (2021). Residues of selected sulfonamides, non-steroidal anti-inflammatory drugs and analgesics-antipyretics in surface water of the Elbe river basin (Czech Republic). Veterinární Medicína, 66(No. 5), 208–218. https://doi.org/10.17221/180/2020-vetmed

Schmidt, S., Hoffmann, H., Garbe, L. A., & Schneider, R. J. (2018). Liquid chromatography–tandem mass spectrometry detection of diclofenac and related compounds in water samples. *Journal of Chromatography A*, *1538*, 112–116. https://doi.org/10.1016/j.chroma.2018.01.037

Straub, J. O. (2015). Aquatic environmental risk assessment for human use of the old antibiotic sulfamethoxazole in Europe. *Environmental Toxicology and Chemistry*, *35*(4), 767–779. https://doi.org/10.1002/etc.2945

Stülten, D., Zühlke, S., Lamshöft, M., & Spiteller, M. (2008). Occurrence of diclofenac and selected metabolites in sewage effluents. *Science of The Total Environment*, *405*(1–3), 310–316. https://doi.org/10.1016/j.scitotenv.2008.05.036

Tang, J., Sun, J., Wang, W., Yang, L., & Xu, Y. (2021). Pharmaceuticals in two watersheds in Eastern China and their ecological risks. *Environmental Pollution*, *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. *Nature Climate Change*, *4*(1), 17–22. https://doi.org/10.1038/nclimate2067
van Loon, A. F., & van Lanen, H. A. J. (2012). A process-based typology of hydrological drought. *Hydrology and Earth System Sciences*, *16*(7), 1915–1946. https://doi.org/10.5194/hess-16-1915-2012

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 and Climate Extremes*, *33*, 100350. https://doi.org/10.1016/j.wace.2021.100350

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

Wilbers, G. J., Zwolsman, G., Klaver, G., & Hendriks, A. J. (2009). Effects of a drought period on physico-chemical surface water quality in a regional catchment area. *Journal of Environmental Monitoring*, *11*(6), 1298. https://doi.org/10.1039/b816109g

Wolff, E., & van Vliet, M. T. (2021). Impact of the 2018 drought on pharmaceutical concentrations and general water quality of the Rhine and Meuse rivers. *Science of The Total Environment*, *778*, 146182. https://doi.org/10.1016/j.scitotenv.2021.146182

Yazdanbakhsh, A., Nemati, R., Massoudinejad, M., Jafari, M., & Dashtdar, M. (2019). Solar photodegradation of carbamazepine from aqueous solutions using a compound parabolic concentrator equipped with a sun tracking system. *Open Chemistry*, *17*(1), 477–484. https://doi.org/10.1515/chem-2019-0060

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. *Science of The Total Environment*, *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. *Journal of Hazardous Materials*, *166*(2–3), 655–661. https://doi.org/10.1016/j.jhazmat.2008.11.070

Zhou, X. F., Dai, C. M., Zhang, Y. L., Surampalli, R. Y., & Zhang, T. C. (2010). A preliminary study on the occurrence and behavior of carbamazepine (CBZ) in aquatic environment of Yangtze River Delta, China. *Environmental Monitoring and Assessment*, *173*(1–4), 45–53. https://doi.org/10.1007/s10661-010-1369-8

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 Research*, *196*, 117052. https://doi.org/10.1016/j.watres.2021.117052

Appendix 1

Table 1a: Showing the spatial distribution of the average Carbamazepine concentration (ug.L^{-1}) for all monitoring station included for the analysis over the period 2010-2020 (Yellow). Monitoring stations are ordered from upstream – downstream location. The average concentrations of the 2010-2020 (Jun-Oct) and 2018 (Jun-Oct) period, represent the concentrations of the selected monitoring stations for the Maps in Appendix 4

Station name	Count 2010-2020	Count 2010-2020 Jun-Oct	Count 2018 Jun-Oct	Average 2010-2020	Average 2010-2020 Jun-Oct	Average 2018 Jun-Oct
Elbe						
Schmilka, right	525	217	24	0.048 ± (0.020)	0.056 ± (0.021)	0.078 ± (0.023)
Zehren, left	523	212	22	0.058 ± (0.022)	0.068 ± (0.024)	0.094 ± (0.021)
Dommitzsch, left	545	219	10	0.064 ± (0.025)	0.074 ± (0.027)	0.106 ± (0.020)
Zollenspieker	131	54	5	0.087 ± (0.033)	0.099 ± (0.032)	0.110 ± (0.021)
Seemanshöft	132	54	5	0.091 ± (0.033)	0.105 ± (0.033)	0.108 ± (0.012)
Brunsbüttelkoog	97	43	4	0.072 ± (0.027)	0.075 ± (0.030)	0.069 ± (0.009)
Rhine						
Weil am Rhein	259	108	11	0.021 ± (0.011)	0.020 ± (0.009)	0.015 ± (0.003)
Worms	143	61	11	0.031 ± (0.013)	0.032 ± (0.012)	0.034 ± (0.010)
Mainz	225	94	7	0.032 ± (0.015)	0.029 ± (0.010)	0.030 ± (0.009)
Koblenz	128	52	5	0.045 ± (0.018)	0.048 ± (0.020)	0.054 ± (0.010)
Bad Honnef	120	48	5	0.045 ± (0.014)	0.046 ± (0.013)	0.050 ± (0.013)
Bimmen	129	52	5	0.052 ± (0.021)	0.053 ± (0.014)	0.058 ± (0.014)

Table 1b: Showing the spatial distribution of the average sulfamethoxazole concentration (ug.L^{-1}) for all monitoring station included for the analysis over the period 2010-2020 (Yellow). Monitoring stations are ordered from upstream – downstream location. The average concentrations of the 2010-2020 (Jun-Oct) and 2018 (Jun-Oct) period, represent the concentrations of the selected monitoring stations for the Maps in Appendix 4

Station	Count 2010-2020	Count 2010-2020 Jun-Oct	Count 2018 Jun-Oct	Average 2010-2020	Average 2010-2020 Jun-Oct	Average 2018 Jun-Oct
Elbe						
Schmilka, right	133	54	10	0.055 ± (0.023)	0.058 ± (0.023)	0.075 ± (0.017)
Dommitzsch, left	155	69	5	0.048 ± (0.021)	0.050 ± (0.023)	0.073 ± (0.016)
Zollenspieker	131	54	5	0.040 ± (0.015)	0.039 ± (0.013)	0.044 ± (0.012)
Seemanshöft	131	54	5	0.042 ± (0.013)	0.042 ± (0.011)	0.046 ± (0.007)
Brunsbüttelkoog	73	33	4	0.034 ± (0.013)	0.032 ± (0.013)	0.038 ± (0.006)
Rhine						
Weil am Rhein	257	108	11	0.015± (0.004)	0.014 ± (0.004)	0.015 ± (0.005)
WORMS	129	55	11	0.023± (0.008)	0.024 ± (0.007)	0.025 ± (0.008)
MAINZ	121	51	7	0.022± (0.008)	0.021 ± (0.007)	0.021 ± (0.006)
Koblenz	179	73	5	0.030± (0.020)	0.029 ± (0.020)	0.012 ± (0.004)
Bad Honnef	104	42	5	0.032± (0.007)	0.032 ± (0.007)	0.034 ± (0.006)
Bimmen	147	60	5	0.037± (0.012)	0.039 ± (0.012)	0.038 ± (0.008)

Table 1c: Showing the spatial distribution of the average diclofenac concentration (ug.L^{-1}) for all monitoring station included for the analysis over the period 2010-2020 (Yellow). Monitoring stations are ordered from upstream – downstream location. The average concentrations of the 2010-2020 (Jun-Oct) and 2018 (Jun-Oct) period, represent the concentrations of the selected monitoring stations for the Maps in Appendix 4

Station	(n) 2010-2020	(n) 2010-2020 Jun-Oct	(n) 2018 Jun-Oct	Average 2010-2020	Average 2010-2020 Jun-Oct	Average 2018 Jun-Oct
Elbe						
Schmilka, right	178	82	9	0.037± (0.029)	0.030 ± (0.030)	0.039 ± (0.019)
Dommitzsch, left	157	67	5	0.055± (0.039)	0.045 ± (0.045)	0.051 ± (0.022)
Zollenspieker	126	54	4	0.036± (0.009)	0.042 ± (0.042)	0.204 ± (0.410)
Seemanshöft	102	53	5	0.071± (0.052)	0.042 ± (0.042)	0.020 ± (0.010)
Brunsbüttelkoog	35	32	4	0.051± (0.026)	0.013 ± (0.013)	0.006 ± (0.008)
Rhine						
Weil am Rhein	920	383	11	0.035± (0.016)	0.024 ± (0.025)	0.023 ± (0.012)
WORMS	111	55	11	0.038± (0.016)	0.020 ± (0.020)	0.017 ± (0.012)
MAINZ	193	94	7	0.049± (0.045)	0.035 ± (0.035)	0.030 ± (0.012)
Koblenz	126	52	5	0.036± (0.026)	0.021 ± (0.020)	0.020 ± (0.012)
Bad Honnef	67	42	5	0.064± (0.032)	0.032 ± (0.032)	0.025 ± (0.012)
Bimmen	123	49	5	0.058± (0.031)	0.037 ± (0.037)	0.030 ± (0.012)

Table 1d: Showing the spatial distribution of the average metoprolol concentration (ug.L^{-1}) for all monitoring station included for the analysis over the period 2010-2020 (Yellow). Monitoring stations are ordered from upstream – downstream location. The average concentrations of the 2010-2020 (Jun-Oct) and 2018 (Jun-Oct) period, represent the concentrations of the selected monitoring stations for the Maps in Appendix 4

Station	(n) 2010-2020	(n) 2010-2020 Jun-Oct	(n) 2018 Jun-Oct	Average 2010-2020	Average 2010-2020 Jun-Oct	Average 2018 Jun-Oct
Elbe						
Schmilka, right	166	75	9	0.043 ± (0.019)	0.041 ± (0.040)	0.050 ± (0.014)
Dommitzsch, left	119	54	5	0.067 ± (0.039)	0.070 ± (0.070)	0.079 ± (0.010)
Zollenspieker	96	49	5	0.066 ± (0.042)	0.057 ± (0.023)	0.068 ± (0.000)
Seemanshöft	124	49	5	0.082 ± (0.045)	0.023 ± (0.057)	0.027 ± (0.031)
Brunsbüttelkoog	78	36	4	0.044 ± (0.032)	0.024 ± (0.024)	0.047 ± (0.063)
Rhine						
Weil am Rhein	242	103	11	0.012 ± (0.005)	0.009 ± (0.009)	0.011 ± (0.006)
WORMS	130	55	11	0.032 ± (0.017)	0.025 ± (0.025)	0.035 ± (0.010)
MAINZ	122	51	7	0.029 ± (0.014)	0.021 ± (0.021)	0.026 ± (0.010)
Koblenz	65	27	5	0.025 ± (0.013)	0.019 ± (0.020)	0.030 ± (0.013)
Bad Honnef	103	42	5	0.048 ± (0.021)	0.037 ± (0.037)	0.034 ± (0.008)
Bimmen	122	51	5	0.064 ± (0.024)	0.052 ± (0.052)	0.045 ± (0.016)

Appendix 2

Appendix 2a

Table 2a: Results of the Shapirov wilk test and the desciptive statistics for Carbamazepine, drouhgt + reference periods (Jan-Dec)

stations	Observations	P-value	Median	Minimum	Maximum	Std. dev
Elbe						
Schmilka	259	<0.001	0.051	0.024	0.160	0.017
Zehren	229	<0.001	0.061	0.026	0.160	0.021
Dommitzsch	244	<0.001	0.065	0.029	0.190	0.023
Zollenspieker	60	0.144	0.087	0.028	0.174	0.026
Seemanshöft	60	0.695	0.090	0.044	0.146	0.023
Brunsbüttelkoog	55	0.002	0.073	0.008	0.100	0.016
Rhine						
Weil am Rhein	129	<0.001	0.017	0.006	0.039	0.008
Worms	103	<0.001	0.028	0.010	0.060	0.011
Mainz	103	<0.001	0.028	0.010	0.054	0.010
Koblenz	64	<0.001	0.040	0.018	0.087	0.014
Bad Honnef	64	<0.001	0.043	0.013	0.082	0.017
Bimmen	64	<0.001	0.050	0.025	0.190	0.024

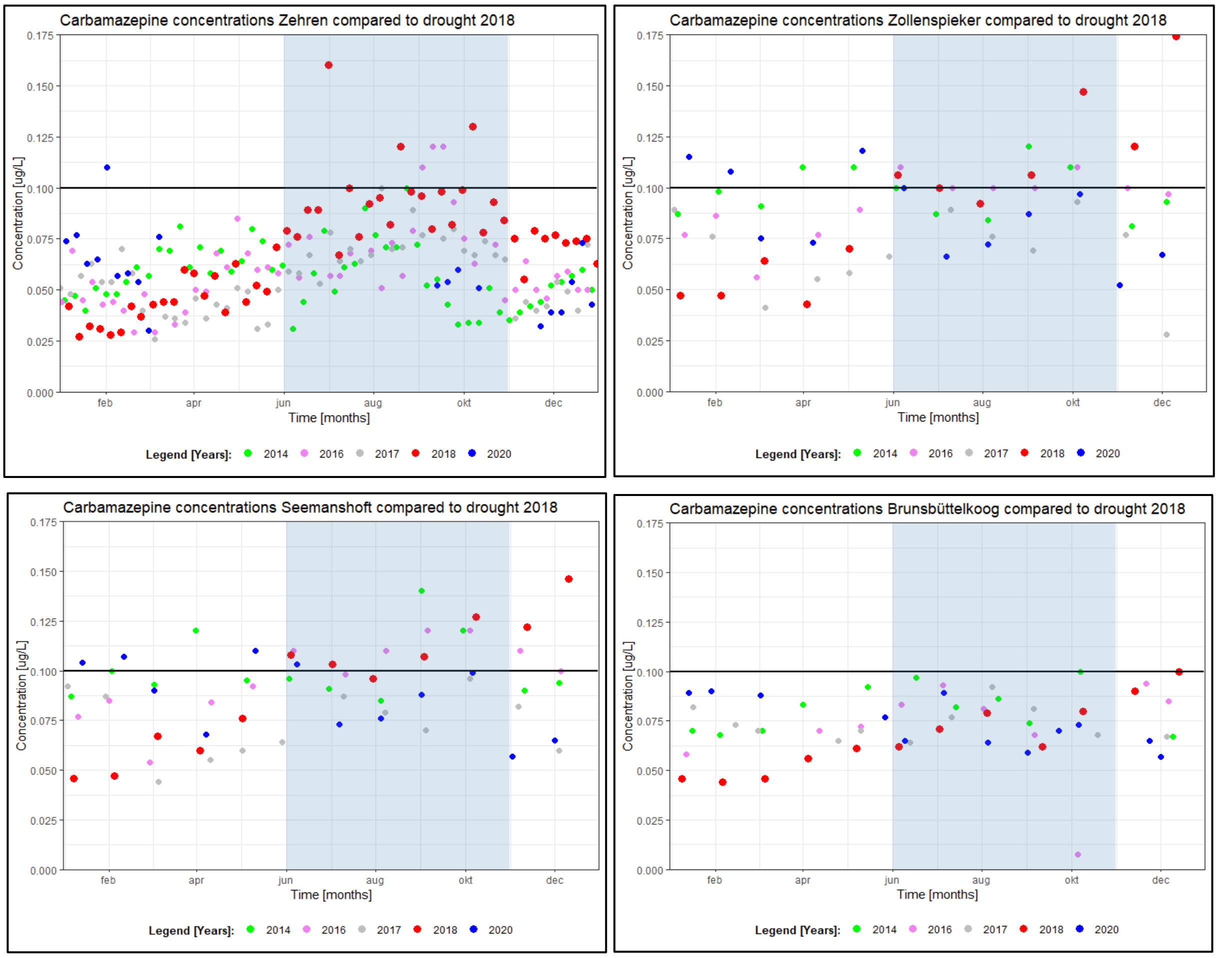


Fig.2a. Carbamazepine concentrations for the monitoring station Zehren, Zollenspieker, Seemanshoft and Brunsbüttelkoog (Elbe) during the drought of 2018 and the reference period. (Blue shade represent the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 µg.L^{-1}.

Statistical breakdown Mann-Whitney U test and Unpaired T-test + plots for the pharmaceutical carbamazepine for 2018 drought compared the reference years.

Table 2A: Carbamazepine Mann-Whitney U test and (Unpaired T-test) conducted for all stations; n is number of measurements. P-value is reference year compared with 2018 drought

Variable	[n]	P-value	Mean	Std. dev		[n]	P-value	Mean	Std. dev
Elbe					**Rhine**				
Schmilka					**Weil am Rhein**				
Drought_18	24	-	0.079	0.022		12	-	0.014	0.004
Ref_14	21	**<0.001**	0.050	0.010		12	**0.019**	0.020	0.007
Ref_16	22	**<0.001**	0.057	0.012		12	**0.040**	0.021	0.009
Ref_17	22	**<0.001**	0.058	0.012		12	0.765	0.013	0.003
Ref_20	20	**<0.001**	0.049	0.011	**Ref_19**	12	**0.001**	0.010	0.002
Zehren					**Worms**				
Drought_18	22	-	0.094	0.021		11	-	0.034	0.010
Ref_14	21	**<0.001**	0.057	0.020		-	-	-	-
Ref_16	22	**<0.001**	0.073	0.021		11	0.910	0.032	0.010
Ref_17	22	**<0.001**	0.071	0.010		11	0.057	0.027	0.003
Ref_20	-	-	-	-	**Ref_19**	11	**<0.001**	0.021	0.005
Dommitzsch					**Mainz**				
Drought_18	11	-	0.103	0.021		8	-	0.031	0.009
Ref_14	21	**<0.001**	0.075	0.032		8	0.388	0.027	0.011
Ref_16	22	**<0.001**	0.083	0.024		8	0.556	0.027	0.010
Ref_17	22	**<0.001**	0.078	0.018		8	**0.021**	0.023	0.006
Ref_20	20	**<0.001**	0.057	0.017	**Ref_19**	8	**0.001**	0.020	0.000
Brunsbüttelkoog					**Bad Honnef**				
Drought_18	5	-	0.071	0.009		5	-	0.050	0.013
Ref_14	5	**0.032**	0.088	0.011		5	0.413	0.042	0.014
Ref_16	5	0.389	0.067	0.034		5	0.341	0.040	0.023
Ref_17	5	0.381	0.076	0.011		5	0.135	0.038	0.005
Ref_20	5	0.952	0.071	0.011	**Ref_19**	5	0.095	0.036	0.017
Zollenspieker (Unpaired T-test)					**Bimmen**				
Drought_18	5	-	0.1102	0.00046		5	-	0.058	0.013
Ref_14	5	0.419	0.1002	0.00023		5	0.683	0.052	0.014
Ref_16	5	0.547	0.104	0.00003		5	0.421	0.046	0.025
Ref_17	5	**0.020**	0.0786	0.00014		5	0.135	0.046	0.004
Ref_20	5	0.058	0.0844	0.00023	**Ref_19**	6	0.052	0.041	0.011
Seemanshöft (Unpaired T-test)									
Drought_18	5	-	0.1082	0.00013					
Ref_14	5	0.8796	0.1064	0.00053					
Ref_16	5	0.6186	0.1116	8.28E-05					
Ref_17	5	**0.0055**	0.0792	0.00017					
Ref_20	5	**0.0324**	0.0878	0.00018					

Reference years that are statistically significant different (P-value <0.05) than the 2018 drought aare highlighted in bold.

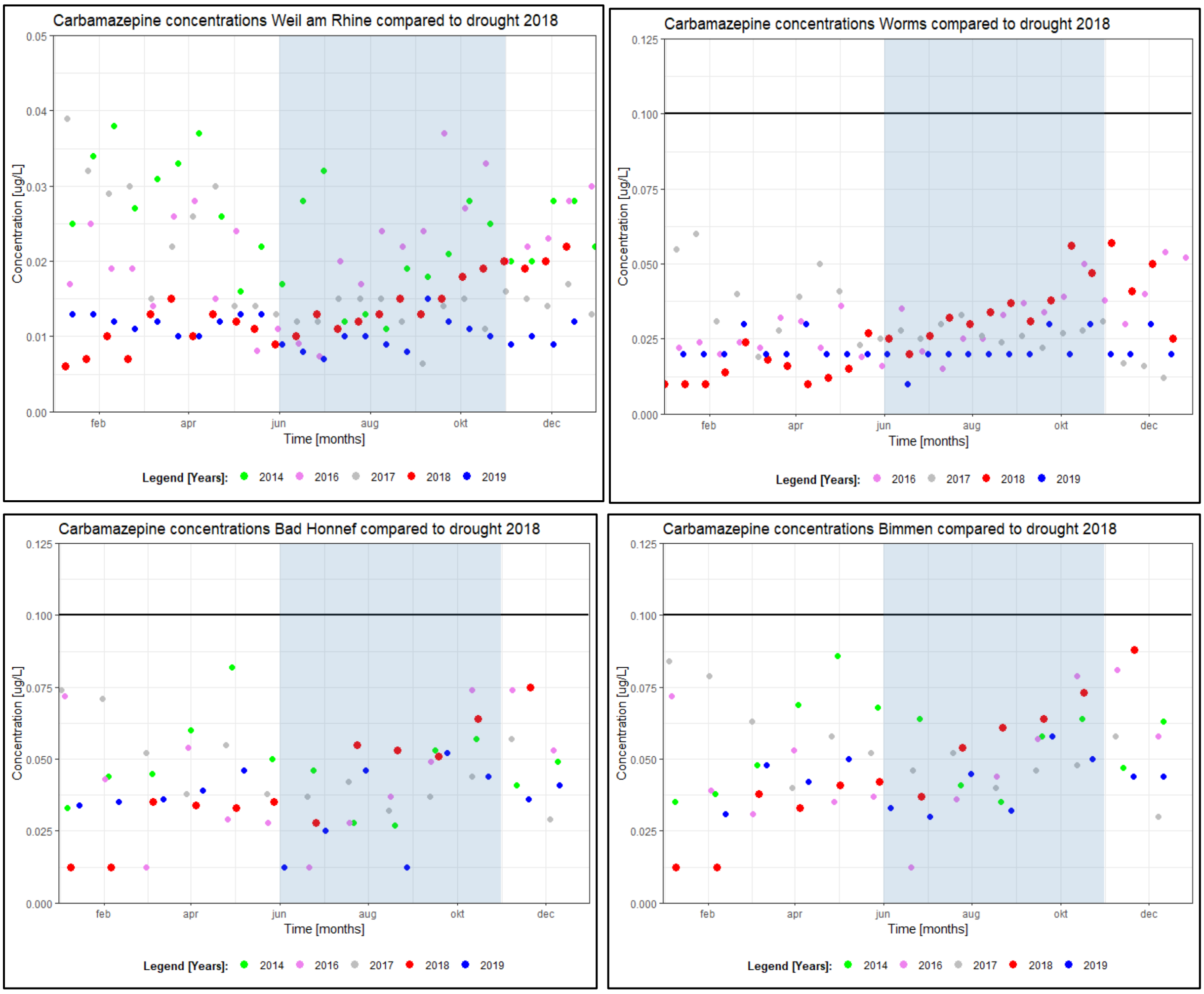


Fig.2A. Carbamazepine concentrations for the monitoring station Weil am Rhein, Worms, Bad Honnef and Bimmen (Rhine) during the drought of 2018 and the reference period. (Blue shade represent the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 µg.L^{-1}.

Appendix 2b

Table 2b. Results of the Shapiro wilk test and the descriptive statistics for Sulfamethoxazole, 2018 drought + reference periods (Jan-Dec) for both the Elbe and Rhine River.

stations	Observations	P-value	Average	Minimum	Maximum	Std. dev
Elbe						
Schmilka	60	0.212	0.063	0.026	0.120	0.021
Dommitzsch	70	0.139	0.056	0.011	0.120	0.024
Zollenspieker	60	0.176	0.043	0.010	0.077	0.012
Seemanshöft	60	0.015	0.043	0.022	0.069	0.010
Brunsbüttelkoog	55	0.016	0.035	0.015	0.067	0.014
Rhine						
Weil am Rhein	129	<0.001	0.013	0.005	0.028	0.0046
Worms	103	<0.001	0.022	0.010	0.043	0.0074
Mainz	120	<0.001	0.022	0.005	0.049	0.0084
Koblenz	63	<0.001	0.013	0.002	0.034	0.0086
Bad Honnef	61	<0.001	0.026	0.0125	0.046	0.0111
Bimmen	61	<0.001	0.032	0.0125	0.052	0.0114

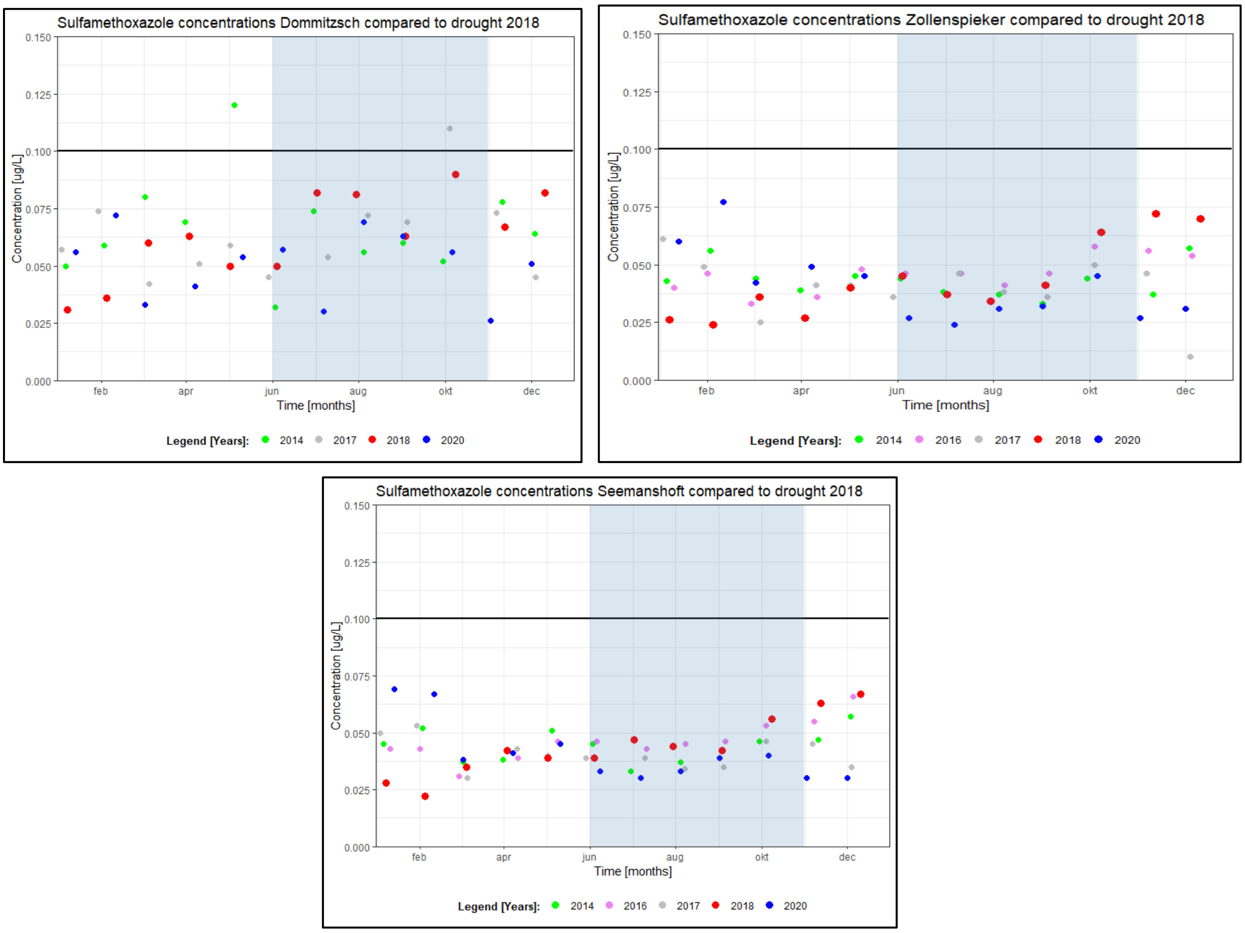


Fig.2b. Sulfamethoxazole concentrations for the monitoring station Dommitzsch, Zollenspieker, Seemanshoft (Elbe) during the drought of 2018 and the reference period. (Blue shade represent the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 µg.L^{-1}

Statistical breakdown Mann-Whitney U test and Unpaired T-test + plots for the pharmaceutical sulfamethoxazole for 2018 drought compared the reference years.

Table 2B: Sulfamethoxazole Mann-Whitney U test and (Unpaired T-test) conducted for all stations; n is number of measurements. P-value is reference year compared with 2018 drought

Variable	[n]	P-value	Mean	Std. dev		[n]	P-value	Mean	Std. dev
Elbe					**Rhine**				
Schmilka (Unpaired T-test)					**Weil am Rhein**				
Drought_18	5	-	0.080	0.017		11	-	0.014	0.006
Ref_14	5	0.105	0.058	0.021		11	0.404	0.012	0.004
Ref_16	5	**0.012**	0.049	0.013		11	0.569	0.013	0.006
Ref_17	5	0.588	0.088	0.025		11	0.321	0.012	0.003
Ref_20	5	**0.017**	0.051	0.014	**Ref_19**	11	**0.037**	0.011	0.002
Dommitzsch (Unpaired T-test)					**Worms**				
Drought_18	5	-	0.073	0.016		11	-	0.025	0.008
Ref_14	5	0.105	0.055	0.015		-	-	-	-
Ref_16	-	-	-	-		11	0.686	0.024	0.009
Ref_17	5	0.103	0.055	0.025		11	0.796	0.023	0.003
Ref_20	5	-	0.073	0.015	**Ref_19**	11	0.349	0.020	0.006
Zollenspieker (Unpaired T-test)					**Mainz**				
Drought_18	5	-	0.044	0.012		8	-	0.022	0.006
Ref_14	5	0.406	0.039	0.005		11	0.633	0.023	0.006
Ref_16	5	0.608	0.047	0.006		11	0.901	0.023	0.008
Ref_17	5	0.631	0.041	0.006		11	0.869	0.021	0.005
Ref_20	5	0.088	0.032	0.008	**Ref_19**	11	0.227	0.018	0.008
Seemanshöft					**Koblenz**				
Drought_18	5	-	0.037	0.007		5	-	0.012	0.004
Ref_14	5	0.249	0.039	0.005		5	**0.016**	0.024	0.005
Ref_16	5	0.675	0.046	0.004		5	0.151	0.008	0.007
Ref_17	5	0.091	0.047	0.005		5	0.865	0.010	0.002
Ref_20	5	**0.027**	0.057	0.004	**Ref_19**	5	0.794	0.012	0.005
Brunsbüttelkoog					**Bad Honnef**				
Drought18	5	-	0.040	0.006		5	-	0.031	0.011
Ref_14	5	0.008	0.026	0.007		5	0.413	0.022	0.013
Ref_16	5	**0.013**	0.021	0.003		5	0.444	0.024	0.012
Ref_17	-	-	-			5	0.206	0.027	0.003
Ref_20	5	**0.025**	0.031	0.004	**Ref_19**	5	0.667	0.027	0.013
					Bimmen				
Drought18	-	-	-	-		5	-	0.038	0.008
Ref_14	-	-	-	-		5	0.746	0.031	0.017
Ref_16	-	-	-	-		5	0.389	0.028	0.016
Ref_17	-	-	-	-		5	0.286	0.033	0.003
Ref_20	-	-	-	-	**Ref_19**	5	0.968	0.037	0.010

Reference years that are statistically significant different (P-value <0.05) than the 2018 drought are highlighted in bold

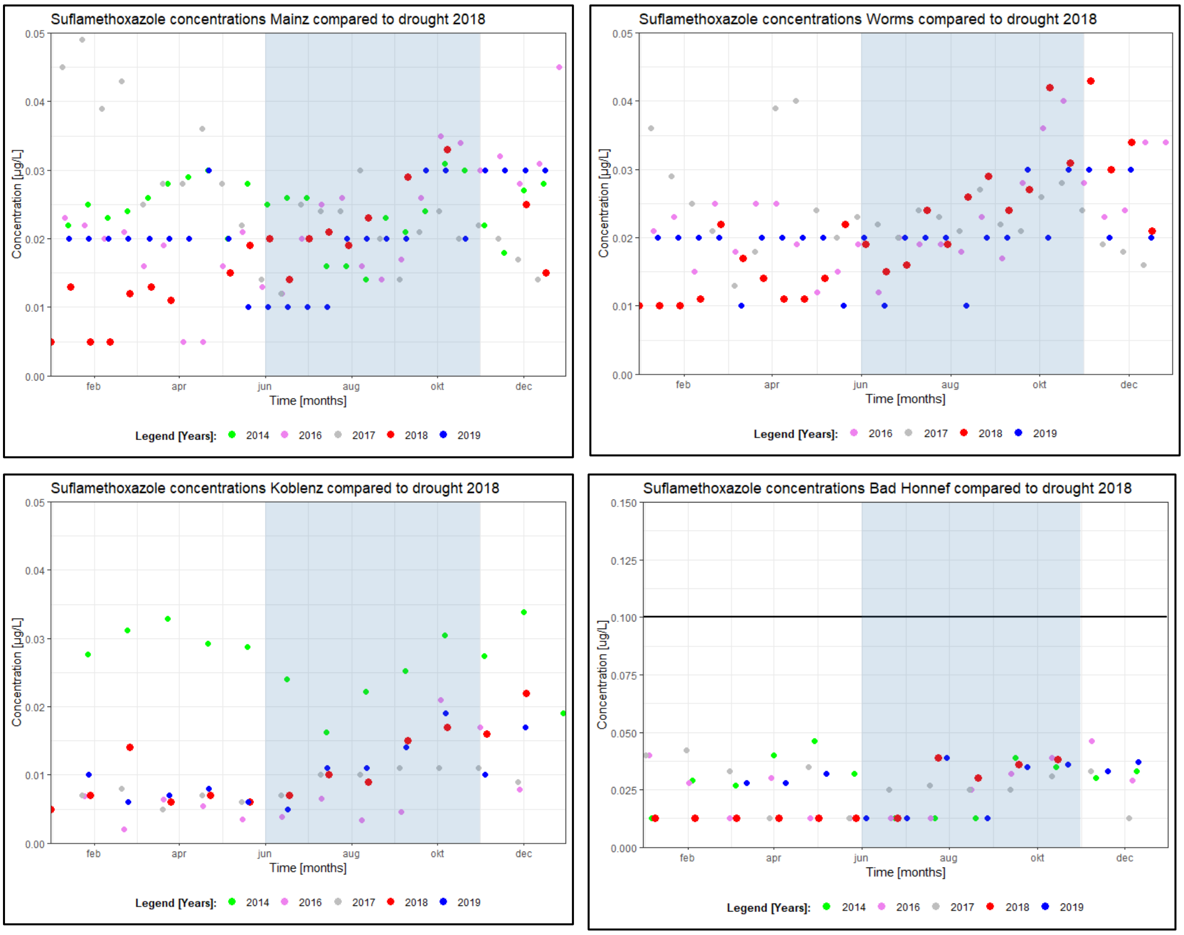


Fig.2B. Sulfamethoxazole concentrations for the monitoring station Worms, Mains, Koblenz and Bad Honnef (Rhine) during the drought of 2018 and the reference period. (Blue shade represent the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 $\mu g.L^{-1}$

Appendix 2c

Table 2c. Results of the Shapiro-wilk test and the descriptive statistics for diclofenac, 2018 drought + reference periods (Jan-Dec) for both the Elbe and Rhine River.

stations	Observations	P-value	Median	Minimum	Maximum	Std. dev
Elbe						
Schmilka	64	<0.001	0.049	0.010	0.250	0.035
Dommitzsch	60	<0.001	0.069	0.010	0.210	0.042
Zollenspieker	60	<0.001	0.079	0.001	0.931	0.128
Seemanshöft	60	<0.001	0.090	0.001	0.480	0.072
Rhine						
Weil am Rhein	129	<0.001	0.032	0.004	0.12	0.017
Worms	103	<0.001	0.035	0.005	0.11	0.027
Mainz	120	<0.001	0.042	0.005	0.27	0.039
Koblenz	63	<0.001	0.036	0.005	0.09	0.024
Bad Honnef	61	<0.001	0.048	0.0125	0.16	0.040
Bimmen	61	<0.001	0.059	0.0125	0.18	0.045

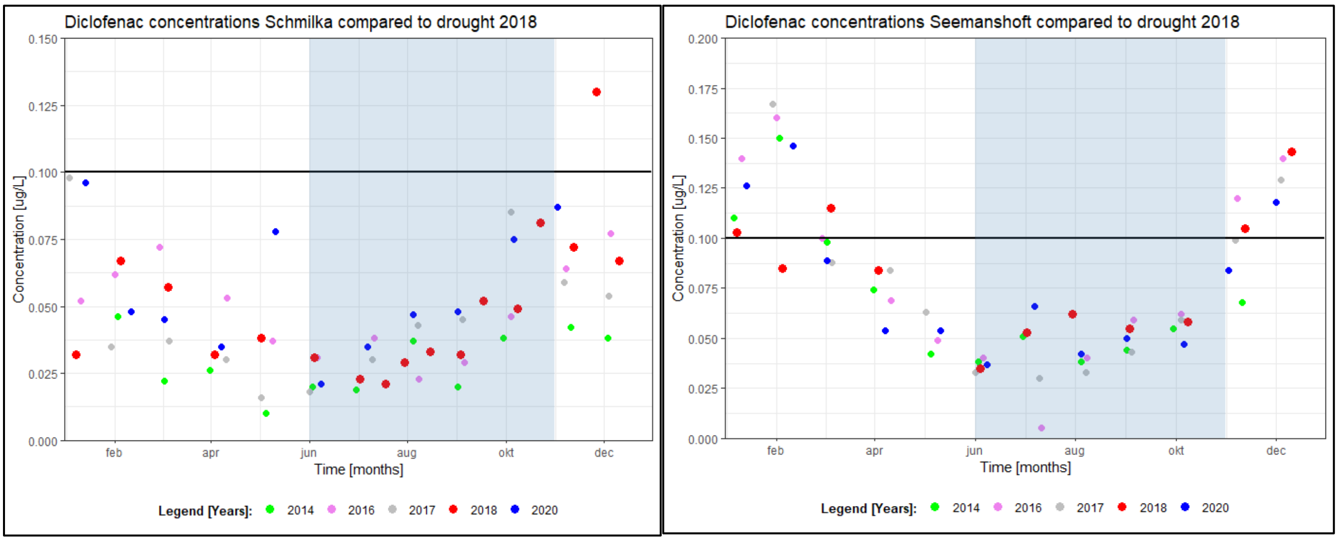


Fig.2c Diclofenac concentrations for the monitoring station Schmilka and Seemanshöft (Elbe) during the drought of 2018 and the reference period. (Blue shade represent the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 μg.L^{-1}.

Statistical breakdown Mann-Whitney U test and Unpaired T-test + plots for the pharmaceutical diclofenac for 2018 drought compared the reference years.

Table 2C: Diclofenac Mann-Whitney U test conducted for all stations; n is number of measurements. P-value is reference year compared with 2018 drought.

Variable	[n]	P-value	Mean	Std. dev		[n]	P-value	Mean	Std. dev
Elbe					**Rhine**				
Schmilka					**Weil am Rhein**				
Drought_18	9	-	0.039	0.019		11	-	0.023	0.015
Ref_14	5	0.176	0.027	0.010		11	0.663	0.022	0.009
Ref_16	5	0.905	0.033	0.009		11	0.467	0.026	0.011
Ref_17	5	0.898	0.044	0.025		11	0.622	0.019	0.011
Ref_20	5	0.637	0.045	0.020	**Ref_19**	11	0.184	0.014	0.007
Dommitzsch					**Worms**				
Drought_18	5	-	0.030	0.007		11	-	0.024	0.029
Ref_14	5	0.095	0.054	0.026		-	-	-	-
Ref_16	5	0.151	0.054	0.034		11	0.756	0.021	0.015
Ref_17	5	0.095	0.051	0.022		11	0.547	0.014	0.012
Ref_20	5	0.151	0.084	0.076	**Ref_19**	11	0.295	0.013	0.012
Zollenspieker					**Mainz**				
Drought_18	5	-	0.041	0.034		8	-	0.015	0.000
Ref_14	5	0.753	0.035	0.030		11	**0.013**	0.050	0.074
Ref_16	5	0.402	0.089	0.153		11	0.746	0.018	0.014
Ref_17	5	0.094	0.272	0.395		11	0.339	0.015	0.015
Ref_20	5	0.168	0.014	0.013	**Ref_19**	11	0.072	0.012	0.012
Seemanshoft					**Koblenz**				
Drought_18	5	-	0.045	0.008		5	-	0.020	0.012
Ref_14	5	0.248	0.040	0.026		5	0.524	0.025	0.014
Ref_16	5	0.753	0.039	0.012		5	0.286	0.014	0.009
Ref_17	5	0.143	0.053	0.010		6	0.970	0.025	0.019
Ref_20	5	0.531	0.048	0.011	**Ref_19**	5	0.460	0.019	0.019
					Bad Honnef				
Drought_18						5	-	0.018	0.007
Ref_14						5	0.683	0.025	0.018
Ref_16						5	0.683	0.022	0.015
Ref_17						5	1.000	0.023	0.017
Ref_20					**Ref_19**	5	1.000	0.023	0.023

Reference years that are statistically significant different (P-value <0.05) than the 2018 drought are highlighted in bold

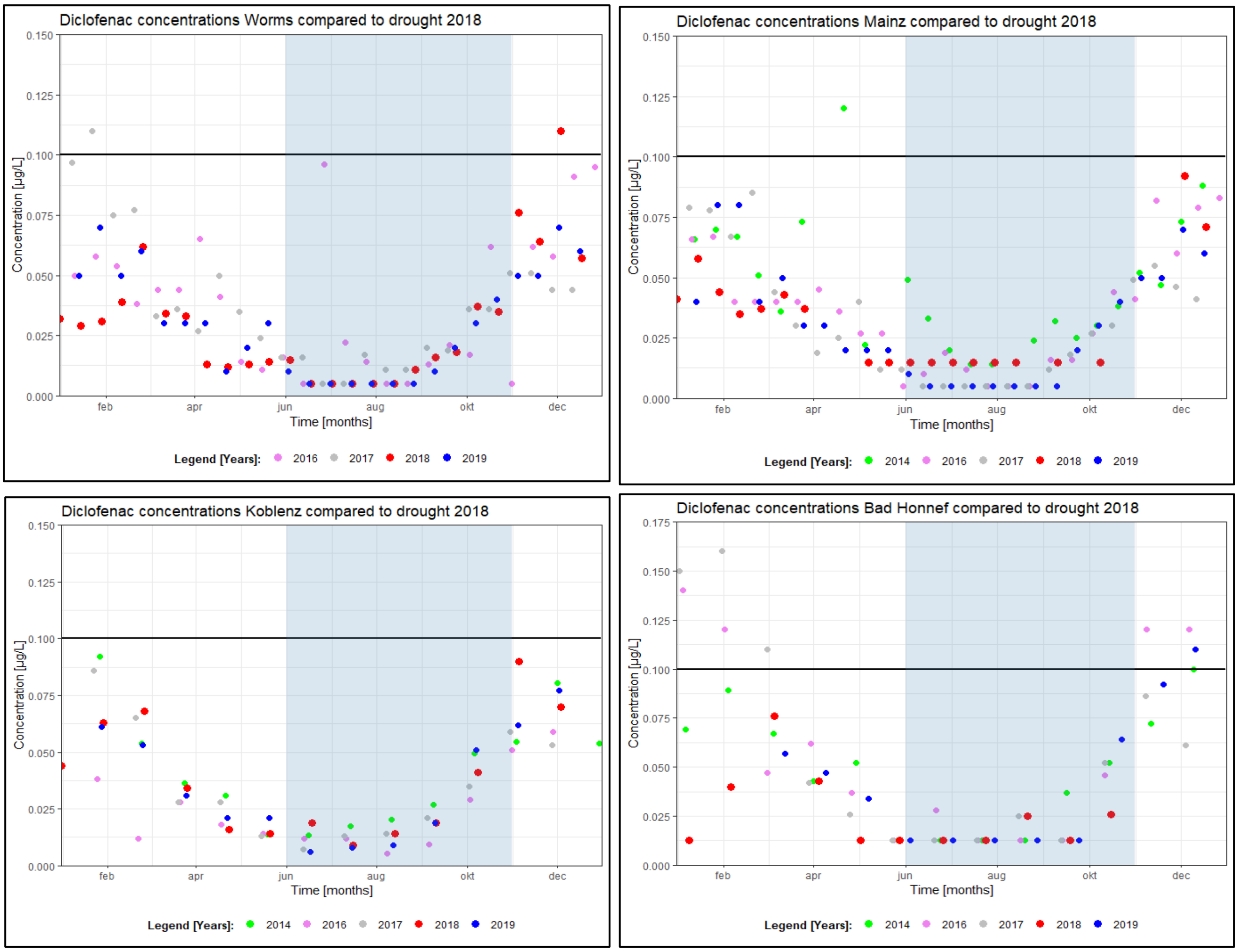


Fig.2C Diclofenac concentrations for the monitoring station Worms, Mainz, Koblenz and Bad Honnef (Rhine) during the drought of 2018 and the reference period. (Blue shade represent the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 $\mu g.L^{-1}$

Appendix 2d

Table. 2d. Results of the Shapiro-wilk test and the descriptive statistics for metoprolol, 2018 drought + reference periods (Jan-Dec) for both the Elbe and Rhine River.

stations	Observations	P-value	Median	Minimum	Maximum	Std. dev
Elbe						
Schmilka	65	0.548	0.047	0.006	0.097	0.021
Zollenspieker	60	<0.001	0.053	0.005	0.193	0.046
Seemanshöft	60	0.012	0.084	0.011	0.191	0.045
Brunsbüttelkoog	44	<0.001	0.043	0.010	0.140	0.032
Rhine						
Weil am Rhein	129	<0.001	0.012	0.004	0.026	0.005
Worms	104	<0.001	0.033	0.005	0.100	0.016
Mainz	120	<0.001	0.029	0.005	0.069	0.014
Koblenz	51	<0.001	0.026	0.0085	0.078	0.015
Bad Honnef	61	<0.001	0.046	0.0125	0.120	0.025
Bimmen	48	<0.001	0.057	0.0125	0.120	0.023

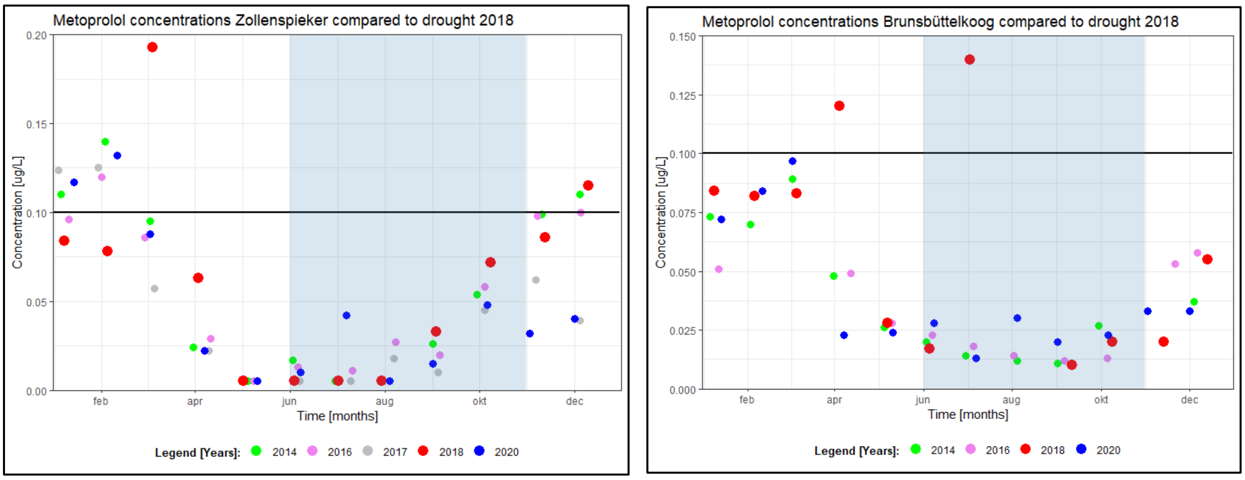


Fig.2d Metoprolol concentrations for the monitoring station Zollenspieker and Brunsbüttelkoog (Elbe) during the drought of 2018 and the reference period. (Blue shade represent the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 $\mu g.L^{-1}$.

Statistical breakdown Mann-Whitney U test and Unpaired T-test + plots for the pharmaceutical metoprolol for 2018 drought compared the reference years.

Table 2D: Mann-Whitney U test conducted for all stations; n is number of measurements (Only at Schmilka unpaired T-test conducted). P-value is reference year compared with 2018 drought

Variable	[n]	P-value	Mean	Std. dev		[n]	P-value	Mean	Std. dev
Elbe					**Rhine**				
Schmilka (Unpaired T-test)					**Weil am Rhein**				
Drought_18	9	-	0.048	0.014		11	-	0.011	0.005
Ref_14	5	0.238	0.037	0.014		11	0.962	0.010	0.003
Ref_16	5	**0.023**	0.030	0.008		11	0.912	0.010	0.004
Ref_17	5	0.216	0.062	0.017		11	0.291	0.009	0.002
Ref_20	5	0.336	0.040	0.013	**Ref_19**	11	**<0.001**	0.006	0.002
Zollenspieker					**Worms**				
Drought_18	5	-	0.024	0.029		11	-	0.035	0.010
Ref_14	5	1.00	0.021	0.020		-	-	-	-
Ref_16	5	0.526	0.026	0.019		11	0.156	0.024	0.017
Ref_17	5	1.00	0.017	0.017		11	**0.024**	0.026	0.006
Ref_20	5	0.590	0.024	0.020	**Ref_19**	11	**<0.001**	0.019	0.007
Seemanshöft					**Mainz**				
Drought_18	5	-	0.068	0.031		8	-	0.026	0.009
Ref_14	5	0.222	0.047	0.012		11	0.123	0.019	0.004
Ref_16	5	1.000	0.058	0.032		11	0.430	0.021	0.012
Ref_17	5	0.087	0.038	0.030		11	0.191	0.020	0.003
Ref_20	5	1	0.063	0.023	**Ref_19**	11	0.168	0.017	0.010
Brunsbüttelkoog					**Koblenz**				
Drought_18	4	-	0.047	0.062		6		0.038	0.023
Ref_14	5	0.778	0.017	0.007		6	**0.024**	0.014	0.007
Ref_16	5	0.730	0.016	0.005		6	**0.005**	0.013	0.003
Ref_17	-	-	-	-		6	0.255	0.025	0.009
Ref_20	5	0.587	0.023	0.007	**Ref_19**	6		0.038	0.023
					Bad Honnef				
Drought_18	-	-	-	-		5		0.034	0.008
Ref_14	-	-	-	-		5	0.571	0.027	0.020
Ref_16	-	-	-	-		5	0.651	0.032	0.018
Ref_17	-	-	-	-		5	0.802	0.031	0.013
Ref_20	-	-	-	-	**Ref_19**	5	0.381	0.028	0.017
					Bimmen				
Drought_18	-	-	-	-		5		0.045	0.016
Ref_14	-	-	-	-		5	0.738	0.047	0.016
Ref_16	-	-	-	-		5	0.952	0.046	0.020
Ref_17	-	-	-	-		5	0.690	0.048	0.009
Ref_20	-	-	-	-	**Ref_19**	5	0.730	0.039	0.021

Reference years that are statistically significant different (P-value <0.05) than the 2018 drought are highlighted in bold

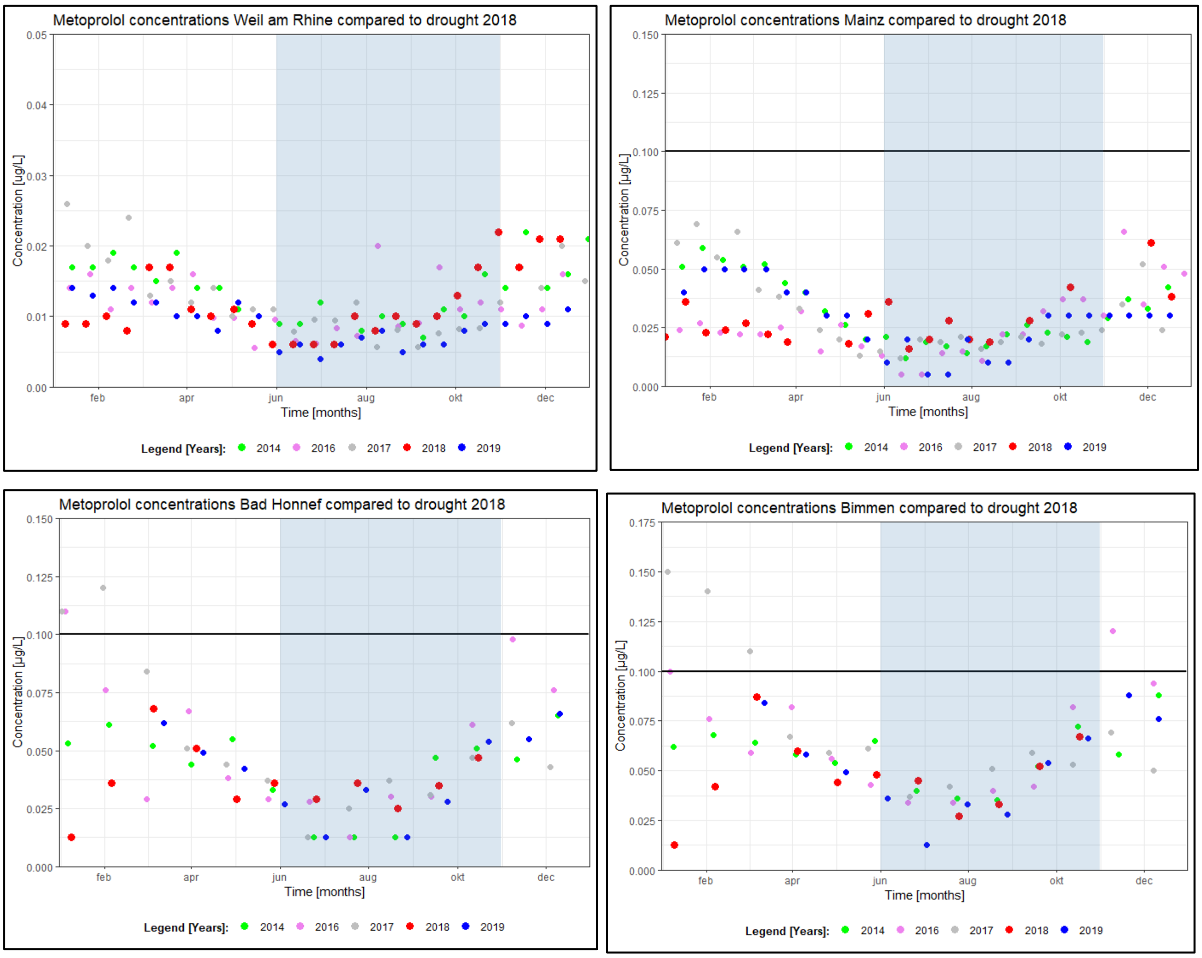


Fig.2D Metoprolol concentrations for the monitoring station Weil am Rhein, Mainz, Bad Honnef and Bimmen (Rhine) during the drought of 2018 and the reference period. (Blue shade represent the drought period (Jun-Oct) and highlights the period of statistical analysis. The black horizontal line represents the ERM target value of 0.1 $\mu g.L^{-1}$.

Appendix 2e

Percentage change anomalies for Carbamazepine

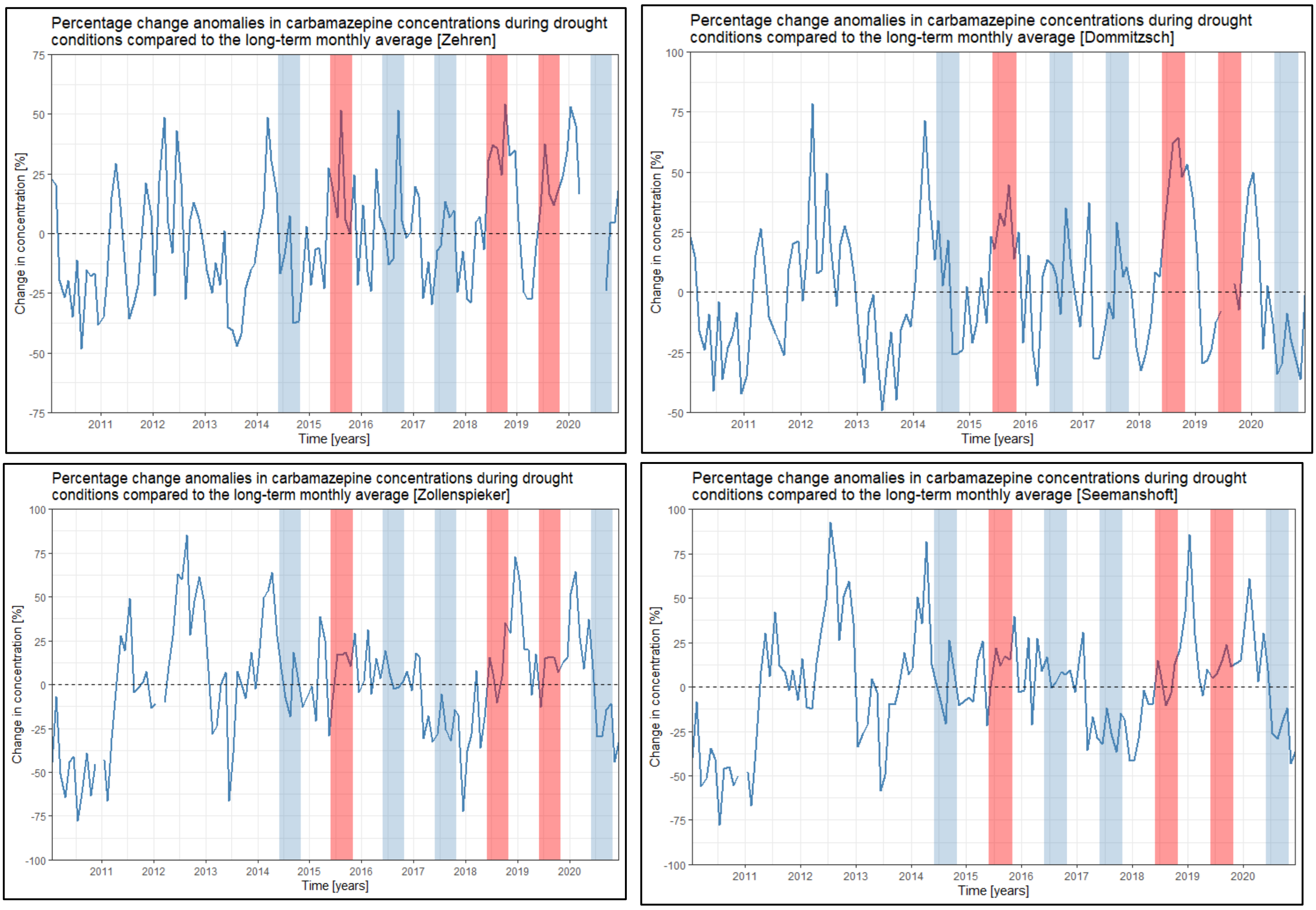
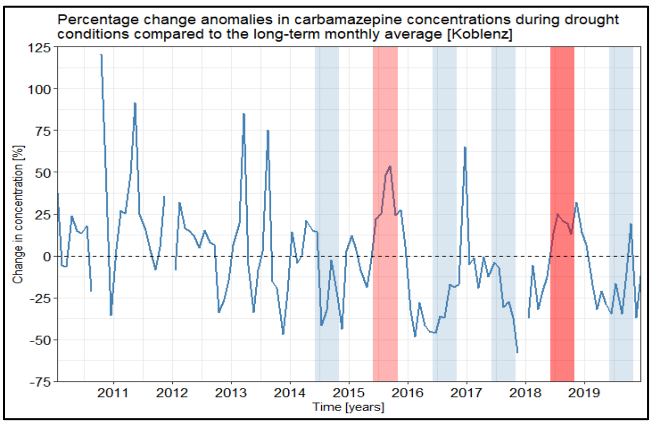


Fig. 2e Percentage change anomalies Carbamazepine during drought conditions compared to the long-term monthly average(2010-2020) at the monitoring stations Zehren, Dommitzsch, Zollenspieker and Seemanshöft (Elbe). Red shade represents the (Jun-Oct) droughts of 2015, 2018 and 2019, the blue shade is the (Jun-Oct) periods for the four reference years. (Note the percentage change after October 2018 for Zollenspieker and Seemanshöft).



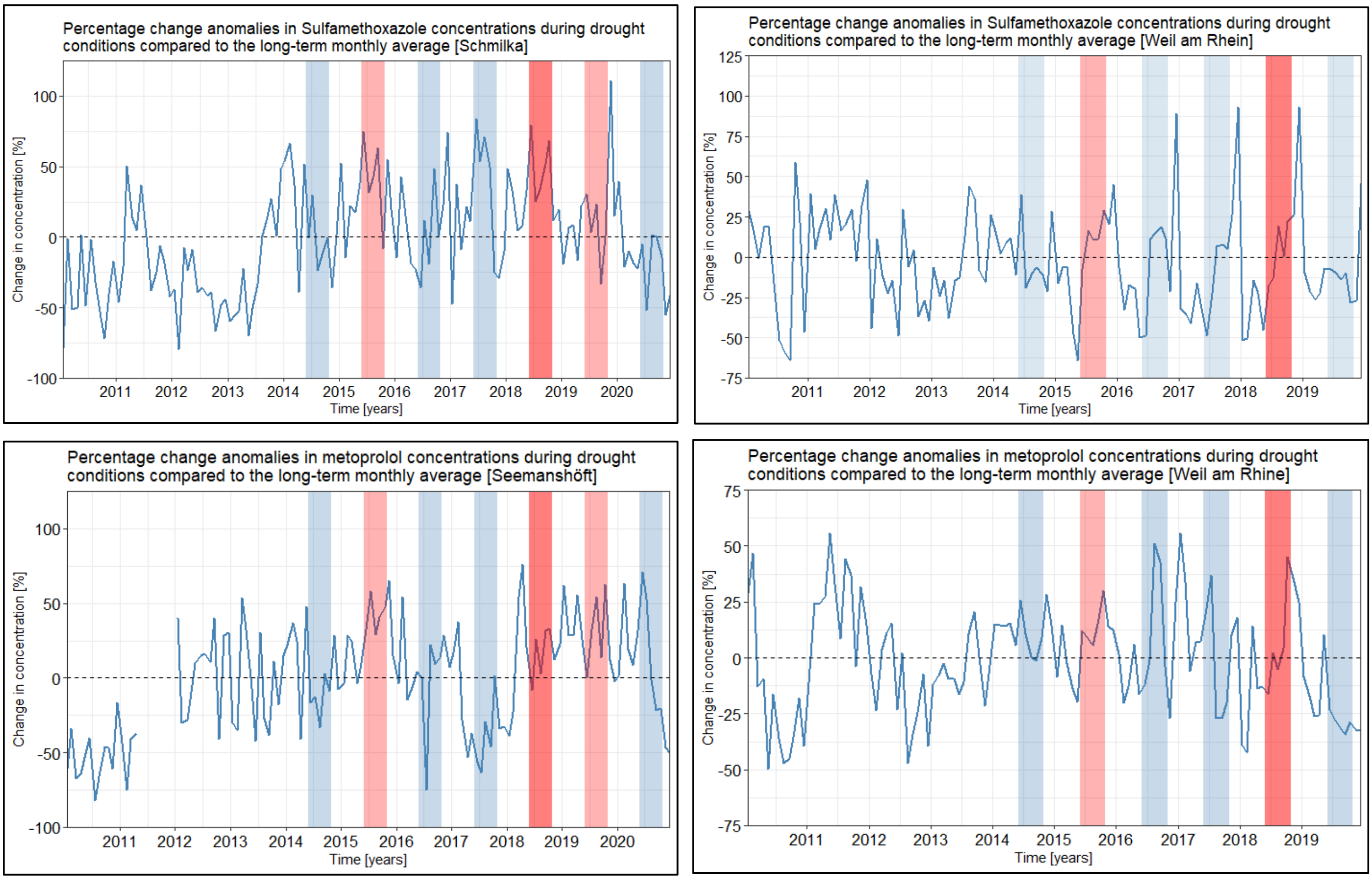


Fig.2E. Percentage change anomalies sulfamethoxazole and metoprolol during drought conditions compared to the long-term monthly average (2010-2020) at two selected monitoring stations along the Elbe and Rhine. (Red shade represents the (Jun-Oct) droughts of 2015, 2018 and 2019, the blue shade is the (Jun-Oct) periods for the four reference years.

Appendix 3

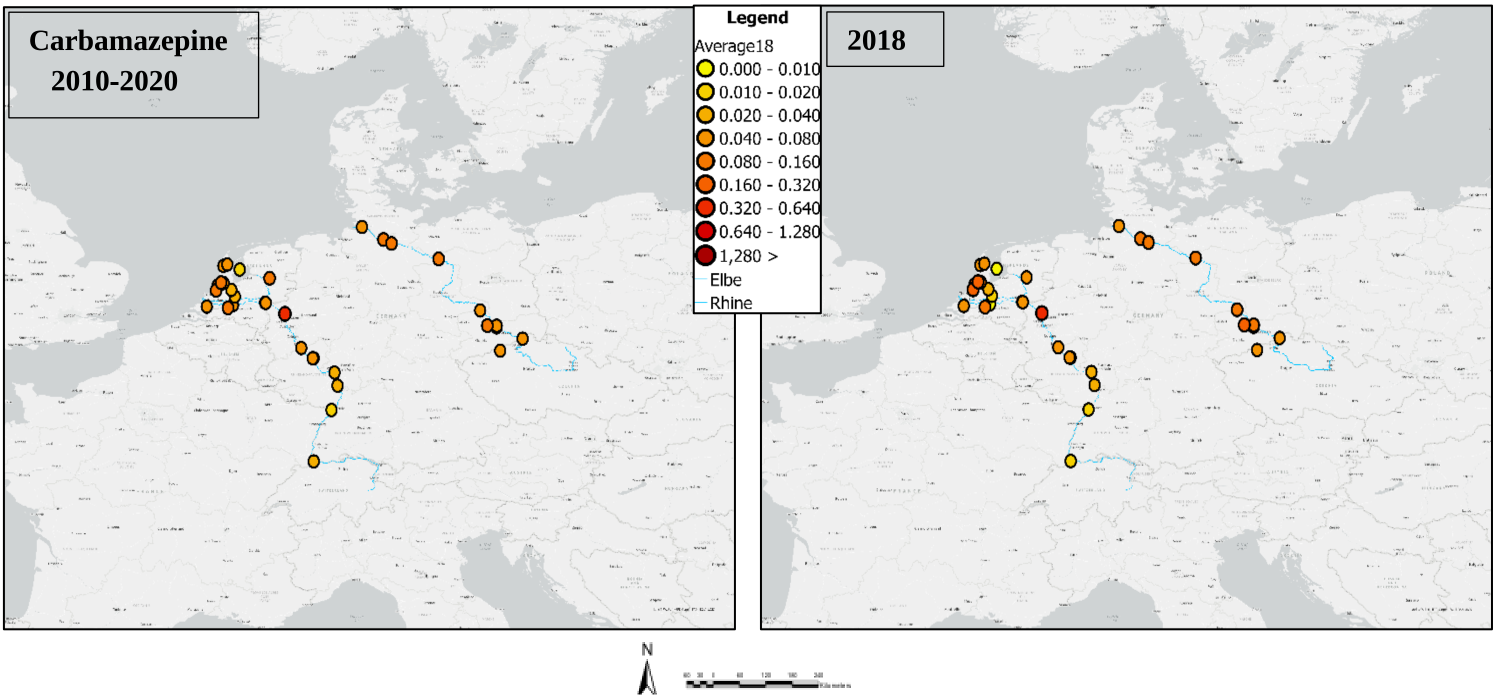


Fig 3a.: Carbamazepine maps of the average concentration 2010-2020 (June-October) period (left) versus the average concentration of the 2018 drought (June-October) (right), all concentrations are in ug.L^{-1}.

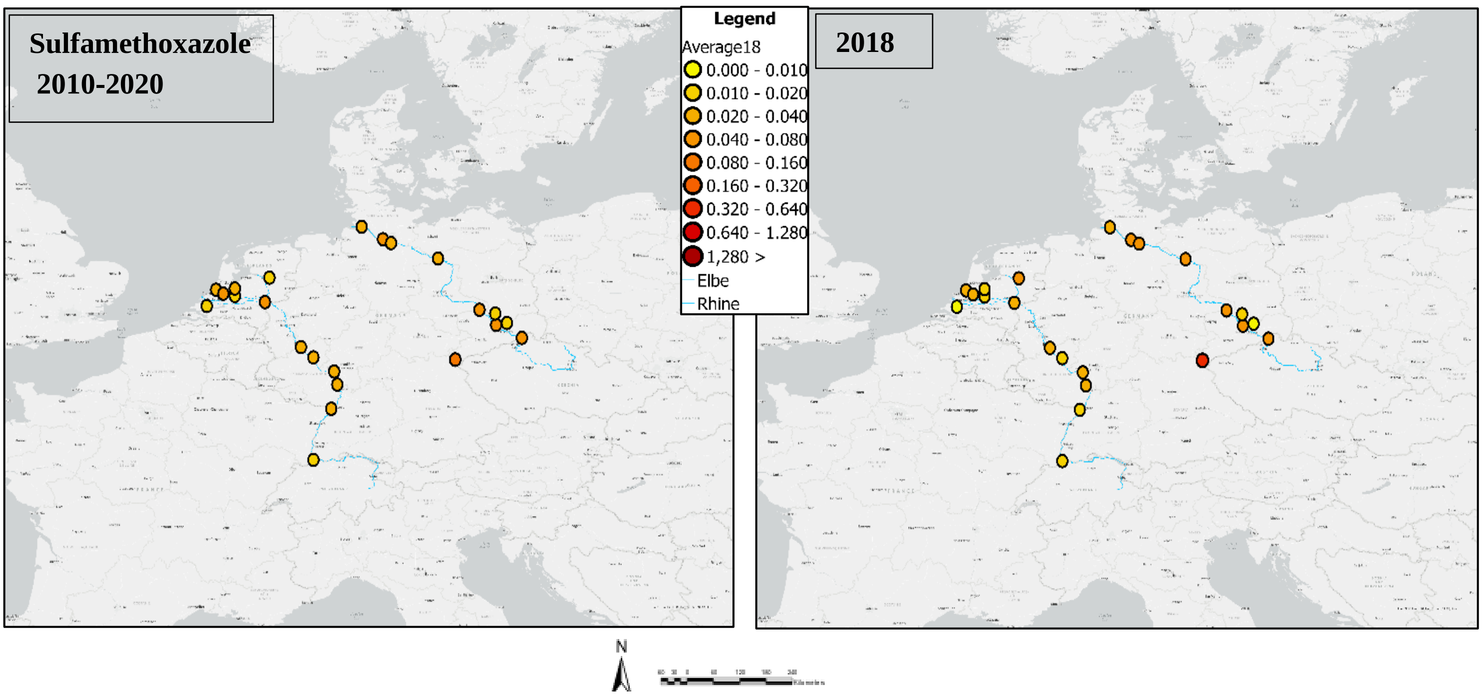


Fig 3b: Sulfamethoxazole maps of the average concentration 2010-2020 (June-October) period (left) versus the average concentration of the 2018 drought (June-October) (right), all concentrations are in ug.L^{-1}

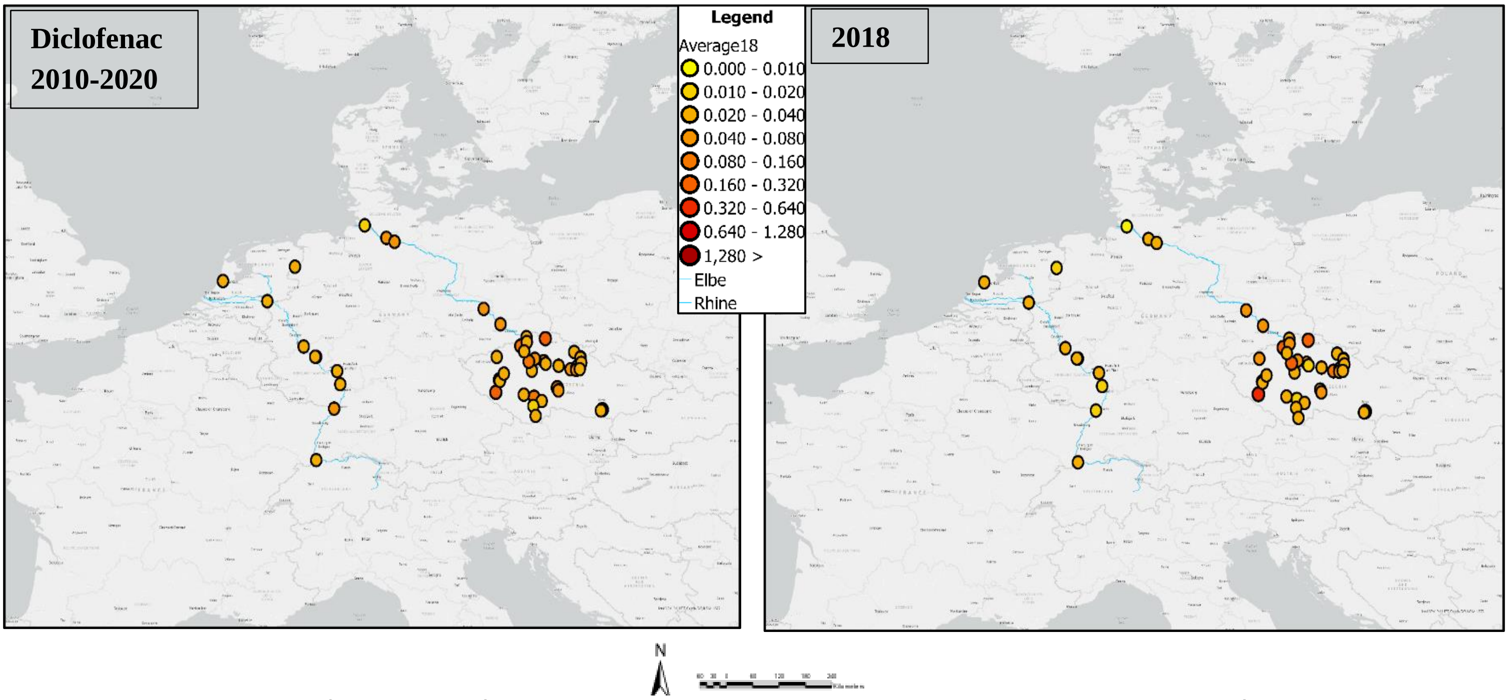


Fig 3c: Diclofenac maps of the average concentration 2010-2020 (June-October) period (left) versus the average concentration of the 2018 drought (June-October) (right), all concentrations are in ug.L^{-1}

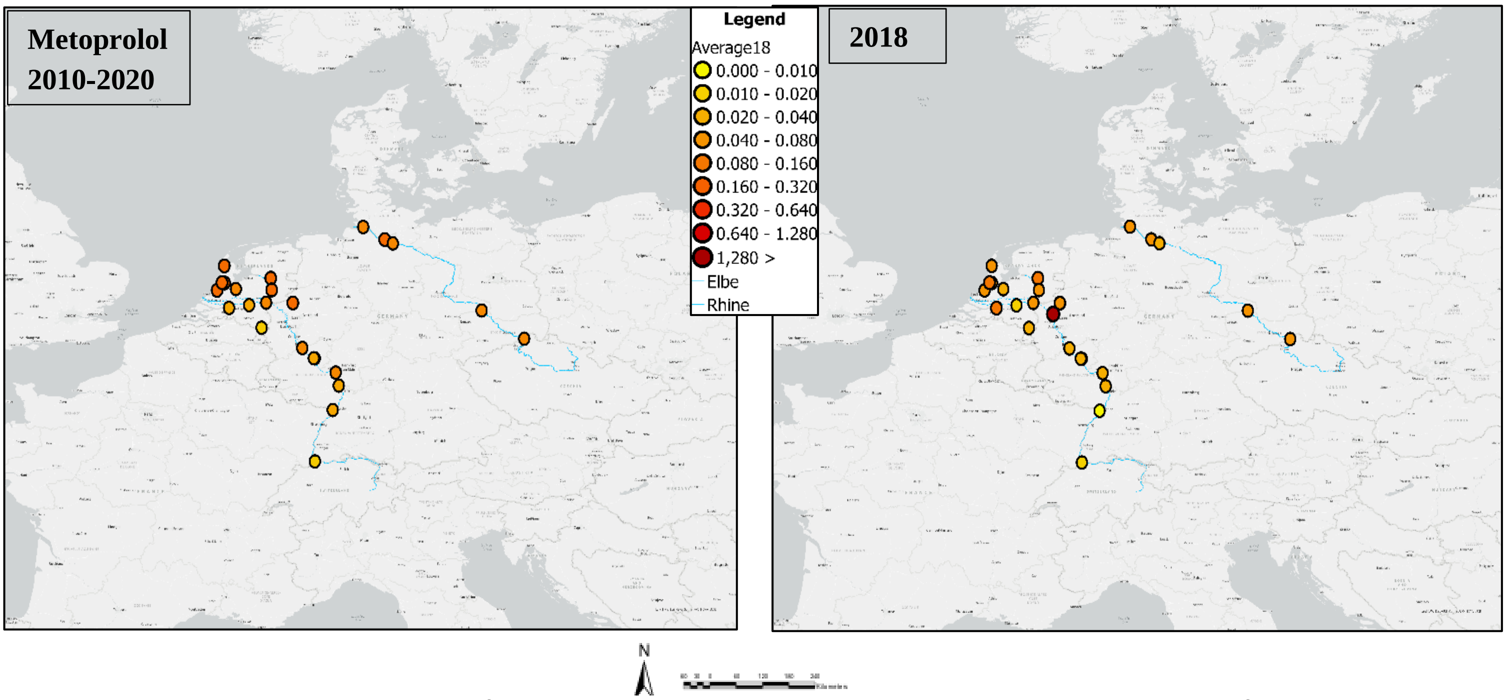


Fig 3d: Metoprolol maps of the average concentration 2010-2020 (June-October) period (left) versus the average concentration of the 2018 drought (June-October) (right), all concentrations are in ug.L^{-1}

Appendix 4

Appendix 4A Relation Discharge vs diclofenac and metoprolol

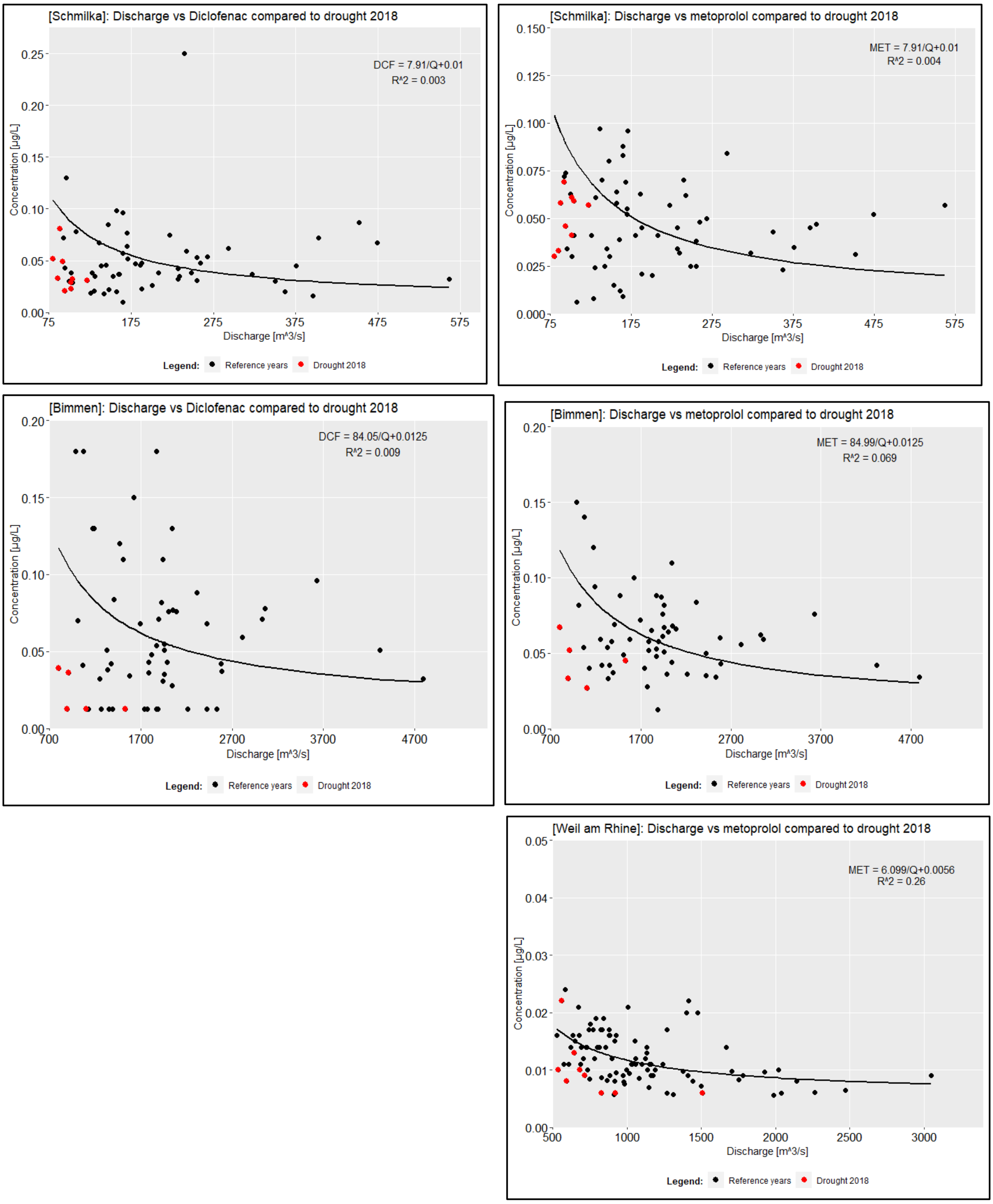


Fig 4a. The relation between the discharge and the diclofenac and metoprolol concentrations for two stations, one alongside the Elbe (Schmilka) and one for alongside the Rhine (Bimmen) for the drought year and corresponding reference years. The black line represents the C-Q relation by Eq. (2). The red dots represent the measurements of the 2018 drought (June–October).

Table 4.a: Parameters of the dilution-based model of van der Weijden & Middelburg (1989, for the monitoring stations along the Rhine river. With (a) chemical load (µg.s^{-1}), (b) background concentration (µg.L^{-1}), and R^2 goodness of fit.

station	(a)				(b)				(R^2)			
Rhine	**CBZ**	**SMX**	**DCF**	**MET**	**CBZ**	**SMX**	**DCF**	**MET**	**CBZ**	**SLF**	**DCF**	**MET**
Weil am Rhein	11.61	7.56	23.69	6.10	0.01	0.01	0.01	0.01	**0.27**	**0.56**	**0.22**	**0.26**
Worms	18.8	13.0	35.5	30.6	0.01	0.01	0.01	0.01	**0.58**	**0.46**	0.09	**0.42**
Mainz	23.18	23.42	52.31	33.53	0.01	0.01	0.01	0.01	**0.43**	**0.39**	0.01	**0.16**
Koblenz	25.64	9.16	40.72	21.62	0.02	0.00	0.01	0.01	**0.68**	**0.34**	**0.14**	**0.22**
Bad Honnef	44.35	17.82	58.75	53.63	0.01	0.01	0.01	0.01	**0.54**	**0.41**	0.02	0.07
Bimmen	59.31	29.94	84.06	84.99	0.01	0.01	0.01	0.01	**0.64**	**0.53**	0.01	0.07

**R^2 > 0.1 are highlighted bold*

Table 4.A: Parameters of the dilution-based model of van der Weijden & Middelburg (1989, for the monitoring stations along the Elbe river. With (a) chemical load (µg.s^{-1}), (b) background concentration (µg.L^{-1}), and R^2 goodness of fit.

station	(a)				(b)				(R^2)			
Elbe	**CBZ**	**SMX**	**DCF**	**MET**	**CBZ**	**SMX**	**DCF**	**MET**	**CBZ**	**SLF**	**DCF**	**MET**
Schmilka	4.53	6.20	7.91	7.86	0,024	0.026	0.01	0.006	**0.47**	**0.30**	0.03	0.04
Zehren	6.24	-	-	-	0,026	-	-	-	**0.52**	-	-	-
Dommitzsch	7.22	6.47	12.28	-	0,029	0.026	0.005	-	**0.40**	**0.32**	0.003	-
Zollenspieker	25.26	14.94	30.73	37.84	0,028	0.01	0.005	0.011	**0.25**	0.06	0.09	0.09

Appendix 4b water temperature vs pharmaceuticals

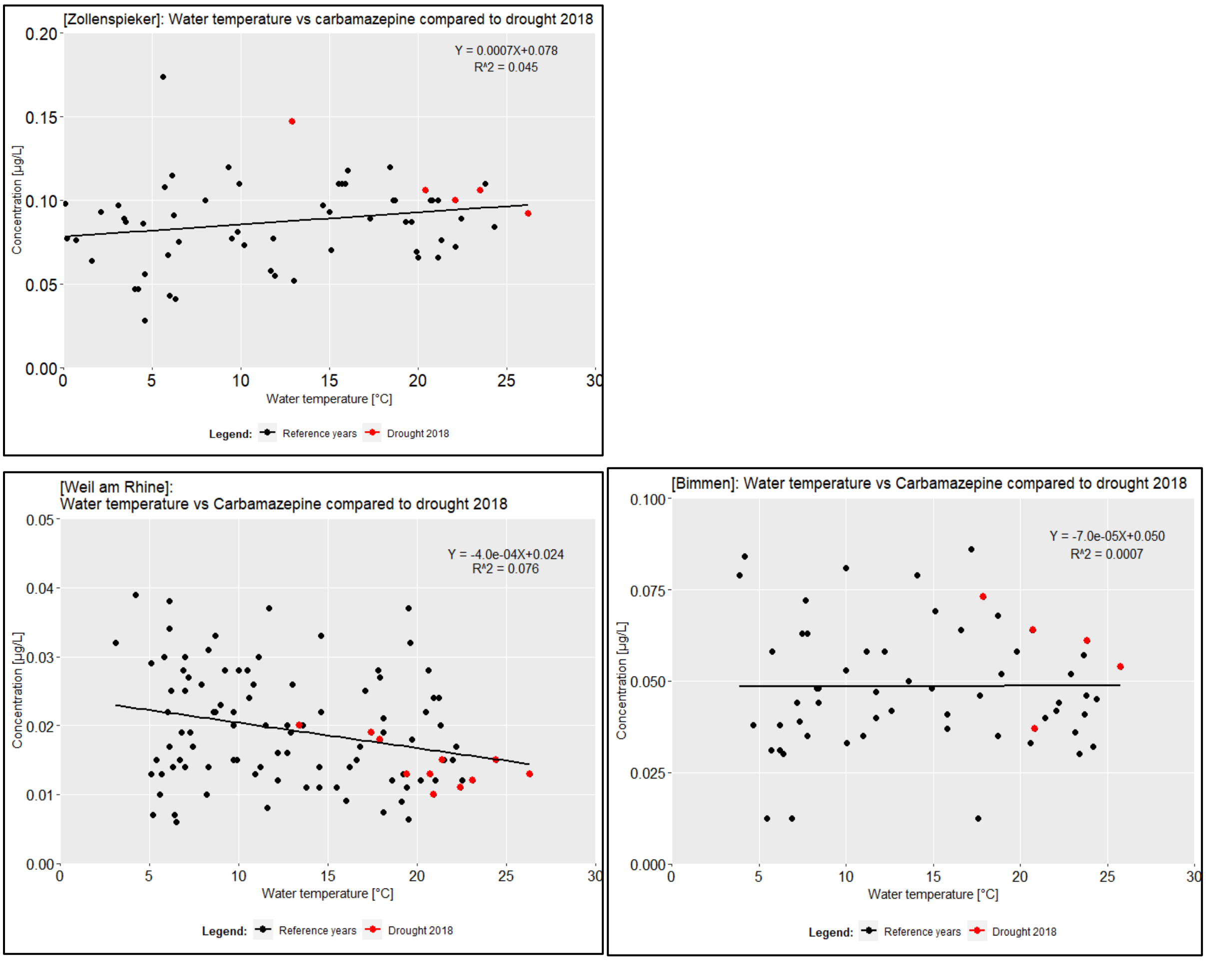


Fig. 4b. The relation between the water temperature and the carbamazepine concentrations for one stations alongside the Elbe (Zollenspieker) and two along the Rhine (Weil am Rhein and Bimmen) for the drought year and corresponding reference years. The black line represents the linear relation, and the red dots represent the measurements of the 2018 drought (June–October).

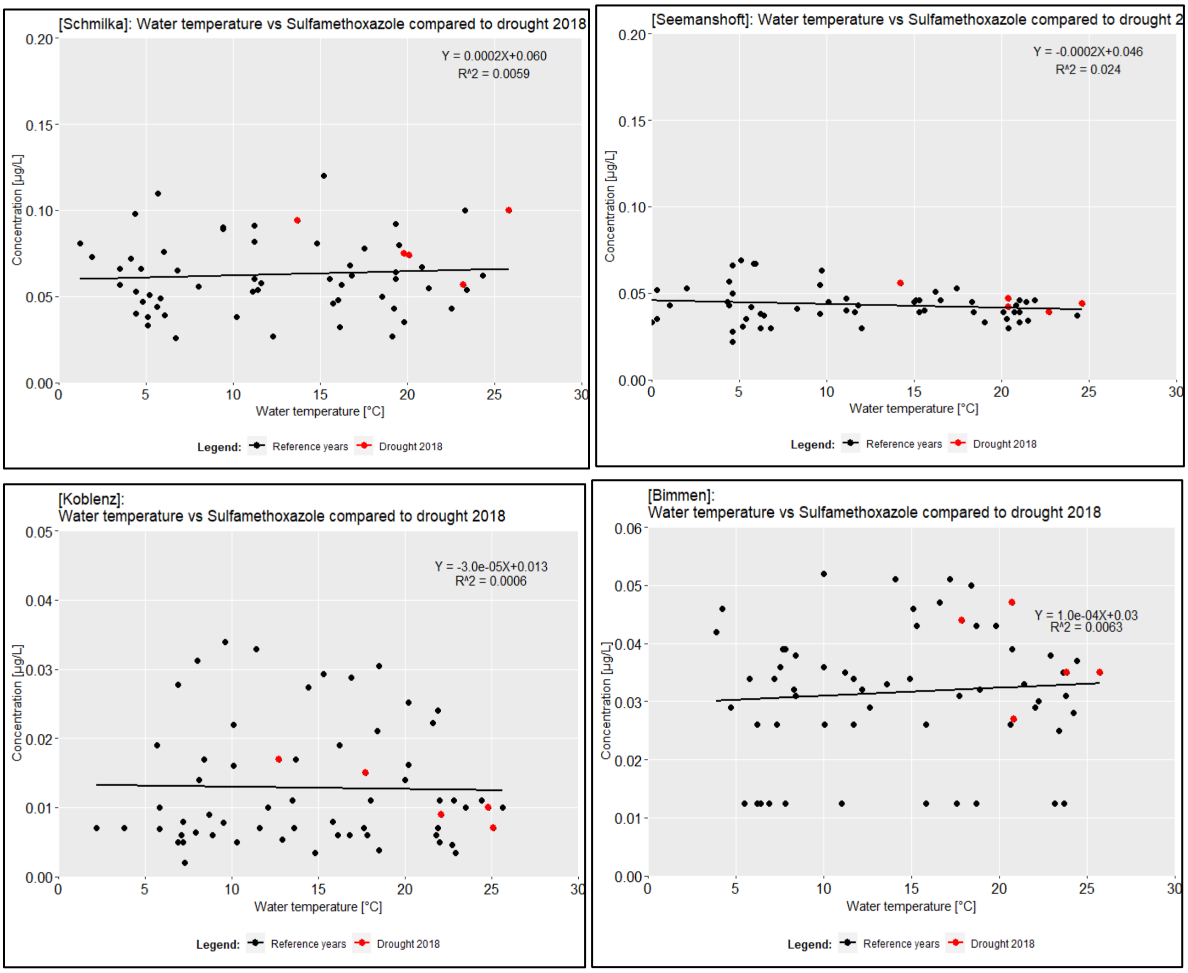


Fig. 4B. The relation between the water temperature and the sulfamethoxazole concentrations for two stations alongside the Elbe (Schmilka and Seemanshöft) and two along the Rhine (Koblenz and Bimmen) for the drought year and corresponding reference years. The black line represents the linear relation, and the red dots represent the measurements of the 2018 drought (June–October).