

Persistent and mobile organic chemicals in water resources: occurrence and removal options for water utilities

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ABSTRACT

Persistent and mobile (PM) substances are being recognized as serious threats to water resources and drinking water suppliers have to use advanced treatment if raw waters are contaminated with such compounds. In this study, analytical methods for 25 micropollutants for which insufficient or no data on their occurrence in surface waters and on their behavior during drinking water treatment were available, were developed. More than 120 surface water samples were analyzed and laboratory tests were performed to evaluate the compounds' behavior during aerobic bank filtration (BF), activated carbon treatment, and ozonation. Ensulizole, 1,3-diphenylguanidine and 2-acrylamido-2-methylpropane sulfonic acid revealed the highest detection frequencies in the Rhine river. Concentration level and detection frequency correlated positively with the wastewater fraction. However, street run-off is likely an additional discharge pathway for 1,3-diphenylguanidine. In simulated BF, seven (six) substances could be classified as persistent (very persistent). By applying powdered activated carbon, 42% of the substances were well removed as was the case for 50% of the compounds when applying 0.2 mg/L O₃. In total, eight of the substances detected in surface waters were weakly removed by at least one of the investigated removal processes and may cause problems for drinking water suppliers.

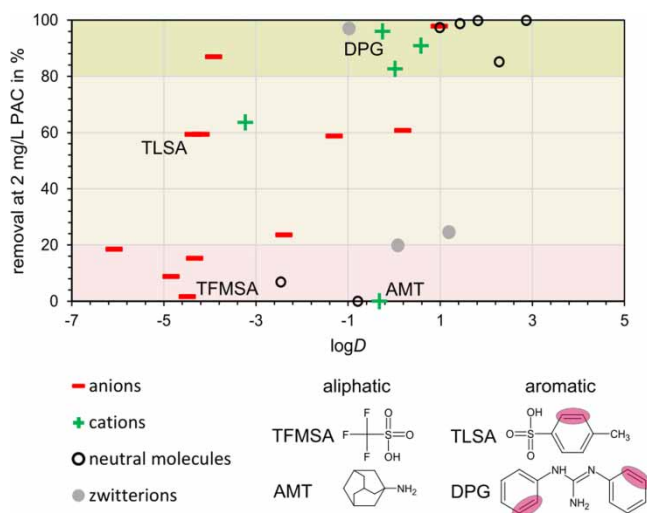
Key words: anticoagulants, drinking water, PMOC, PMT, vPVM

HIGHLIGHTS

- First time detections of the four anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in surface waters on a worldwide scale.
- Evaluation of treatment options for waterworks to remove persistent and mobile organic chemicals.
- Reduction of the existing analytical gap for polar compounds.

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GRAPHICAL ABSTRACT



INTRODUCTION

As early as the 1960s, warnings were issued about the increasing occurrence of persistent compounds in the environment (Jensen *et al.* 1969). First chemicals classified as persistent like the insecticide DDT or polychlorinated biphenyls (PCB) were hydrophobic and prone to bioaccumulation in nature (European Commission 2017). This subsequently led to the enactment of many environmental regulations for persistent (P) chemicals that are bioaccumulative (B) and toxic (T) (PBT) or very persistent and very bioaccumulative (vPvB; v = very) in the following decades. But only recently, the question has been raised whether the persistence of a substance is *per se* a cause for concern (Cousins *et al.* 2019), since its continuous release leads to a steadily increasing contamination.

In addition to persistence, the mobility of a substance has recently been the subject of increasing criticism. Mobility can increase chemical exposure and thus potentially the risk to human health and the environment. Persistent, mobile and toxic (PM(T)) or very persistent very mobile (vPvM) compounds, in fact, have the potential to reach largely anthropogenically unaffected environmental compartments because of their longevity and their unimpeded passage through the aquatic environment. Unlike PBT substances, which accumulate in soil, on sediments and/or in biota, PM substances are hardly retarded in soils or by sorption on sediment particles. Thus, they are more easily transferred between environmental compartments and in this way can contaminate groundwater, surface waters and aquatic ecosystems in general. In consequence, there is an immediate risk of contamination for water resources used for drinking water production.

Despite concerns that PM substances can lead to deterioration of raw and drinking water quality, there is no systematic screening of these substance properties in legislation (Neumann & Schliebner 2017). This is especially true for chemicals registered under REACH, which require a better interlinking with drinking water-related and environmental regulations (Neumann & Schliebner 2019). This is evidenced by a literature study conducted by Arp & Hale (2019), which found that 43% of substances detected in drinking water were registered under REACH. For substances detected above 0.1 µg/L, the proportion even increased to 58%.

In order to assess the occurrence of PM substances in surface and raw waters and to develop regulatory measures, the development of analytical detection methods for substances with PM(T) and vPvM criteria is required. However, the high polarity of substances that is often associated with high mobility (Zahn *et al.* 2020), complicates their integration into classical multi-analyte target methods. Although the polarity range of analyzable trace organic compounds has enormously expanded since the early 1990s, highly polar compounds continue to pose major challenges for environmental analysis and have therefore been termed ‘gap compounds’ by Reemtsma *et al.* (2016). According to the authors, these include in particular organic trace compounds that exhibit a negative pH dependent n-octanol/water partitioning coefficient ($\log D$) at environmentally relevant pH values. The development of such methods is urgently needed as the intrinsic substance properties of PM substances not only make their occurrence in the aquatic environment and in raw water resources likely, but also because they suggest

that such compounds are difficult to remove during drinking water treatment. The lack of suitable methods to analyze PM substances consequently results in a lack of monitoring data and makes it impossible to evaluate removal options for water suppliers.

Van der Hoek *et al.* (2014) reported that 59% of the European population are supplied with untreated drinking water or water that has been treated only with conventional technologies. Only 41% of the drinking water is treated with more advanced technologies, such as ozonation, filtration by granular activated carbon, and reverse osmosis (RO). However, the effectiveness of ozonation and granular activated carbon (GAC) filtration can be questioned in the presence of aliphatic molecular structures of PM substances and even for RO it has been shown that some micropollutants cannot be completely retained (Albergamo *et al.* 2019).

This study aims to further close the analytical gap for PM substances and to provide insights regarding the occurrence of PM substances in a major European raw water resource, the Rhine river. Furthermore, removal options commonly used by waterworks along the Rhine river were evaluated in terms of their effectiveness for PM substances.

MATERIALS AND METHODS

The substance selection was made against the background of the current scientific discussion on PM substances and the associated analytical challenges. Based on previous theoretical considerations and assessments of the persistence and polarity of REACH chemicals by Arp & Hale (2019) and initial detections of newly discussed substances in the aquatic environment (e.g. Schulze *et al.* 2019), the following criteria were considered in the selection of substances: (i) suspected persistence and polarity of the substance, (ii) tonnage, (iii) successful detection in environmental samples in previous studies with simultaneous lack of information on behavior during drinking water treatment, (iv) assessment of analytical feasibility, and (v) complete lack of knowledge regarding environmental occurrence (e.g. anticoagulants). There was no weighting of criteria. However, a log *D* value below <4.5 was mandatory for the selection of individual compounds as Neumann & Schliebner (2019) suggest for estimating the mobility of a substance a log K_{OC} of ≤ 4.0 for mobile compounds and a log K_{OC} of ≤ 3.0 for very mobile compounds or, in the absence of K_{OC} a log $D < 4.5$.

In addition, the antiepileptic drug carbamazepine (CBZ) and the analgesic paracetamol (PCMT) were analyzed. CBZ is known for its persistence to biodegradation and has been widely used as a conservative wastewater tracer in the past (e.g. Gasser *et al.* 2011). Paracetamol is considered to be readily biodegradable and was used to demonstrate biological activity in the degradation study conducted.

Chemicals and analytical instrumentation

Trifluoromethanesulfonic acid (TFMSA), 2-acrylamido-2-methylpropane sulfonic acid (AMPESA), benzyltrimethylammonium (BTMA), 1,3-diphenyl-2-thiourea (DPT), sulisobenzene (SUB), benzoguanamine (BGUA), amantadine (AMT), sodium toluenesulfonic acid (TLISA), xylenesulfonic acid (XYSA), ensulizole (ESZ), 4-(2-hydroxyethyl)morpholine (HEM), ramipril (RMP), and losartan carboxylic acid (LSA) were purchased from Merck KGaA (Darmstadt, Germany).

1,3-Diphenylguanidine (DPG) was purchased from TCI Deutschland GmbH (Eschborn Germany), N,N-dimethylbenzylamin (DMBA) from Sigma Aldrich (St. Louis, USA), ditolyguanidine (DTG) from Alfa Aesar (Heysham, United Kingdom), and carbamazepine (CBZ) from LGC Standards GmbH (Wesel, Germany).

Ramipril-d5, ramiprilat (RMPL), enalaprilat (ENLPL), enalaprilat-d5 sodium salt, ramiprilat-d5, losartan carboxylic acid-d4 were obtained from Santa Cruz Biotechnology, Inc. (Dallas, USA). Edoxaban (EDXB), apixaban (APXB), rivaroxaban (RVRXB) and dabigatran (DBGT) were purchased from TRC Toronto Research Chemicals Inc. (Toronto, Canada).

Perfluoropropanesulfonic acid (PFPrS) was purchased from Campro Scientific GmbH (Berlin, Germany). Perfluoroethanesulfonic acid (PFEtS) was kindly provided by Maria K. Bjoernsdotter from the University of Örebro (Sweden).

Stock solutions with concentrations between 0.1 g/L and 1 g/L were prepared in methanol (MeOH). From these, methanolic working solutions were made at different concentrations by further dilutions.

The chemical structures, molecular formulas, molecular weights and log*D* values of all target analytes can be found in Table S1 in the supplementary material. Solvents and chemicals that are not analytical standards, as well as a list of analytical instruments, are listed in Text S1.

The following compounds were used as isotopically labeled internal standards (IS): acesulfame-d4 (ACE-d₄), AMT-d₁₅, APXB-d₅, DPG-d₁₀, RVRXB-d₄, trifluoroacetate-¹³C₂ (TFA-¹³C₂) (all TRC Toronto Research Chemicals Inc.), ENLPL-d₅, LSA-d₄, RMP-d₅, RMPL-d₅ (all Santa Cruz Biotechnology, Inc.), perfluorobutanesulfonic acid-¹³C₃ (PFBS-¹³C₃; Wellington

Laboratories Inc., Guelph, Canada), CBZ-d₁₀ (CDN Isotopes, Pointe-Claire, Canada). The assignment of IS to native compounds was made at the end of method development based on similar retention time and comparable matrix effects in several surface water samples (Table S2).

Method development and validation

For method development, 12 chromatographic columns with different functionalities (reversed phase, hydrophilic interaction, mixed mode, ion exchange) were tested (Table S3). The optimal column and method were determined in an iterative process in four steps, in which different high-performance liquid chromatography (HPLC) buffer systems and solvents were tested. With the optimized column/eluent combination the developed methods were validated and substance specific limits of detection and limits of quantification (LOD, respectively LOQ) were determined according to DIN 32645:2008-11 (Table S2). Furthermore, stability tests with focus on hydrolysis at different pH values and photodegradation under ambient light were conducted in order to gain information on optimal storage of water samples.

Surface water sampling

Sampling of the river Alb

The Alb is one of the most important Rhine tributaries in the state Baden-Wuerttemberg in southern Germany. It has a length of 51 km and a catchment area of 448 km². The wastewater treatment plants (WWTPs) of the cities of Waldbronn and Karlsruhe discharge into the Alb before it flows into the Rhine on the right bank near Karlsruhe. Sampling on the Alb was performed on 10 December 2020 during dry weather. Figure 1 shows the location of the sampling points and the WWTPs. The exact coordinates of the sampling points can be found in Table S4 in the supplementary material.

Sampling of the river Rhine and selected tributaries

In addition to the longitudinal sampling of the Alb, the river Rhine and two of its tributaries (Neckar near Mannheim and Main near Frankfurt a. M.) were sampled at the sampling points Basel, Karlsruhe, Mainz, Cologne and Duesseldorf between January 2020 and December 2020 ($n = 11 - n = 13$). These samples were taken during the regular surveys of the Association of Rhine Waterworks (ARW) and Association of Lake Constance and Rhine Waterworks (AWBR). Additional samples along

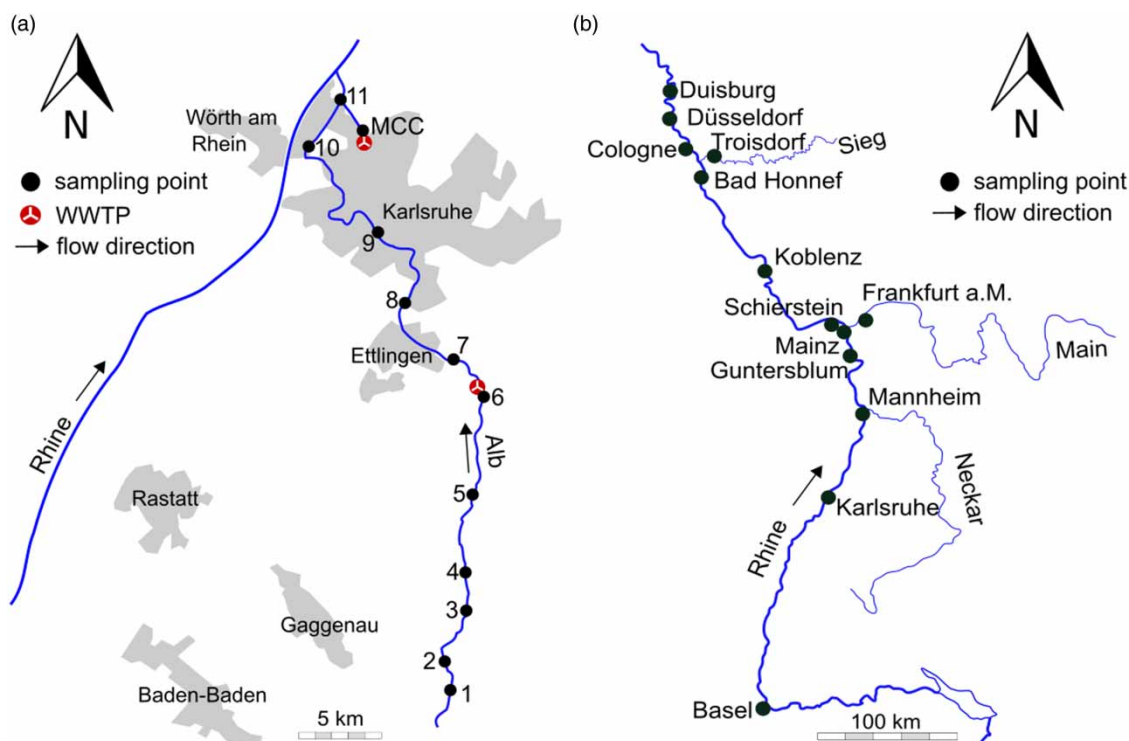


Figure 1 | Sampling points along the Alb and location of the wastewater treatment plants discharging into the Alb (a). Sampling sites on the Rhine and some tributaries (b). MMC = main collection channel.

the Rhine accrued as part of a special monitoring program of the ARW in Guntersblum, Schierstein, Koblenz, Bad Honnef, Duisburg and from the tributary Sieg (near Troisdorf) in the second half of 2020. Samples were collected as bulk samples in 1 liter brown glass bottles and stored at 4 °C in the dark. No preservatives were added, and sampling was performed every 28 days regardless of the prevailing weather conditions. Filtration proved unnecessary and was avoided as some compounds were found to be partially adsorbed on certain filter materials.

Laboratory batch tests for removal options during drinking water treatment

Various laboratory tests were carried out in order to give initial recommendations on removal options for waterworks. The focus was laid on the processes employed by water suppliers that use surface water impacted raw water for drinking water production.

Fixed-bed bioreactor for simulating bank filtration

Fixed-bed bioreactors (Börnigk *et al.* 2001) operated in duplicate were used to simulate biodegradation processes during aerobic bank filtration. A 10-L white glass bottle filled with surface water (Rhine near Karlsruhe) was used as a reservoir. Selected target compounds were added (10 mL) from a methanolic 1 mg/L substance mix, resulting in a spiking concentration of 1 µg/L per compound. The spiked MeOH was evaporated in the fume hood before replenishing the test mixtures with 10 L surface water. To ensure water-saturated conditions, water was pumped bottom up in a circular flow through a cylinder filled with sintered glass beads (Schott Engineering GmbH, Mainz, Germany) (flow rate approximately 18 mL/min), which represent a non-adsorptive, porous material that provides optimal growth conditions for microorganisms and should allow microbiological growth similar to the colmatation layer in bank filtration. The experimental set-up was darkened and operated at a temperature of 20 °C ± 2 °C. Sampling was carried out over a period of 69 days.

Ozonation experiments

Ozonation experiments were conducted as batch experiments in 100 mL white glass bottles in tap water. The tap water had a pH of 7.3 and a dissolved organic carbon (DOC) content of approximately 0.9 mg/L. The substance concentration used was 1 µg/L. Ozone was generated using a COM-AD-02 ozone generator (Anseros, Tuebingen, Germany). Ozone gas was passed through a cooled glass column filled with distilled water in order to produce an ozone stock solution. The stock solution had an ozone concentration between 15 mg/L and 25 mg/L and was added to the test batches to obtain ozone concentrations of 0.2 mg/L, 0.5 mg/L and 1 mg/L. To achieve even and rapid distribution of the ozone stock solution, the test set-ups were gently stirred using a magnetic stirrer. After defined ozone contact times of 1 minute to 60 minutes, samples were taken and the residual ozone was reduced using sodium thiosulfate. The pH after the maximum contact time was unchanged.

Adsorption on activated carbon

To evaluate the removability of the target substances by activated carbon, batch adsorption tests were set up with eight different concentrations of powdered activated carbon (PAC) (0.3; 0.5; 1; 2; 5; 10; 20 and 50 mg/L; $n = 2$) in ultra-pure water. This was added to the test mixtures from a stirred 1 g/L suspension, except for the two highest concentrations. The PAC Filtrasorb 300 (F 300; Chemviron Carbon, Feluy, Belgium) used in this test set-up is derived from stone coal and is widely used in waterworks practice. The test mixtures were treated on a horizontal shaker for a period of 48 h and the coal was subsequently filtered off. The spiked concentration of the target analytes in the batch was 1 µg/L.

RESULTS AND DISCUSSION

Method development, sample filtration and hydrolysis

The method development resulted in two different analytical methods. Except for AMPSA, TLISA, TFMSA, CYA, PFPrS and PFEtS, all substances could be separated with the RP column Kinetex PS using ultra-pure water (A) and MeOH (B) both with 5 mM ammonium formate as eluents. For the remaining substances (AMPSA, TLISA, TFMSA, CYA, PFPrS and PFEtS), the IonPac AS17 (eluents: ultra-pure water +50 mM ammonium bicarbonate(A) and MeOH (B)) provided the best resolution and retention. Details on matrix effects in real water samples, mass transitions and IS assignments can be found in the supplementary material (Table S2). Stability tests showed that the substances were stable at neutral pH for at least 14 days in drinking water, no matter if exposed to ambient light or kept in the dark.

Occurrence in wastewater and surface waters

Sampling at the Alb River

At the day of sampling the discharge at the Ettlingen gauge was $0.62 \text{ m}^3/\text{s}$ at a water level of approximately 32 cm. Thus it was close to the three-year low of $0.42 \text{ m}^3/\text{s}$, but can be considered representative of discharge values measured in this time of the year (Figure S1). During the years 2018–2020, the median discharge was $1.0 \text{ m}^3/\text{s}$, and the maximum discharge was $17.1 \text{ m}^3/\text{s}$. The measured analyte concentrations indicate that the two WWTPs discharging into the Alb have a major impact on the number and concentration level of the trace substances detected at the particular sampling points (Figure 2(a)). While at the first six sampling points only DPG was detected at sampling points 4 and 5 with 10 ng/L , 10 of the 26 investigated compounds could be detected after the discharge of the WWTP in Waldbronn. The total concentration of all investigated compounds there was 680 ng/L and remained largely constant up to sampling point 9 with 750 ng/L . The dominant compounds in this river section were ESZ, RVRXB, and LSA. In particular, the detection of RVRXB at 98 ng/L , as well as two other blood thinners (DBGT at 50 ng/L and EDXB at 42 ng/L) is noteworthy, as these compounds have never been detected in surface waters before.

Although the same total number of compounds was detectable at sampling point 10, the total concentration decreased significantly to 560 ng/L . In addition, there was also a shift in the substance pattern and TLSA was the dominant compound. The reduction in concentration as well as the detection of substances not detected upstream can most likely be attributed to the influence of the Federbach river. With a length of over 40 kilometers and a catchment area of 135 km^2 , it is the most important tributary of the Alb and flows into the Alb between sampling points 9 and 10. At sampling point 11 the

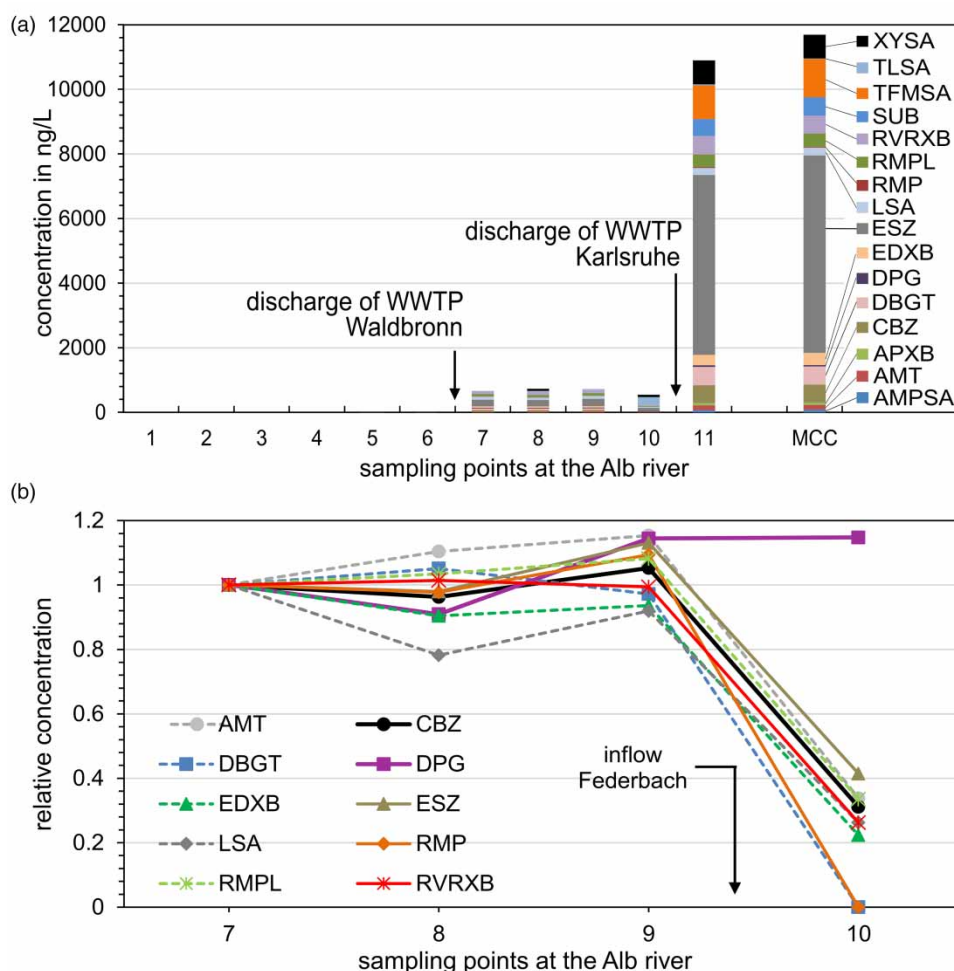


Figure 2 | Sum concentrations of the individual substances detected in the Alb river (a). (b) Shows the concentration curves normalized to sampling point 7 between sampling points 7–10.

total concentration increased by a factor of 20, which can be attributed to the influence of the discharge of the WWTP Karlsruhe. Here, the Alb sampling also revealed the broadest substance spectrum of 16 substances. AMPSA, APXB, SUB and TFMSA were detected here for the first time. It should be noted that sampling point 11 could only be sampled approximately 300 m after the confluence with the main collection channel (MCC) of the Karlsruhe WWTP for reasons of accessibility to the Alb. The MCC represents an approximately 2 km long connecting structure that directs the effluent of the WWTP to the Alb. Since the sampling took place on the right side of the Alb, from which the MCC flows in, it can be assumed that there is insufficient mixing at this point. For this reason, the concentration level and substance pattern at sampling point 11 and in the MCC, which was also sampled, largely corresponds. Again, the dominant substance was ESZ, which was detected at 5.6 µg/L at sampling point 11. *Ahmadi et al. (2017)* detected ESZ concentrations of 4 µg/L in the Grand River (Ontario, Canada) below a WWTP discharge. ESZ has also been detected in some Baltic Sea tributaries. Here maximum concentrations of 840 ng/L have been reported in the Mühlenfließ River, which is also influenced by wastewater (*Fisch et al. 2017*). TFMSA, only found at sampling site 11 and in the MCC, was the compound with the second highest concentrations and the only one besides ESZ with a concentration of >1 µg/L.

The usefulness of the wastewater indicator CBZ became obvious at sampling point 7. In *Figure 2(b)* all compounds are shown that were detectable for the first time at this point; concentrations of subsequent sampling points were normalized accordingly. It becomes obvious that all substances, with the exception of DPG, follow the concentration curve of CBZ and that the dilution by the Federbach river mentioned before is also very well represented. The somewhat steeper curve of DBGT and RMP is due to the fact that these compounds were no longer detectable at sampling point 10 and their concentration was set to zero. DPG shows a pronounced contrary curve progression and a dilution of the concentrations was not observed. Instead, an input of the substance via the Federbach river can be assumed. Since no WWTPs discharge into the Federbach river, DPG cannot be considered as a solely wastewater-borne substance. This is also proven by the detection at sampling points 4 and 5 before the discharge of the WWTP in Waldbronn. According to the current state of knowledge on DPG, it can be assumed that diffuse inputs of the compound can also occur. The European Chemical Agency (ECHA) refers to a high release rate of DPG from tires and brake pads, among other sources (*ECHA 2021*), and *Zahn et al. (2019)* confirmed leaching of the substance from tire material in laboratory tests.

In the discussion so far, the compound CYA has been excluded. CYA did not meet the performance criteria for analytical detection defined by the *EU Commission (2002)*, as only one product ion was available for analyte identification. For this reason, the concentrations presented here are to be considered semi-quantitative, especially since no suitable isotopically labeled standard was available for the compound either. CYA is known as an intermediate and transformation product in melamine manufacturing (*Bischoff 2011*) and is ubiquitously present in food packaging in the USA (*Zhu & Kannan 2019*). However, since CYA was detected at comparatively high concentrations, the compound is separately discussed here and in subsequent sections. In the Alb river, CYA was detected at 0.95 µg/L starting at sampling point 9. In addition, a clear influence of the Federbach river on the CYA concentration was evident, too, resulting in a concentration increase to over 5 µg/L at sampling point 10. In the further course, 2.0 µg/L and 1.6 µg/L were measured at sampling point 11 and in the MCC, respectively. The results at least allow the conclusion that the measured signals are not artifacts attributable to sampling or sample preparation, since CYA was not detected in samples from the upper reaches of the Alb river.

Occurrence of target substances in the Rhine and in selected tributaries

For the Rhine and its tributaries, there are 11–13 measured values each for Basel, Karlsruhe, Mainz, Cologne and Düsseldorf (Rhine) as well as for Mannheim (Neckar) and Frankfurt (Main). In the following, these are referred to as the main measuring points (MMP) and were sampled between January and December 2020. In addition, there are five to six measured values for the secondary measuring points (SMP) Guntersblum, Schierstein, Koblenz, Bad Honnef and Duisburg (Rhine) as well as Schierstein (Main) and Troisdorf (Sieg), all from the second half of 2020. In total 122 samples were analyzed.

The present data set for MMP and SMP consequently differs in terms of sample size due to the special measuring program carried out at the SMP. In addition, there is a temporal imbalance in the data. Both aspects had to be taken into account accordingly when evaluating the analytical data. In total, for 15 of the 25 trace substances investigated, as well as the wastewater tracer CBZ, median values could be calculated for the MMP (*Figure 3*). Concentrations increase continuously in the course of the Rhine, which can be justified with the parallel increasing wastewater share. The sum concentrations observed at the mouths of the tributaries clearly exceed even those measured at the Lower Rhine, which can also be justified by the increased proportion of treated wastewater present there. *Drewes et al. (2018)*, for example, indicate a wastewater fraction

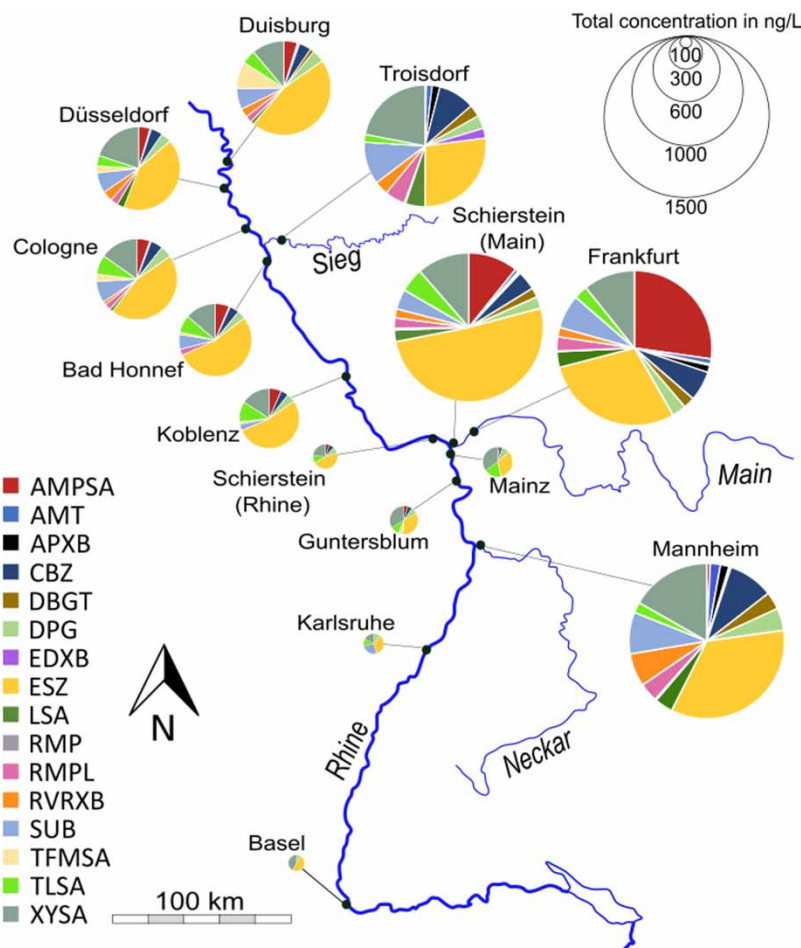


Figure 3 | Median sum concentrations of the analyzed trace substances detected in at least half of the analyzed samples in the second half of 2020.

of 10%–20% at mean discharge for the mouth of the Neckar River, whereas it is below 5% in the Rhine just upstream the confluence.

Median values for all MMP could only be calculated for DPG and ESZ. In particular, at the Upper Rhine monitoring sites in Basel and Karlsruhe for many analytes only in very few samples findings above the LOQ could be recorded.

As mentioned above, it can be assumed for DPG that there is also a considerable diffuse input of the substance due to its release from tires and brake pads, additionally to the input through WWTPs. Nevertheless, an increase in concentrations could be observed both along the course of the Alb and the Rhine. In the course of the Rhine, the median concentration increased from 15 ng/L from the most downstream sampling point in Basel to 26 ng/L in Düsseldorf at the Lower Rhine. Additionally, the measured concentrations in the Neckar and Main rivers were at a significantly higher concentration level than in the Rhine. This also indicates some correlation with the wastewater fraction present at the respective sampling points. The maximum concentration at the MMP was measured in the Neckar near Mannheim at 93 ng/L. The concentrations measured for DPG are on a similar level as already reported by Schulze *et al.* (2019). The authors examined a total of 14 samples from Germany, the Netherlands, and Spain (seven surface water samples, four groundwater samples, one bank filtrate sample, and one concentrate and permeate sample each from an RO plant). DPG was detected in each sample. Concentrations ranged up to 100 ng/L, but no information was provided as to which sample the measured concentrations were assigned. Unfortunately, information on which German surface waters were analyzed is also lacking, so that a direct comparison with the concentrations detected herein is not possible. Kolkman *et al.* (2021) also detected DPG in 11 of 24 surface water, groundwater, and drinking water samples from the Netherlands and Belgium. However, only qualitative statements on DPG were made in the study and no concentrations were given.

A significantly higher concentration level was observed for ESZ. The median at the most highly polluted measuring points in Düsseldorf, Mannheim and Frankfurt was about a factor of 10 higher than for DPG. At the same time, strong outlier values were observed at some monitoring sites. At the Rhine sampling points, these occurred in July and August, respectively. However, whether this can actually be attributed to an increased use of sunscreen products in which ESZ is used as an ultraviolet (UV) light filter, cannot be conclusively answered at this point. Production-related discharges or the increased input due to heavy rain events in summer time could be responsible for high ESZ concentrations, too.

As for DPG, the highest ESZ median concentrations were detected in the Rhine tributaries. In the Neckar (Mannheim), this was 460 ng/L and thus more than twice as high as at the Lower Rhine monitoring sites. Wick *et al.* (2010) analyzed ESZ in one Rhine sample collected in Koblenz and reported a concentration of 48 ± 3 ng/L. In two wastewater-influenced tributaries of the Main river, 1,300 ng/L and 3,200 ng/L were measured, respectively. It becomes clear that ESZ concentrations in the aquatic environment can vary over a wide range. Overall, the values published by Wick *et al.* (2010) are in good agreement with those presented herein. For example, a median value of 87 ng/L was calculated at the measuring site in Mainz, which is closest to the Rhine sampling point of Wick *et al.* (2010).

Downstream from Mainz, four additional compounds could be detected in more than half of the Rhine samples. At the sampling point furthest downstream in Düsseldorf a total of 11 compounds and in both Rhine tributaries 13 compounds were found. This basically confirms the results of the sampling at the Alb, that a large number of the investigated compounds are discharged into the aquatic environment via municipal wastewater. Their number and concentration increase in the course of the Rhine with increasing wastewater content and they appear at a higher level in the tributaries which have a higher wastewater burden.

The summed median concentrations of the most polluted Rhine monitoring site in Duisburg and of the tributary monitoring sites point out differences in composition patterns and concentration. The summed concentrations at the tributaries are about 50% higher than those measured in Duisburg (740 ng/L). At all monitoring sites ESZ contributes the largest share to the total concentration. However, other compounds show a clearly heterogeneous picture. While AMPSA is the substance with the second highest median concentration (390 ng/L) in the Main, it plays a minor role in the Neckar river and the Sieg river. Other important compounds were the second UV blocker SUB as well as XYSA. Although the Rhine tributaries showed a higher summed median concentration, TFMSA was detected with the highest concentrations at the Duisburg sampling site. There, the two highest concentrations of all 122 samples were detected at 240 ng/L in September 2020 and 380 ng/L in November 2020. While only 54 ng/L was quantified on average at the other four sampling dates, this represents a level of contamination that is significantly higher than at any other sampling site. Furthermore, the Duisburg sampling site, along with the Düsseldorf site, was the only one where TFMSA was above the LOQ in every sample in the second half of 2020. Possible sources of TFMSA are wastewater discharges of industrial applications or by manufacturers of the compound itself. According to Kazakova & Vasilyev (2017) and Montes *et al.* (2019) TFMSA is used in organic synthesis, in natural and organometallic compounds chemistry, for manufacturing other chemicals and in the production of electrical, electronic and optical equipment.

The dominant anticoagulants were DBGT and RVRXB, which were detected at all tributary monitoring sites and partly in the Rhine samples (medians: 11 ng/L–50 ng/L, respectively 8.2 ng/L–95 ng/L). APXB was detected at three of the five tributary measuring sites (median: 17 ng/L–25 ng/L) and EDXB at one measuring site in all samples taken (median: 29 ng/L). To the best of our knowledge this represents the first detections of these substances in surface waters on a world wide scale.

By using discharge data, the contrasting behavior of purely wastewater-borne trace substances and those substances that increasingly enter the streams during heavy rainfall events, as it can be assumed for DPG, could be demonstrated (Figure S2). For demonstration the discharge of the Main River and the concentrations of DBGT and DPG were used. In the Main river a significantly increased discharge was observed in February and March 2020. No concentrations above the LOQ were detectable for DBGT due to the high dilutions. With the exception of the 22 July 2020 sampling, concentrations during the months of increased discharge (April through July) were lower than the months at the end of the year that had the lowest discharge values. The negative correlation of discharge values and measured concentrations is typical for substances that are constantly released into streams in similar absolute amounts, as can be assumed for pharmaceutical agents. For DPG, the picture was much more heterogeneous and the lowest concentrations were not measured on sampling days with the highest discharge values. If the daily load is calculated from concentration and discharge, the differences between the two compounds become even more apparent. For the sampling days on which it was possible to calculate the load for DBGT, it is in a very narrow range between 0.16 kg/d and 0.27 kg/d. For DPG, conversely, the loads measured

in February and March are about a factor of 10 higher than those measured in April and September. This supports the hypothesis that a significant input of DPG can occur as a result of heavy rain events, probably through tire and brake abrasion.

An integral evaluation of all results of the monitoring program on the Rhine and its tributaries is presented in Table 1. Of the 25 target substances, 17 compounds as well as CBZ could be detected in the investigated surface waters at least once.

The number of compounds detected in the Rhine tributaries (18) is only slightly higher than the number of trace substances detected in the Rhine itself (16), however, the detection frequency (DF) in the tributaries is significantly increased. As mentioned above, TFMSA is an exception which is almost exclusively detected at the Lower Rhine monitoring sites in Cologne and Duisburg. For the Upper Rhine near Basel and near Karlsruhe, all TFMSA values were below the LOQ of 13 ng/L. The five compounds with the highest DF in the Rhine were in descending order ESZ, DPG, XYSA, TLSA and CBZ, whereas in the tributaries ESZ, DPG, LSA, RMPL and CBZ dominated with 100% each. Thus, based on the substances examined in this study, it becomes obvious that industrial chemicals play a more important role in the Rhine than in the studied tributaries, in which pharmaceutical agents are more significant. However, such a conclusion should not be overinterpreted, since it is strongly dependent on the considered substance spectrum.

The two compounds detected exclusively in the Rhine tributaries were the pharmaceuticals APXB and EDXB. APXB showed a high DF of 71%. In particular, the Sieg river showed a notably load of APXB and EDXB, since both compounds

Table 1 | Median values and detection frequency (DF) of the investigated trace substances in the Rhine and its tributaries

Substance	Median Rhine in ng/L	DF Rhine in %	Median Rhine tributaries in ng/L	DF Rhine tributaries in %	Maximum total in ng/L
AMPSA	15	61	25	80	770
AMT	<LOQ	18	14	83	45
APXB	<LOQ	0	17	71	35
BGUA	<LOQ	0	<LOQ	0	22
BTMA	<LOQ	0	<LOQ	0	<LOQ
CBZ	16	63	85	100	240
CYA	2,800	95	4,400	91	20,000
DBGT	<LOQ	17	31	89	57
DMBA	<LOQ	0	<LOQ	0	<LOQ
DPG	23	91	41	100	140
DPT	<LOQ	0	<LOQ	0	<LOQ
DTG	<LOQ	0	<LOQ	0	<LOQ
EDXB	<LOQ	0	<LOQ	26	40
ENLPL	<LOQ	0	<LOQ	0	<LOQ
ESZ	120	100	460	100	3,300
HEM	<LOQ	0	<LOQ	0	<LOQ
LSA	<LOQ	25	44	100	90
PFEtS	<LOQ	0	<LOQ	0	<LOQ
PFPrS	<LOQ	0	<LOQ	0	<LOQ
RMP	<LOQ	2	3.9	60	7.5
RMPL	<LOQ	37	47	100	75
RVRXB	<LOQ	38	34	97	130
SUB	<LOQ	43	91	94	520
TFMSA	<LOQ	45	<LOQ	6	380
TLSA	28	69	34	91	640
XYSA	83	81	150	94	410

The maximum concentrations are the maximum values of the respective substance from all investigated samples. CYA does not reach the required number of identification points.

could be detected there in every sample. The two other anticoagulants DBGT and RVRXB showed an even higher DF of 89 and 97%, respectively, in the tributaries. The maximum concentration for this group of substances was measured at 130 ng/L for RVRXB in the Neckar river near Mannheim.

CYA was the dominant compound in the Rhine, Neckar, Main and Sieg compared to the concentration levels of all trace substances considered. Concentrations tended to increase along the Rhine and were above 3 µg/L (median values) downstream of the Bad Honnef sampling point. The median values in the Neckar river (Mannheim) and Main river (Frankfurt and Schierstein) were between 3.8 µg/L and 4.6 µg/L and thus on a slightly higher level. Peak concentrations of up to 20 µg/L (median 12 µg/L), however, were measured in the Sieg river.

Removal options for target compounds in waterworks

Since most of the target substances were supposed to have intrinsic substance properties that make their occurrence in raw waters used for drinking water production likely, important treatment processes used in waterworks were investigated for their effectiveness in removing them.

Simulated river bank filtration

The behavior of the target substances with regard to their biodegradation during aerobic bank filtration passage was investigated over a period of 69 days. In each case, the trace substance concentration measured after two hours was used as the reference value for the initial concentration. Twenty-two of the substances listed in Table S1 were included in the evaluation. In addition, the analgesic paracetamol (PCTM) was added to the experiment, and is classified as readily biodegradable (Lin *et al.* 2018; Bisognin *et al.* 2019). PCTM served both as a reference substance to show the biological activity of the test *per se* and allowed the biodegradability of the other substances to be classified. CBZ was also included as a biologically persistent compound. DPT could not be detected at any time in the samples, although it was present in the spiking solution. Since the spiking was carried out from a methanolic solution, the test batch was filled with Rhine water only after the organic solvent had completely evaporated, to not provide the microorganisms with an additional carbon source. Thus, the absence of DPT may in principle be due to its volatilization or a lack of redissolution after addition of the surface water. Immediate biodegradation cannot be completely ruled out, but seems unlikely, since the biowin models of the United States Environmental Protection Agency (EPA 2021) predict a higher stability for DPT than for PCTM, which was degraded only to 50% after 10 days.

To evaluate the data sets, the substances were classified into three groups as follows:

(i) Readily biodegradable substances: This group included all compounds that exhibited a biological half-life shorter than PCTM; (ii) Moderately biodegradable substances: The classification applies to substances with a higher biological half-life than PCTM, but less than 40 days; (iii) Persistent substances: The classification follows the Umweltbundesamt (UBA) recommendation and thus also Annex XIII of the REACH Regulation as part of the PBT/vPvB assessment for persistent substances, which stipulates a half-life >40 days. Substances with a half-life >60 days can be classified as vP.

Figure 4 shows the degradation curves of the target compounds. While a typical lag phase of about five days was observed for PCTM, some other compounds which had a shorter biological half-life than PCTM showed a much more rapid onset of degradation. These are important findings for water utilities using bank filtrate as a raw water resource. Since the residence time in the subsurface is usually several weeks to months, it can be assumed that the readily degradable compounds cannot be detected there. However, a general absence of these substances in raw waters cannot be excluded, since surface water is also used as raw water without prior underground passage or under different redox conditions.

It is striking that the compounds classified as readily degradable can be divided in three groups, that are rather different from each other but show strong structural similarities within the group: all guanidine compounds investigated in this work (DPG and DTG), which represent strong bases; the two benzenesulfonate derivatives TLISA and XYISA representing strong methylated benzene sulfonic acids; and the four anticoagulants APXB, DBGT, EDXB and RVRXB all with a rather high molecular mass and rich in heterocyclic structures and nitrogen hetero atoms are found exclusively in this group.

Substances that had a longer biological half-life than PCTM but were more than 50% degraded in the test mixtures after 40 days were the two UV filter substances ESZ and SUB and the pharmaceuticals or metabolites RMP, RMPL and ENLPL. For ENLPL, the degradation curves for the two parallel test set-ups are plotted separately in Figure 4 to illustrate that the substance behavior was comparable in both. Similar good agreements were also obtained for all other compounds investigated. With the exception of ENLPL, the substances classified as moderately biodegradable exhibited longer lag phases and less steep degradation curves than the readily biodegradable substances. ESZ shows a comparatively linear

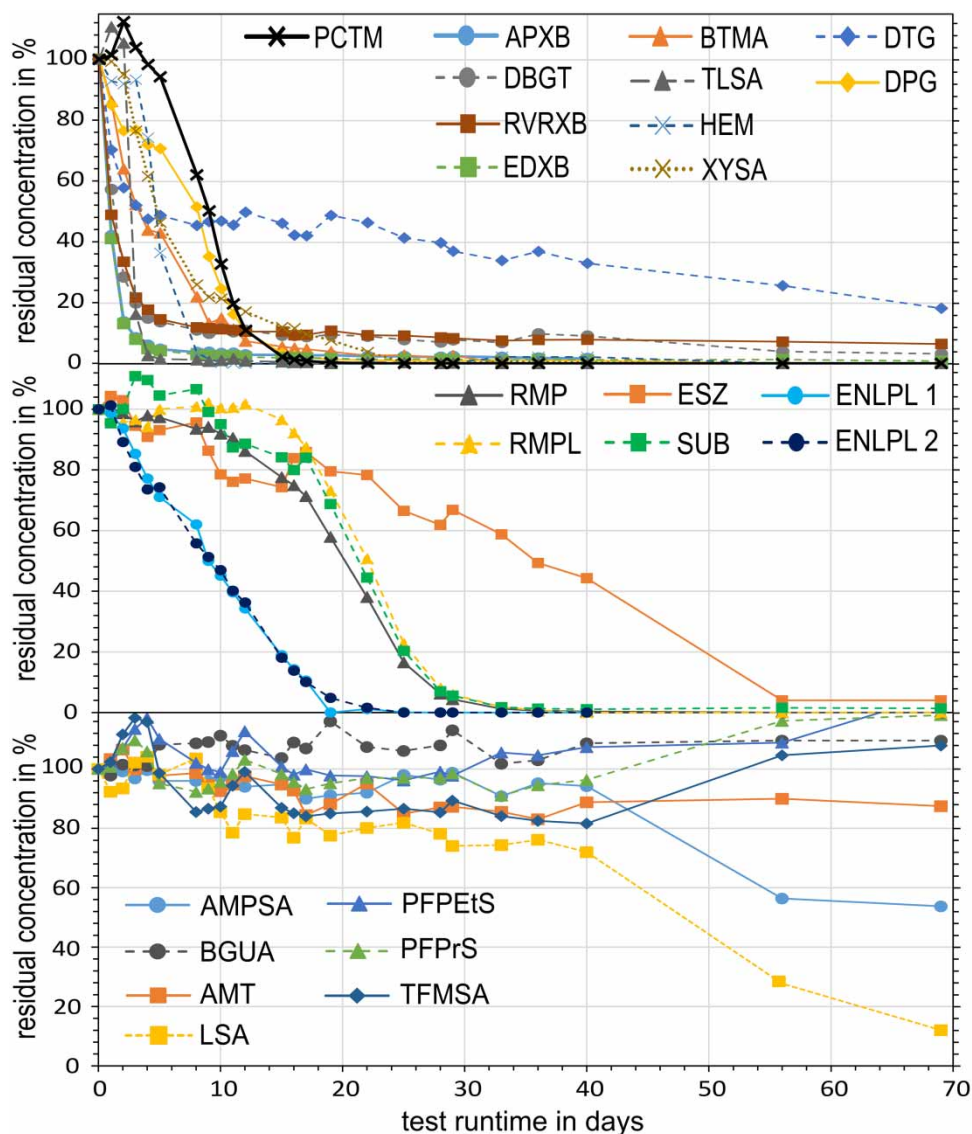


Figure 4 | Results from the simulated river bank experiment. The upper and the middle coordinate system show those substances which are classified as readily, respectively moderately biodegradable. At the bottom, investigated compounds which could be classified as (very) persistent are plotted.

curve progression, as it has already been observed for the hydrolysis of other organic trace substances, such as the thiazide diuretic hydrochlorothiazide (Scheurer *et al.* 2014). However, the results from the stability studies argue against this hypothesis. In principle, ESZ, as a UV filter, is designed to absorb solar energy, especially in the UV-B range. Thus, it can be assumed that the substance is subject to direct photodegradation, which has already been described in the scientific literature (Ji *et al.* 2013). However, this cannot be used as an explanation for the decreasing concentrations of ESZ here, as the test vessels were darkened over the entire run-time of 69 days.

The compounds AMPSA, AMT, BGUA, LSA, PFPEtS, PFPrS and TFMSA were found to be persistent. As expected, the three perfluorinated sulfonic acids belong to this group. The persistence of perfluorinated compounds to biodegradation has been widely reported (e.g. Goldenmann *et al.* 2017; Cousins *et al.* 2020). However, until now, no knowledge was available on how the three shortest-chain perfluoroalkyl sulfonic acids behave during bank filtration, which was due to the lack of analytical detection methods. Only recently, several research groups succeeded in closing this analytical gap for the first time (Björnsdotter *et al.* 2019; Montes *et al.* 2020). The remaining four persistent compounds were either industrial chemicals (AMPSA and BGUA) or pharmaceuticals/metabolites (AMT and LSA).

Of the 22 compounds investigated, at least the seven substances classified as persistent – if they occur in surface water – have a high potential not to be completely degraded during bank filtration. Of these, all except BGUA have a $\log D$ value <0 and thus potentially fall into the analytical gap mentioned by Reemtsma *et al.* (2016) as analytical possibilities were not available or used until recently. A verification of the results by the analysis of riverbank filtration (RBF) wells should be carried out by determination of PMOCs present in surface waters and declared here as persistent.

Ozonation

In the evaluation for reaction of the target compounds with ozone, 23 of the substances listed in Table S1 could be included. Similar to the biodegradation study, no statements could be made for DMBA and DPT. Since the presence of MeOH during ozonation would have led to an unwanted ozone depletion, the experiments were again carried out after its complete evaporation. The reasons for the lack of detection for DPT may thus be those mentioned above.

To classify the removability of the target compounds, the following boundary conditions were set for the residual concentration after 60 minutes of ozone contact time: (i) readily degradable (residual concentration $<20\%$); (ii) moderately degradable (residual concentration 20% to 80%); (iii) persistent (residual concentration $>80\%$).

Already at an ozone concentration of 0.2 mg/L , more than half of the compounds can be classified as readily degradable with ozone. The remaining approximately 50% are divided in roughly equal proportions between compounds that are moderately degradable with ozone and persistent substances. For many of the compounds classified as readily degradable, complete degradation was already observed after a contact time of five minutes. This was the case, for example, for all investigated drugs and metabolites and for the two guanidine derivatives DPG and DTG.

Increasing the ozone concentration to 0.5 mg/L had no effect on the compounds previously classified as persistent, but resulted in residual concentrations of $<20\%$ for APXB and RVRXB after an ozone contact time of 60 minutes, which had been 35 and 41% , respectively, at 0.2 mg/L ozone. Even a further doubling of the ozone concentration to 1 mg/L resulted in a change in classification only for selected trace substances. A complete list of the residual concentrations of all substances for all contact times and ozone concentrations investigated can be found in Table S4 and Table S5.

Activated carbon

Since it was assumed that the adsorption by means of PACs would be in a wide range due to the quite different $\log D$ values, quantities of PACs were used that covered more than two orders of magnitude (0.3 mg/L – 50 mg/L). Figure 5 shows the removal of the compounds applying different amounts of PAC. The figure is divided into substances that are very well adsorptively removed and those that show sufficient removability only at higher PAC concentrations. Here, 11 of 26 compounds were nearly totally removed ($\geq 80\%$) with 2 mg/L PAC, which corresponds to 42% of all substances investigated. At the lowest PAC level of 0.3 mg/L , DPT and the two anticoagulants RVRXB and EDXB showed the highest removal. The three compounds also possessed the highest, third highest, and sixth highest $\log D$ values of all compounds studied. This initially suggested a certain positive correlation between $\log D$ value and adsorption tendency.

CBZ has been classified as very good absorbable onto activated carbon in previous studies by different authors (e.g. Sperlich *et al.* 2017). However, most of the studies on adsorption to PACs have been performed for wastewater, since GAC, which is installed in an appropriate filter, is used almost exclusively for drinking water treatment. Even in studies with a real wastewater matrix, both for batch tests and pilot tests at wastewater treatment plants, removal rates for CBZ close to 100% were achieved by the application of 15 – 20 mg/L PACs, despite the existing competitive adsorption by other organic water constituents (Boehler *et al.* 2012; Altmann *et al.* 2014). Thus, it can be concluded that substances with removal rates similar to CBZ can also be classified as readily removable with. Eight substances proved to be difficult to remove by PAC. Five of the eight substances are permanently negatively charged compounds that were measured with the established IC detection method and eluted in the void volume with the Kinetex column used. This supports the observations on removability by PAC, since apparently hydrophobic interactions seem to be weak in both cases. A closer look reveals the following ascending order with respect to removability with 50 mg/L PAC: TFMSA $<$ AMT = HEM $<$ PFETs $<$ BTMA $<$ CYA $<$ AMPSA = PFPrS. TFMSA, one of the compounds least controllable with PAC, is also one of the most polar trace compounds considered in this work, with a $\log D$ value of -4.49 . This also holds true for AMPSA, PFETs and PFPrS. For the latter two perfluorinated compounds, the additional CF_2 unit of PFPrS is not only reflected in a higher $\log D$ value, but also results in a better adsorption compared to PFETs.

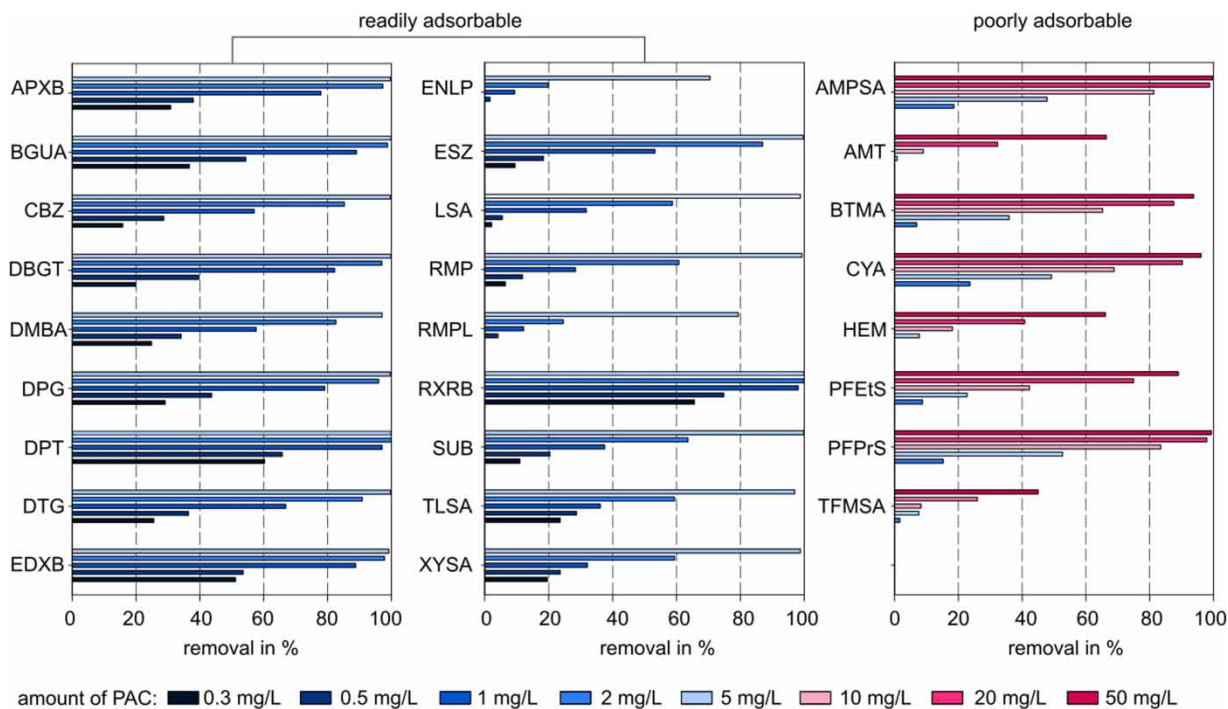


Figure 5 | Removal of the investigated compounds applying different amounts of PAC. Note: In the left and in the middle part of the figure removal is depicted for 0.03–5 mg/L PAC; for compounds displayed in the right part of the figure the removal is shown for 5 mg/L to 50 mg/L PAC.

The previous explanations suggest that there is a clear dependence between the mobility expressed by low $\log D$ values and poor removability with PAC. To test this hypothesis, in [Figure 6](#) the removal of the target compounds at 2 mg/L PAC was plotted against their $\log D$ values. As can be seen, there is no correlation (coefficient of determination $R^2 = 0.29$) that confirms the hypothesis. On the contrary, it becomes clear that for substances that have an almost identical $\log D$ value, as it is the case e.g. for AMT and DPG, a very different behavior was observed. The same is true for compounds such as TLSA and TFMSA, which also have similar but much lower $\log D$ values. The results are in line with those of [Piai et al. \(2019\)](#) who also reported a non-existent correlation between removability of trace compounds and their $\log D$ for GAC.

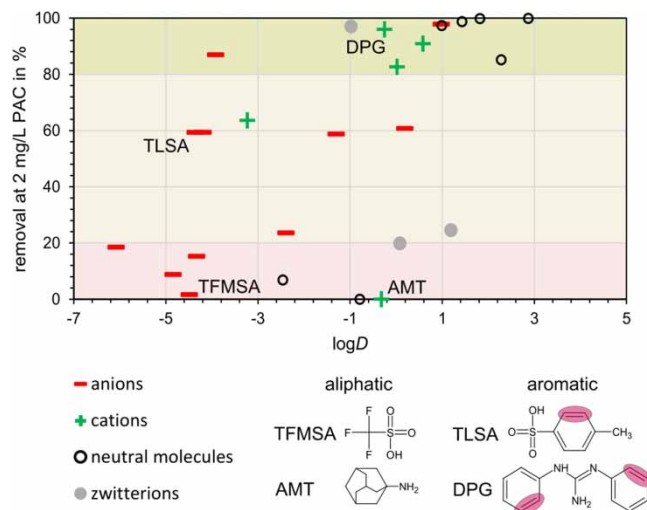


Figure 6 | Removal of target compounds when using 2 mg/L PAC as a function of their $\log D$ values, and structural formulas of selected compounds to illustrate the importance of aromatic structures in the molecule for effective removal.

Ridder *et al.* (2010) were able to show that, especially for compounds with low log D values, the presence of π - π bonds is a pre-requisite for good removability with activated carbon. A closer look at the structural formulas reveals that aromatic structural elements also play a crucial role for removal of the compounds studied in this work. Thus, an organic trace compound such as TLSA, which carries very polar as well as aromatic molecular components, is adsorbed much better than TFMSA, which also carries a sulfonic acid group but lacks an aromatic structural unit (Figure 6). In addition, other structural properties such as molecular size or molecular structure (cyclic vs. linear) can influence adsorption to activated carbon (Piai *et al.* 2019).

Nevertheless, Figure 6 also shows that a lack of aromaticity leads to a low adsorbability of the compounds investigated in this study.

As it is known that activated carbon can have a natural or designed ion exchange capacity, the charge state of the investigated compounds was taken into account to test a possible correlation with removal of the compounds by PAC. For this reason, the compounds included in this study were divided into acids, bases, zwitterions and neutral molecules. As can be seen from Figure S2 there were individual compounds for all four charge states with rather low and rather high removal rates. No overall clear trend was observable although, in general, cations and neutral molecules contemplated in our study were better removed than acids, but one has to keep in mind that the number of compounds investigated was rather small.

Overall assessment

Summarizing the data collected on the occurrence of the target substances in the Rhine and its tributaries and on their removability, results in the assessment from the water supply perspective as shown in Figure 7. The hierarchical clustering of the data considers removal during bank filtration after 40 days, removal by means of 2 mg/L PACs, and at 0.2 mg/L ozone at a contact time of 60 minutes. In addition, the average DFs (occurrence) in the Rhine and the investigated tributaries Neckar, Main and Sieg were included in the evaluation.

Dividing the dendrogram results in two clusters, which differ especially with respect to the attribute 'occurrence'. Many of the target substances that showed no or hardly any positive findings could also be removed comparatively well with at least one of the investigated options. An exception to this are the three perfluoroalkyl sulfonic acids, which have a high degree of similarity. Of these three compounds, only TFMSA was detected, but this was partially with high concentrations of up to 380 ng/L. For PFEtS and PFPrS no detection in surface waters occurred in this work. Using solid phase extraction for enrichment could probably lead to significantly lower LOQ and an occurrence of the compounds at lower concentrations cannot be excluded due to the nearly ubiquitous occurrence of many perfluorinated alkyl acids.

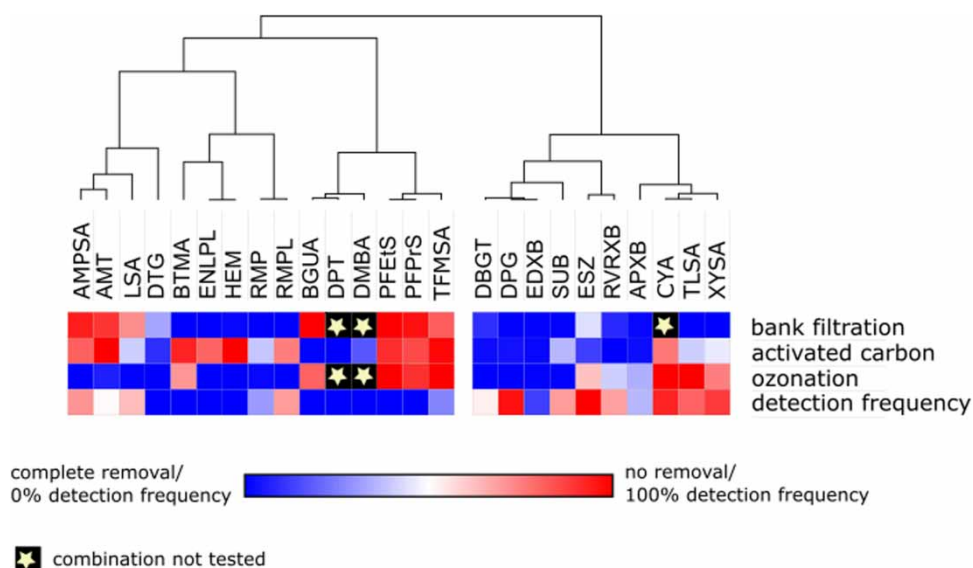


Figure 7 | Heatmap and hierarchical clustering for the degree of removal and occurrence of the studied compounds in the Rhine and major tributaries.

Compounds with a higher DF form the second cluster. For these, an even wider range of removal possibilities is available. ESZ and XYSA are the most critical here. This is especially true when bank filtration is not available or activated carbon filtration is not applied. As previously discussed, CYA occupies a special position. The compound was detected in almost all surface water samples but could be removed only insufficiently in laboratory tests using ozone and the application of activated carbon. However, no data are available for simulated aerobic bank filtration. In addition, the mentioned non-fulfilment of analytical performance criteria does not allow a final evaluation of the substance. Therefore, further data should urgently be collected for CYA. These data should be validated by means of high-resolution mass spectrometry measurements in order to achieve the required performance points for the analytical method.

CONCLUSIONS

Despite decades of research on anthropogenic trace substances and their occurrence in the aquatic environment, there are still a large number of compounds for which no or very little analytical data are available to assess their environmental relevance and their presence in drinking water resources. For the behavior of these compounds in various drinking water treatment processes, the data situation can be considered as even more precarious.

In the recent past, the topic gained new momentum through the discussion on persistent and mobile compounds. In this context, the term 'analytical gap' was coined for compounds with a $\log D < 0$. As a consequence of the non-analyzability of certain compounds, measurement and monitoring data are lacking, resulting in deficient regulation.

The present study could show that it is possible to develop liquid chromatographic methods for the detection of these compounds in water samples. It can thus be concluded that an analytical gap does not exist *per se*. However, the difficulties of successfully chromatographing very polar compounds became apparent here as well, so that no multi-analyte method could be developed for all target compounds. In practice, the establishment of such special chemical analysis in laboratories will depend very much on economic incentives and whether the analysis of the compounds is requested by clients or by legal requirements.

The need for improved protection of drinking water resources was also demonstrated by the compounds investigated in this study. In the Rhine, Main, Neckar and Sieg rivers, all of which are used indirectly by water suppliers for drinking water production via bank filtration, the majority of anthropogenic trace substances analyzable by the methods developed could be detected. Since it could be shown in laboratory experiments that the current drinking water treatment processes are not suitable to remove all regarded compounds from contaminated raw waters, it is strongly recommended to include them in future measurement programs and to investigate their behavior in full-scale waterworks using anthropogenically influenced raw water. Since research institutes or water utilities still have to conduct complex studies on the biodegradability and efficacy of treatment processes in waterworks, future approaches need to develop more appropriate predictive tools that facilitate the classification of trace organic compounds in terms of their persistence and mobility.

A widely understudied area of research is that many persistent and polar micropollutants might also be transformation products and can be formed from (various) precursor compounds. Because these precursors potentially originate from multiple sources, regulating them is challenging when there are concurrent jurisdictions for initiating countermeasures. If yet unknown PMT/vPvM substances are also formed during technical water treatment in WWTPs or waterworks is largely unknown and should be elucidated by widening the analytical window of high-resolution mass spectrometry by coupling it to alternative chromatographic techniques.

In order to quickly gain more data about the environmental relevance and existing hotspots of PMT/vPvM substances, future studies should not only focus on method development/improvement but also utilize the few already published (multi-analyte) methods for their analysis.

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CONFLICTS OF INTEREST

The authors declare no competing interest.

DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

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