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Rapid and sensitive speciation analysis of established and emerging gadolinium-based contrast agents in the aquatic environment by IC-ICP-MS†

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Gadolinium-based contrast agents (GBCAs) are well established and frequently used to enhance image contrast in magnetic resonance imaging (MRI). After their administration, GBCAs leave the patient's body unmetabolised, enter the wastewater system with insufficient elimination during wastewater treatment, and get discharged into the aquatic environment as trace-level contaminants. An increasing number of applications and rising environmental concentrations with unknown ecotoxicological long-term effects express the need for sensitive and selective GBCA speciation analysis. Furthermore, the recent approval of the newly developed GBCA gadopiclenol with a reduced Gd dose and generally updated regulations might alter environmental discharge and require advanced chromatographic separation. A rapid and automated GBCA speciation analysis method based on ion chromatographic (IC) separation and elemental detection with inductively coupled plasma-mass spectrometry (ICP-MS) of six clinically relevant GBCAs, including gadopiclenol, was achieved in 175 s. Excellent single-digit pico-molar (pM) detection limits and high matrix robustness for macrocyclic GBCAs allow the straightforward analysis of surface waters. River water samples from the densely populated Ruhr metropolitan area in Germany showed substantial GBCA contamination with up to 300 nM total GBCA concentrations in the river Lippe, exceeding typical concentrations in the aquatic environment. The combination of total metal analysis and GBCA speciation analysis allowed tracing different contaminants to potential discharge sources and investigating their environmental fate. Additionally, an unidentified species of undetermined origin was detected. Although the new GBCA gadopiclenol was not detected in the aquatic environment, the method is capable of ongoing monitoring and further studies on its stability and environmental behaviour.

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1 Introduction

Magnetic resonance imaging (MRI) is a well-established and highly valuable non-invasive medical tool for a wide range of diagnostic and therapeutic applications with an increasing number of applications worldwide. In up to 50% of MRI scans, gadolinium-based contrast agents (GBCA) are administered to improve image contrast and are therefore of medicinal value.[1–3] Due to its f^7 electronic configuration, Gd^{3+} has optimal electronic parameters for contrast enhancement, but the free ion exhibits acute toxicity.[4,5] To overcome this, thermodynamically stable and kinetically inert complexes were developed, which can be categorised as linear and macrocyclic based on their ligand structure and as neutral and ionic based on their total net charge.[6] GBCAs were generally considered stable and safe until, in 2006, nephrogenic systemic fibrosis (NSF) was associated with the administration of linear GBCAs in renally impaired patients.[7,8] Additionally, depositions of Gd after the administration of GBCAs in several organs, including the brain, bones, liver, and skin, have been detected but show no clinical symptoms, although currently unknown long-term effects cannot fully be excluded.[7–9] This led to the restriction of the use of linear GBCAs in the European Union by the European Medicines Agency (EMA) in 2017 (ref. 10) and a drastic increase in the market share of macrocyclic GBCAs.[11] The structures of the clinically most relevant GBCAs in the European Union and potentially emerging GBCAs with their categorisation are shown in Fig. 1.

After the intravenous injection, GBCAs are excreted mainly renally and unmetabolised with a half-time of around 90 min.[12,13] Consequently, the intact GBCAs enter the wastewater system, where wastewater treatment plants (WWTPs) only eliminate around 10% of the contrast agents. Subsequently,

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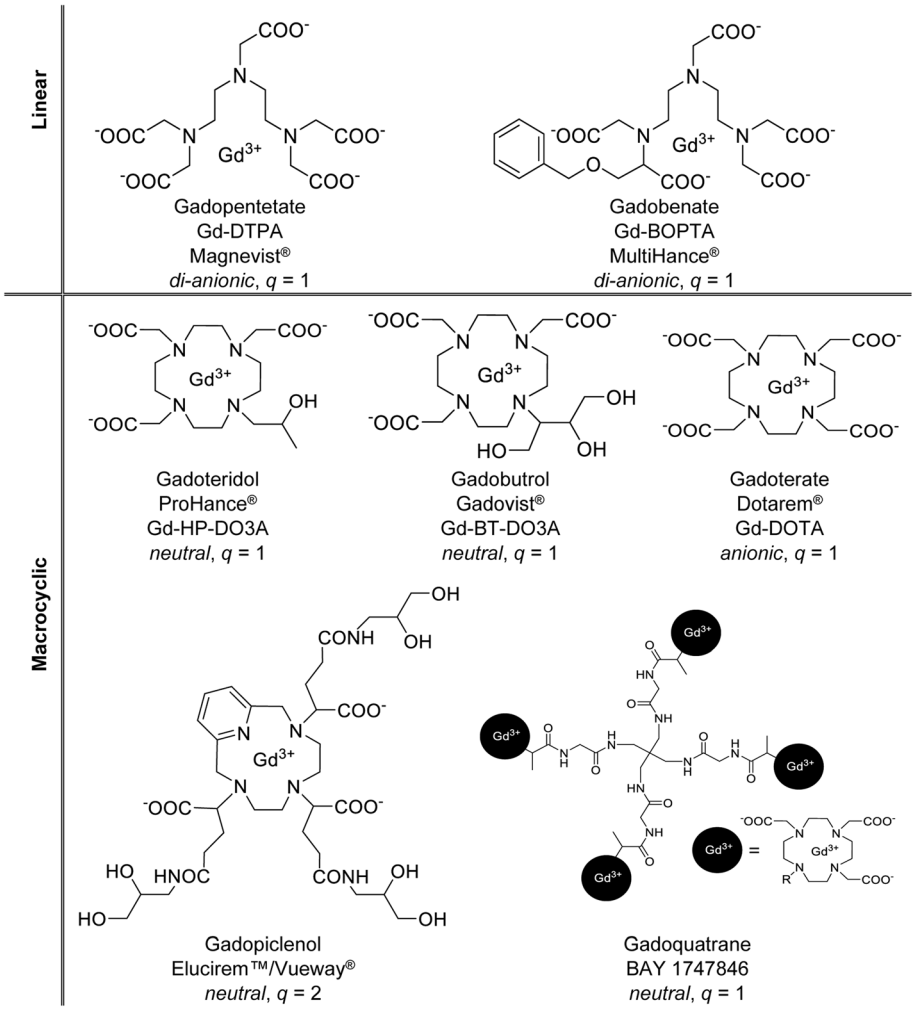

Fig. 1 Chemical structure, commercial name, charge state, and hydration number q per Gd of clinically relevant and emerging GBCAs in the European Union, categorised as macrocyclic or linear agents.[8,20]

intact GBCAs are discharged into surface waters like lakes or rivers and enter the aquatic environment.[12,14] Anthropogenic Gd from GBCAs has been detected worldwide with increasing concentrations over the last few decades and is expected to increase further. Total Gd concentrations range from single-digit picomolar (pM) to single-digit nanomolar (nM) concentrations.[12,15–18] The ecotoxicological effects, potential metabolization or degradation, accumulation, and long-term effects of these increasing Gd concentrations resulting from GBCA discharges are mostly unknown, and further research is crucial.[12,19,20] As tap water is partly sourced from surface waters, GBCAs can also be detected in municipal tap water in densely populated regions in pM concentrations and therefore enter the human food chain.[13,21] Due to the anticipated limited absorption in the human digestive system, no health risks are expected.[20] Because of the discharge of GBCAs into the environment, efforts to reduce the Gd footprint are taken into consideration. Here, the use of non-contrast-enhanced MRI, the development of new GBCAs with reduced Gd doses, the recycling of unused GBCA injection solutions, the collection of urine from patients, and advanced water treatment methods are considered potential ways for achieving this goal.[8] Based on the population of Germany (84.75 million in September 2024),[22] the MRI scan rate of 156 per 1000 inhabitants,[23] a GBCA administration rate of up to 50%, and a dosage of around 1.3 g Gd per scan,[3] a total discharge volume of up to 8.59 tons of Gd into the aquatic environment per year in Germany can be estimated. This figure excludes not only the potential disposal of leftover GBCA injection solution but also potential efforts to reduce the Gd footprint.

Due to the safety concerns about NSF, Gd retention, and the environmental Gd footprint, next-generation GBCAs are developed to reduce the Gd dose per scan while keeping its medicinal value by increasing the relaxivity.[24,25] One potential approach, conducted for gadoquatrane, is increasing the relaxivity by employing a tetrameric complex with four Gd central atoms, which stabilises the molecule and reduces the rotational motion. This results in a 2- to 3-fold higher relaxivity per Gd, allowing the reduction of Gd dose per scan by 60% to 0.04 mmol Gd per kg body weight. Also, its pharmacokinetics are the same

as already approved GBCAs.[8,25,26] Bayer has filed for approval of Gadoquatrane with the Food and Drug Administration (FDA) in June 2025.[27] Another approach is followed for gadopiclenol: the hydration number q per complex is increased from one to two by employing a heptadentate ligand, leaving two coordination sites for water molecules, which increases the relaxivity. This results in half the dose of Gd (0.05 mmol Gd per kg body weight) to provide the same or improved medicinal value.[28] Gadopiclenol is marketed as Vueway by Bracco Imaging and as Elucirem by Guerbet, both of which were approved by the FDA in 2022 (ref. 29 and 30) and by the EMA in 2023.[31,32] The ongoing safety evaluation study supports its good safety profile.[33] Although gadopiclenol is already being used for over a year, to the best of our knowledge, no analytical techniques have been developed to identify and quantify this potentially new emerging contaminant in the aquatic environment. A study conducted by Maimouni *et al.*[34] investigated gadopiclenol in the aqueous rat liver tissue extract with a speciation analysis approach and identified the formation of a stable ionic decoupled complex, but only this single GBCA was examined in the analysis.

For the already established and better-studied GBCAs, several instrumental methods for GBCA speciation analysis have been published with separations based on hydrophilic interaction liquid chromatography (HILIC) or ion chromatography (IC) of the polar or ionic analytes and elemental detection *via* inductively coupled plasma-mass spectrometry (ICP-MS). Compared to a total metal analysis with ICP-MS, species related information is obtained and provides further insight into the natural or anthropogenic origin of increased Gd concentrations.[20,35] The development of recent GBCA speciation analysis methods focused on a rapid separation and low limits of detection (LODs) to investigate trace-level contaminants. In 2015, Lindner *et al.*[36] published a method based on a zwitterionic HILIC separation coupled to ICP-MS capable of separating five GBCAs within 30 min to investigate tap water with LODs in the range of 8.9 pM to 22 pM. Birka *et al.*[37] employed HILIC-ICP-sector field-MS and achieved a separation of four GBCAs within 15 min with similar LODs. An even faster separation time of 3 min for four GBCAs was realised by Horstmann *et al.*[38] with a HILIC-ICP-MS methodology employing bandpass mass filtering to increase the sensitivity for the analysis of seawater. Recent studies also focused on fulfilling the facets of Green Analytical Chemistry, like the reduction of the use of organic solvents, which also offers additional instrumental advantages.[39] A HILIC separation solely based on aqueous eluents was published by Okabayashi *et al.*[40] with a run time of 13 min and the possibility of separating six GBCAs, which was hyphenated to ICP-MS to analyse river samples. A fully automated hyphenation of anion-exchange chromatography also only based on aqueous eluents with ICP-MS shown by Macke *et al.*[39] was able to separate five commonly administered GCBAs in 2 min and reached LODs in the range of 11 pM to 19 pM for the analysis of river water samples.

Based on a similar setup of Macke *et al.*[39] the IC-ICP-MS methodology should be expanded and validated to also include the currently emerging GBCA gadopiclenol to enable the speciation of all currently clinically relevant GBCAs in the European Union to allow monitoring of water samples. The advantages of the fully automated prepFAST IC system regarding high sample throughput, rapid analysis time, easy combination with total metal analysis, and achieving the essential facets of Green Analytical Chemistry should be utilised while improving robustness, including the selective detection and quantification of gadopiclenol, and figures of merit. The new method should be employed to investigate GBCA speciation in the densely populated Ruhr metropolitan area in Germany and its main rivers to discover if the newly emerging GBCA gadopiclenol is already present in the aquatic environment after more than one year of approval.

2 Experimental

2.1 Chemicals and consumables

Nitric acid (HNO_3, 65% (w/w), for analysis) from Thermo Fisher Scientific (Bremen, Germany) was purified with a DST 1000 acid purification system from Savillex (Eden Prairie, MN, USA), and water was doubly distilled with an Aquatron A4000D system (Barloworld Scientific, Nemours, France). Ammonia solution (25–27% (w/w), for metal trace analysis) from VWR International LLC (Radnor, PA, USA) was used.

1.0 M Gadovist® (gadobutrol, Gd-HP-DO3A) and 0.5 M Magnevist® (gadopentetate, Gd-DTPA) from Bayer Vital GmbH (Leverkusen, Germany), 0.5 M MultiHance® (gadobenate, Gd-BOPTA) and 0.5 M ProHance® (gadoteridol, Gd-BT-DO3A) from Bracco Imaging Deutschland GmbH (Constance, Germany), and 0.5 M Dotarem® (gadoterate, Gd-DOTA) and 0.5 M Elucirem™ (gadopiclenol) from Guerbet GmbH (Sulzbach, Germany) were used as GBCA species standards. Elemental ICP standards of Gd (1000 ppm, Gd_2O_3 in 2–3% HNO_3) and Rh (1000 ppm, $Rh(NO_3)_3$ in 2–3% HNO_3) from Merck KGaA (Darmstadt, Germany) and In (1000 ppm, In in 2% HNO_3) from Sigma-Aldrich (St. Louis, MO, USA) were utilised for total metal analysis and as post-column internal standards (PCIS).

Samples were stored in polyethylene bottles from VWR International LLC (Radnor, PA, USA) and filtered with hydrophilic polytetrafluoroethylene (PTFE) syringe filters (25 mm, 0.45 μm) from BGB Analytik AG (Boeckten, Switzerland) and syringes from B. Braun Melsungen SE (Melsungen, Deutschland).

2.2 Sampling

On a single day in February 2025, river water was sampled from the banks of the Ruhr, Rhine, Emscher and Lippe rivers in the Ruhr metropolitan area using a polyethylene bottle attached to a stick. Care was taken to ensure that flowing water was sampled. The bottle was rinsed three times with the sample matrix before sampling. The sample was then immediately cooled, frozen as soon as possible, and stored at −20 °C. Sampling locations and labelling are given in Fig. S1.† The exact locations and sampling times are provided in Table S1.†

2.3 Instrumentation

For the GBCA speciation analysis and Gd total metal analysis, a prepFAST IC system from Elemental Scientific Inc. (Omaha,

NE, USA) was used for sample dilution, chromatographic separation and addition of the (post-column) internal standard. More detailed explanations of the operation procedure of the prepFAST IC system were previously described by Macke *et al.*[39] The system was equipped with 1.5 mL sample and dilution loops for Gd total metal analysis and 0.5 mL loops for GBCA speciation analysis. IC separation was conducted with the Bio-Pro IEX QA column (50 × 4.6 mm) from YMC Co. (Kyoto, Japan). The prepFAST IC was hyphenated to the iCAP TQ ICP-MS system from Thermo Fisher Scientific (Bremen, Germany) with a MicroFlow PFA-ST nebuliser from Elemental Scientific. The ICP-MS system was equipped with a 2.5 mm quartz injector, nickel sampler, and nickel skimmer with a high-sensitivity insert. The instruments were controlled with their respective software, Xceleri Online 1.1.0.213 developed by Elemental Scientific and Qtegra 2.14 developed by Thermo Fisher Scientific. For all analyses, triple quadruple mode with oxygen was used to increase the selectivity and sensitivity. Dwell times of 100 ms were used. The instrument was tuned daily with the provided tune mix, and the automatic interface was tuned to reach an oxide rate below 2.5% and maximum sensitivity. General operating conditions for ICP-MS and analytes monitored for Gd total metal analysis (Section 2.4) and GBCA speciation (Section 2.5) are given in Table 1.

2.4 Gd total metal analysis by ICP-MS

For the determination of Gd total metal by ICP-MS, the previously published and validated method by Macke *et al.*[39] with slight modifications was used. Sample preparation, including filtration with a PTFE filter device and digestion by nitric acid with Rh as an internal standard, was performed accordingly. For highly concentrated samples, after filtration, solutions were diluted with water to match the calibration range and then digested. A volume of 1500 μL sample and dilution loops and a carrier flow of 300 μL min^{-1} 2% nitric acid were used. During the automatic sample dilution (2× for water samples and 4× for GBCA counter quantification), In as an internal standard was added to reach a final concentration of 500 ng L^{-1} to monitor the performance of the instrument and correct for signal drift. Analysis time was set to 60 s, and a reset time of 60 s was applied to refill the carrier syringe and rinse the system. ICP-MS parameters were set accordingly and are given in Table 1. The mass-to-charge ratios of $^{115}In^+ \rightarrow {}^{115}In^+$, $^{103}Rh^+ \rightarrow {}^{103}Rh^+$, and $^{157}Gd^+ \rightarrow {}^{157}Gd^{16}O^+$ were recorded. External calibration was conducted by automatic dilution of two mixed Gd/Rh stock standards (20 ng L^{-1} and 2000 ng L^{-1} for each element) to reach a calibration range from 0.5 ng L^{-1} to 1000 ng L^{-1} with the calibration points 0.5 ng L^{-1}, 1 ng L^{-1}, 2 ng L^{-1}, 5 ng L^{-1}, 10 ng L^{-1}, 40 ng L^{-1}, 100 ng L^{-1}, 250 ng L^{-1}, 500 ng L^{-1} and 1000 ng L^{-1}. 2% nitric acid was used as a blank, and each sample was analysed as an instrumental triplicate. To evaluate the effect of the sample filtration on the removal of particular matter, additional experiments with centrifugation were conducted. Here, GBCA standards (500 nM) and two river water samples (Lip1 and Rhi4) were centrifuged for 20 min at 5000 G with a Rotina 380R centrifuge (Hettich, Tuttlingen, Germany) and then extracted.

Table 1 ICP-MS instrument conditions for GBCA speciation with IC-ICP-MS and Gd total metal analysis with ICP-MS. Daily tuned parameters are marked (∼)

General ICP-MS conditions					
RF power [W]	1550				
Plasma gas flow rate [L min^{-1}]	14				
Auxiliary gas flow rate [L min^{-1}]	0.8				
Nebulizer gas flow rate [L min^{-1}]	∼1.2				
Sampling depth [mm]	7.0				
Spray chamber temperature [°C]	2.7				
O_2 cell gas flow rate [mL min^{-1}]	0.23				
He cell gas flow rate [mL min^{-1}]	0.8				
Dwell time [ms]	100				
ICP-MS analytes	GBCA speciation		Gd total metal		
Q1 analyte	$^{115}In^+$	$^{158}Gd^+$	$^{115}In^+$	$^{157}Gd^+$	$^{103}Rh^+$
Q3 analyte	$^{115}In^+$	$^{158}Gd^{16}O^+$	$^{115}In^+$	$^{157}Gd^{16}O^+$	$^{103}Rh^+$

2.5 GBCA speciation analysis by IC-ICP-MS

Samples were thawed and filtered with a PTFE filter device to remove particulate matter. Analysis was conducted with the filtrate. Optionally, samples were diluted manually with doubly distilled water to match the calibration range. In the prepFAST IC system, 650 μL of sample was loaded into the sample loop by a syringe pump and then automatically diluted by a factor of two (except for highly concentrated samples, which were diluted by a factor of 8–30) with doubly distilled water. The chromatographic flow rate was set to 900 μL min^{-1} to stay within the pressure limit of the used column. Injection was performed by redirecting the chromatographic flow for 6.6 s to reach an injection volume of 100 μL. Eluents were composed of nitric acid and ammonia, and ammonia was used to adjust the pH. Eluent A consisted of 1.5 mM ammonium nitrate at pH 10.5 and eluent B consisted of 150 mM ammonium nitrate at pH 9.2. The employed step gradient is given in Table 2. In in 2% nitric acid (1 μg L^{-1}) was constantly added to the chromatographic efflux with a flow rate of 100 μL min^{-1} as a PCIS to control the instrument performance and correct for potential signal drift over long instrument runtimes. Doubly distilled water was used as a blank. Each sample was analysed as an instrumental triplicate.

Table 2 Gradient and rinsing used for GBCA speciation with eluent A consisting of 1.5 mM ammonium nitrate at pH 10.5 and eluent B consisting of 150 mM ammonium nitrate at pH 9.2 at a total flow rate of 900 μL min^{-1}

Step	Time [s]	Share eluent A [%]	Share eluent B [%]
G0	0–20	100.0	0.0
G1	20–75	70.5	29.5
G2	75–120	5.5	94.5
G3	120–175	100.0	0.0
R1	270	100.0	0.0

The mass-to-charge ratios of $^{115}In^+ \rightarrow {}^{115}In^+$ and $^{158}Gd^+ \rightarrow {}^{158}Gd^{16}O^+$ were recorded. External calibration was performed on two GBCA standard mixtures in doubly distilled water (500 pM and 5000 pM), which were automatically diluted by the prepFAST IC with dilution factors from 2–100 to 5 pM, 10 pM, 16.7 pM, 25 pM, 50 pM, 100 pM, 250 pM, 500 pM, 1250 pM and 2500 pM calibration points to obtain a calibration range from 5 pM to 2500 pM for each individual GBCA. The Gd concentration of each GBCA standard was counterquantified by Gd total metal analysis with ICP-MS by acid digestion in 2% nitric acid (Section 2.4). To evaluate the used storage containers and conditions, GBCA standard mixes (100 pM, 1000 pM and 4000 pM) were stored for 18 days and analysed with the GBCA speciation methodology to determine the species recovery from the weigh-in. For quality control, two river samples (Lip1 and Rhi4) were spiked with a standard mix to reach a final concentration of 500 pM for each GBCA, and the recovery was determined by the expected concentration *via* weigh-in of the standard and the determined sample concentration. Additionally, the sample filtration was compared to centrifugation (Section 2.4) for both samples.

2.6 Data processing

Raw data were exported, and further processing was performed with Excel 2021 from Microsoft Corporation (Redmond, WA, USA) and OriginPro 2024 version 10.1.0.170 from OriginLab Corporation (Northampton, MA, USA). Chromatographic data were normalised by dividing the Gd signal with the In signal to account for signal drift of the ICP-MS. Then, a second polynomial order Savitzky–Golay filter over 10 data points was used for smoothing. Peak integration was performed after the subtraction of a blank injection. For the Gd total metal analysis, the average signal over 60 s for Gd and Rh was corrected by the average internal standard signal of In over 60 s. Rh recoveries were determined to verify the successful acid digestion. Exact concentrations after weigh-in were used for calibration and sample dilutions. External calibration functions were calculated by weighted linear calibration according to Funke *et al.*[41] to take the heteroscedasticity of the ICP-MS data into account. Errors are provided as three times the standard deviation (SD) of instrumental triplicates if not stated otherwise. LOD and LOQ were determined by the 3σ and 10σ criteria by dividing the SD of the lowest calibration point by the slope of the calibration.[42]

3 Results and discussion

3.1 Method development

Separation of the six GBCAs poses a challenging separation by ion chromatography, as not only neutral and polar GBCAs like gadopiclenol, gadoteridol, and gadobutrol but also the singly negatively charged GBCA gadoterate and even doubly negatively charged species like gadopentetate and gadobenate should be included. In particular, the efficient separation of the three neutral species with similar structures and polarity demands proficient optimisation. For this reason, a porous anion exchange column with 5 µm particles with 100 nm pore size was selected to achieve high retention and increased capacity. The high capacity additionally tackles chromatographic interferences caused by the increased matrix load of the analysed river samples and a high injection volume of 100 µL, which was chosen to increase the analyte load and therefore reduce LODs. To achieve rapid separation, a column length of 50 mm (I. D. 4.6 mm) and the maximum flow rate of 900 µL min^{-1} within the pressure limit of the column were selected. To further increase the polarity of the neutral GBCAs by potential deprotonation, an alkaline pH for the eluent was selected, as previously described by Macke *et al.*[39] Here, 1.5 mM ammonium nitrate at pH 10.5 as eluent A and 150 mM ammonium nitrate at pH 9.2 as eluent B were proficient. A three-step gradient was employed, which started with only eluent A, was increased to around 30% eluent B and ended up with almost 95% eluent B to elute all species. Additionally, after the separation, a rinse and syringe refill time of 270 s was necessary to recondition the column prior to the following injection to gain a reproducible and efficient elution

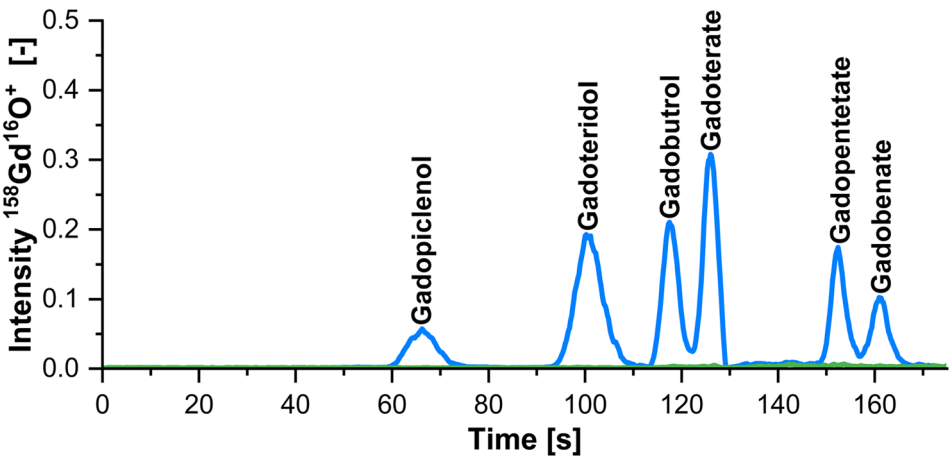

Fig. 2 IC-ICP-MS chromatogram of a 100 pM GBCA mix (blue) and a blank injection (green). $^{158}Gd^{16}O^+$ intensity is normalised with the PCIS signal. GBCAs are labelled.

of gadopiclenol and gadoteridol. Also, during the runtime starting from 120 s, the column was already rinsed with the initial conditions to further increase the potential sample throughput of the method. This had no effects on the ongoing separation due to the column's void volume and decreased sample-to-sample time by around 55 s. For monitoring the performance of the ICP-MS and potential correction of signal drift, a constant flow of In PCIS to reach a final concentration of around 100 ng L^{-1} was introduced after the chromatographic separation with an additional syringe pump. The chromatogram of a GBCA standard mix is shown in Fig. 2. Due to the PCIS correction, the intensity signal of $^{158}Gd^{16}O^{+}$ is unitless. The employed gradient resulted in a rapid and sufficient separation of all six GBCAs in 175 s. First, gadopiclenol elutes, followed by gadoteridol, then refocused peaks of gadobutrol and gadoterate, and finally the doubly negatively charged GBCAs gadopentetate and gadobenate elute in the last gradient step. The differences in peak size results from the employed gradient and the PCIS correction. The rapid separation, fully automatic sample dilution and external calibration, monitoring of the performance of the instruments with a PCIS, and an optimised sample-to-sample time of around 8 min enable high-throughput screening of several samples over long analysis run times.

3.2 Figures of merit

To monitor the performance of the instrument and potential signal drift, a PCIS was employed. For long run times, signal correction was necessary to consider the occurring signal drift of the ICP-MS instrument. All species retention times were confirmed by the injection of single species standards. External calibration was performed by automatic dilution of two GBCA standard mixes (500 pM and 5000 pM) in the range of 5 pM to 2500 pM from low to high concentration as a triplicate (1st calibration followed by 2nd calibration and 3rd calibration). Relative standard deviations (RSD) of each species retention time were primarily below 1%. The RSDs of the peak areas were mostly below 5% with higher RSDs for lower concentrated calibration points. The blank injection before the analysis was used for baseline correction by subtraction of the blank signal before integration to consider potential changes in the baseline signal. To take the heteroscedasticity of the ICP-MS data into account, weighted linear calibration was performed.[41] To describe the goodness of the fit for the weighted linear calibration, percent residual accuracy (% RA) was used, which is based on the relative error for each calibration point and takes the entire calibration range into account.[43] The determined % RA, LODs and LOQs calculated with the 3σ and 10σ criteria are provided in Table 3. In general, good fits with % RA above 90% were achieved with almost 100% for the macrocyclic GBCAs and Gd total, indicating the suitability of the calibration curve over the whole calibration range. Overall, excellent LODs in the single-digit pM concentration range were obtained. For the linear GBCAs gadopentetate and gadobenate, slightly increased LODs and decreased % RA were determined due to the higher background signal resulting from the increased gradient concentration. For samples analysed with higher dilution factors than the minimum automatic dilution factor of two, individual manual and automatic dilutions need to be considered regarding the individual sample LOD. Overall, these LODs can be considered excellent and are the lowest published so far, compared to Lindner *et al.*[36] (LODs: 8.9-22 pM), Birka *et al.*[44] (LODs: 8-14 pM), and Macke *et al.*[39] (LODs: 11-19 pM). The method for the determination of Gd total was already previously validated, and a similar LOD was achieved.[39] Additionally, the filtration for the removal of particular matter was compared with centrifugation. For the total Gd methodology, GBCA standards and two river water samples (Lip1 and Rhi4) were centrifuged and investigated. Both sample preparations resulted in comparable total Gd concentrations for all GBCA standards and the two river water samples. The same results were also determined for the GBCA speciation for both river water samples. This shows that both sample preparations were suitable, but filtration was preferred due to easier handling.

Species stability under the used storage conditions was tested by storing mixed GBCA standards for 18 days and determining species recoveries compared to the weigh-in. For all tested GBCAs and concentrations (100 pM, 1000 pM and 4000 pM), complete recoveries for macrocyclic GBCAs (≥95% for almost all tested species and concentrations) were achieved. For the linear GBCAs, incomplete recoveries were determined with increasing recoveries with higher concentrations of up to around 70% for the 4000 pM concentration. To evaluate matrix effects, two river water samples (Lip1 and Rhi4) were spiked with a GBCA mix to reach a final added concentration of 500 pM for each GBCA. For all GBCAs, no shifts in retention time occurred, allowing straightforward species assignment in river samples without additional spiking experiments. As both samples already contained the GBCAs gadoteridol, gadobutrol, and gadoterate, the determined concentrations were acknowledged, and the recovery was calculated by dividing the analysed concentration by the expected concentration from initial sample weights (including the previously determined GBCAs in the used water samples). Recoveries for the macrocyclic GBCAs were in the range from 99% ± 11% to 104.4% ± 6.8% with an average of 101.5%. For the linear GBCAs, recoveries were only around 60% with high fluctuations, indicating the influence of the river water matrix due to the increased elution power within the third gradient step. Additionally, for some of the river water samples, the background signal during the third gradient step

Table 3 Percent residual accuracy (% RA), method LOD and LOQ for GBCA speciation by IC-ICP-MS and the Gd total metal analysis by ICP-MS

Analyte	% RA [%]	LOD [pM]	LOQ [pM]
Gadopiclenol	98	2.2	7.4
Gadoteridol	99	2.1	7.1
Gadobutrol	99	3.3	10.9
Gadoterate	98	0.8	2.7
Gadopentetate	91	5.1	17.0
Gadobenate	92	5.8	19.5
Gd total	99	0.8	2.6

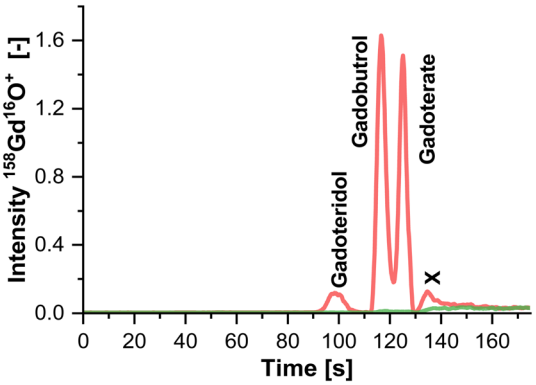

Fig. 3 IC-ICP-MS chromatogram of the sample Emr2 from the river Emscher (red) and a blank injection (green). $^{158}Gd^{16}O^+$ intensity is normalised with the PCIS. Peaks are assigned to GBCAs and an unknown species X was detected.

increased and was present over the following blank injections, potentially interfering with the detection and quantification of the linear GBCAs. For this reason, the baseline correction was performed with the blank chromatogram before each analysis. For spiked doubly distilled water samples, similar results were determined with complete recoveries for macrocyclic GBCAs and recoveries around 70% for the linear GBCAs. Overall, the limited recoveries of the linear GBCAs regarding storage stability and spiking of river water can be neglected, as the linear GBCAs lost clinical relevance due to the regulations of the European Medicine Agency in 2017.[10] Also, linear GBCAs could not be detected in any of the analysed river water samples.

Overall, good reproducibility regarding the peak area and retention time, wide calibration and linear range, excellent LODs in the single-digit pM range, analyte stability during sampling and storage, and complete recoveries for macrocyclic GBCAs in the river water matrix highlight the applicability of the developed method for the analysis of macrocyclic GBCAs in environmental water samples.

3.3 Anthropogenic GBCAs in the Ruhr metropolitan area in Germany

The developed IC-ICP-MS method for GBCA speciation in combination with the determination of Gd total metal analysis by ICP-MS was employed to investigate anthropogenic Gd and GBCAs in the rivers Rhine, Lippe, Emscher, and Ruhr in the Ruhr metropolitan area. With a total number of 95 hospitals (2019) and a high population density of 1163 persons per square kilometre (2023),[45] a significant number of MRI scans with GBCA injections, excretion into hospital and household wastewater, and efflux into the aquatic environment are expected in this area, highlighting the necessity of GBCA monitoring. To show the collected data and discuss its evaluation, Fig. 3 shows an exemplary chromatogram of the sample Emr2 from the Emscher River.

In the chromatogram, four peaks can be identified, three of which can be assigned to the GBCAs gadoteridol, gadobutrol, and gadoterate based on their retention time. The fourth peak detected at the retention time of 135 s does not match the retention time of one of the GBCA species standards and is therefore labelled as an unknown Gd species and is referred to as X. Due to the sole species identification based on the chromatographic retention time and elemental detection by ICP-MS, no further molecular information about the unknown species X can be obtained. All peaks were integrated with a prior blank injection as a baseline correction and quantified by the species-specific calibration functions. For the unknown species X, quantification was performed with the calibration function of gadoterate, as a similar response to Gd can be expected in the ICP. In general, the signal response is element-specific under similar ICP conditions within a single gradient step. This allows the elemental quantification, while no molecular information can be achieved. For all samples, no notable shifts in retention time were observed for the determined GBCAs, showing the robustness of the developed method regarding the river water

Table 4 GBCA and Gd-total concentrations of all sampling sites with retention times for all detected species. Gd recovery was determined as the fraction of total GBCAs from Gd total. The unknown species X was quantified with a species-unspecific calibration with the calibration function of gadoterate. Errors are given as the three-fold SD of the triplicate analysis of each sample

	Concentration [nM]						
Sample	Gadoteridol	Gadobutrol	Gadoterate	X	ΣTotal GBCAs		
RT [s]	102	118	126	135	—	Total Gd	Recovery GBCA total from Gd total
Lip1	0.008 ± 0.002	0.030 ± 0.001	0.158 ± 0.012	<LOD	0.196 ± 0.015	0.198 ± 0.006	99%
Lip2	<LOD	164.4 ± 8.2	127.9 ± 4.3	7.7 ± 1.3	300 ± 14	262.82 ± 0.64	114%
Lip3	<LOD	21.80 ± 0.37	18.6 ± 1.6	0.95 ± 0.15	41.3 ± 2.1	34.88 ± 0.26	118%
Lip4	<LOD	10.41 ± 0.26	9.79 ± 0.47	0.472 ± 0.048	20.67 ± 0.77	18.32 ± 0.46	113%
Emr1	0.009 ± 0.005	0.252 ± 0.018	1.402 ± 0.095	<LOD	1.66 ± 0.12	1.787 ± 0.005	93%
Emr2	0.149 ± 0.009	1.686 ± 0.035	1.051 ± 0.050	0.152 ± 0.025	3.04 ± 0.12	3.386 ± 0.038	90%
Ruh1	0.015 ± 0.002	0.035 ± 0.003	0.235 ± 0.023	<LOD	0.285 ± 0.028	0.296 ± 0.012	96%
Ruh2	0.045 ± 0.003	0.018 ± 0.012	0.437 ± 0.052	<LOD	0.500 ± 0.067	0.568 ± 0.009	88%
Rhi1	0.018 ± 0.001	0.057 ± 0.010	0.112 ± 0.006	<LOD	0.188 ± 0.016	0.210 ± 0.006	89%
Rhi2	0.019 ± 0.005	0.054 ± 0.005	0.120 ± 0.010	<LOD	0.192 ± 0.020	0.215 ± 0.001	89%
Rhi3	0.018 ± 0.002	0.056 ± 0.008	0.118 ± 0.012	<LOD	0.192 ± 0.022	0.212 ± 0.007	91%
Rhi4	0.018 ± 0.001	0.055 ± 0.006	0.113 ± 0.013	<LOD	0.186 ± 0.020	0.215 ± 0.005	87%

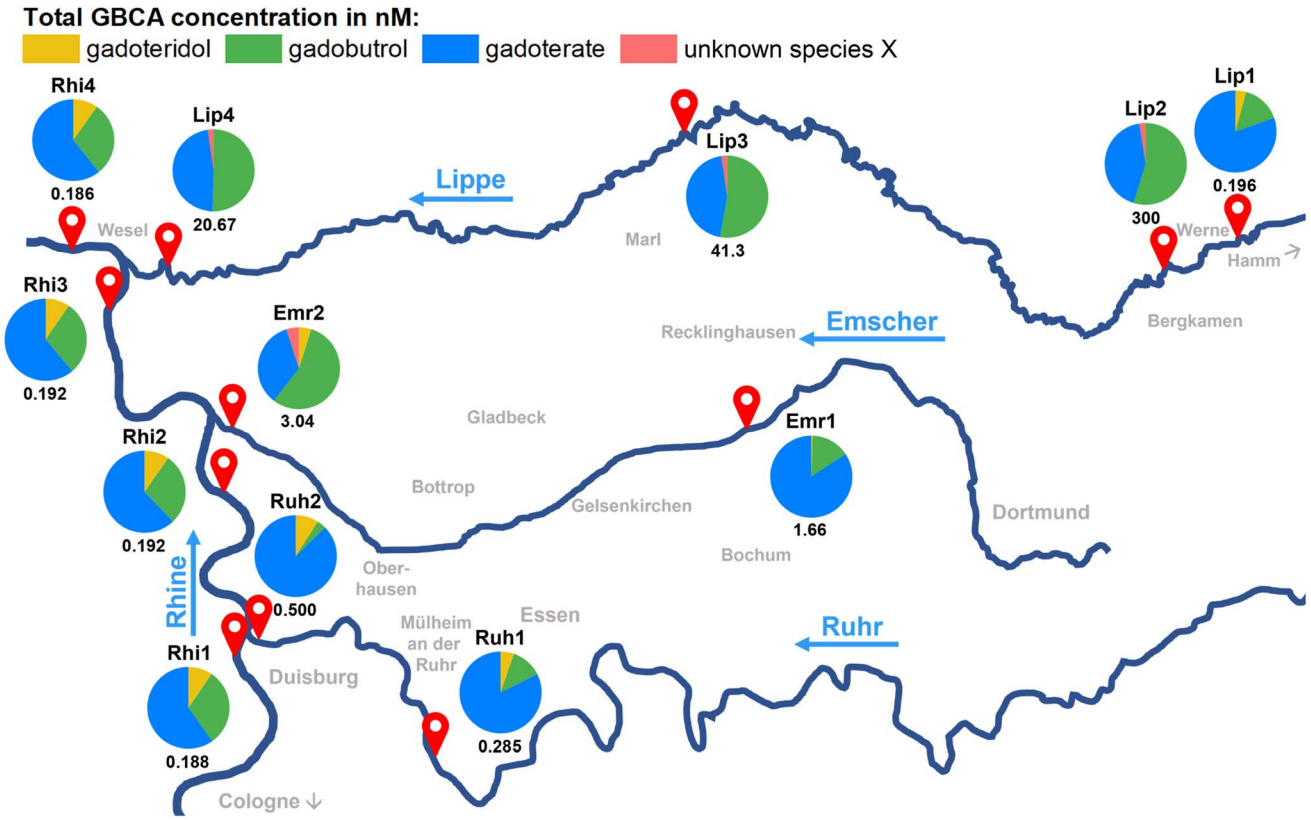

Fig. 4 Schematic river course of the sampled rivers, sampling points and major cities. For each sampling point, the total GBCA concentration in nM is given, and the GBCA speciation is shown by a pie chart. Gadoteridol is shown in yellow, gadobutrol in green, gadoterate in blue and the unknown species X in red. Side branches of the rivers, lakes, canals, and further rivers are not shown. A detailed map is given in the Fig. S1.† Map data are from https://Mapcreator.io and openstreetmap (https://openstreetmap.org/copyright).

matrices. A detailed discussion about the potential origin of the unknown species X is provided below.

The determined concentrations for different GBCA species, total GBCAs and Gd total with the recovery of the total GBCAs from the Gd total for all samples are given in Table 4. Fig. 4 shows the sampling locations and schematics of the courses of the sampled rivers Lippe (Lip), Emscher (Emr), Ruhr (Ruh) and Rhine (Rhi). The total GBCA concentrations and their corresponding GBCA speciation (distribution of each species) are given. Exact sampling locations and a detailed map are given in Table S1 and Fig. S1.†

Overall, the GBCAs gadoteridol, gadobutrol, and gadoterate were detected and quantified in the analysed river water samples. Additionally, the unknown Gd species X with a retention time of around 135 s was detected in four samples. Linear GBCAs were not detected, which is most likely due to the updated regulations by the EMA since 2017, limiting their use to special occasions[10] and therefore limited market share and consecutive discharge into the aquatic environment. The new GBCA gadopiclenol could not be detected in any of the analysed samples. Although this GBCA has been approved for over a year, it might not yet be used by hospitals and MRI specialists in the region and therefore is not discharged into the aquatic environment or its concentration does not reach its LOD. Another possibility might be sufficient elimination of gadopiclenol or limited stability during wastewater treatment, causing potential transformation or decomposition. However, the developed method has the capability to further monitor the aquatic environment to potentially detect gadopiclenol caused by future discharges and to analyse its environmental fate. Regarding the origin of the unknown species X, only assumptions can be made, as no molecular structure can be assigned. Previous studies also found the occurrence of unidentified Gd species.[39,40] A potential transformation of a GBCA might occur due to metabolism, environmental decomposition or advanced wastewater treatment. Also, the discharge of an unknown GBCA species in development or the re-complexation of free Gd^{3+} might be possible.

The Gd total is in general agreement with the GBCA total, considering an error margin for the direct comparison of both methods. Recoveries of the total GBCA from the total Gd are in the range of 87% to 118% with an average of 97%. To evaluate the method equivalence for the analysed samples, a two-sided paired sample *t*-test was conducted, which confirmed the method comparability at the 5% significance level with a *p*-value of 0.247. Internal standard recoveries of Rh for the digestion are in the range of 93.0% to 96.4% with an average of 94.5%, indicating a successful digestion and sample preparation. In particular, for highly concentrated samples, the additional manual dilution before the digestion might have caused

increased divergences. In the following discussion, the total GBCA concentrations based on the sum of all quantifiable GBCA species and the individual GBCA concentrations and their percentual share will be discussed. Detailed positions and data regarding catchment area and served hospitals of municipal and industrial WWTPs and their discharge points into the aquatic environment were collected from the ELWAS-WEB tool provided by the state office for the Environment, Nature Conservation and Transport North Rhine-Westphalia, Germany (LANUV).[46] Additionally, their routine monitoring includes the determination of total Gd in filtered and unfiltered river water samples with acid digestion and ICP-MS (based on DIN EN ISO 17294-2: Jan 2017) for several years and provides comparison data to confirm the total Gd concentration range.[46] The exact locations of the sampling points used for comparison are given in Table S1.†

The river Lippe is contaminated with GBCAs at all sampling points with concentrations of up to 300 nM total GBCAs and changing speciations. At the sampling point Lip1, gadoterate is the main species and a total GBCA contamination of 0.196 nM was detected. This contamination most likely originates from upstream discharges of the WWTPs from the major cities Hamm, Lippstadt, and Paderborn. The total GBCA concentration at Lip2 drastically increases to 300 nM with a different speciation. Here, gadobutrol with 55% is the main species, followed by gadoterate with 43% and the unknown species X with 3%. Following the river downstream to Lip3 and Lip4, a similar GBCA speciation is detected, while the total GBCA concentration decreases to 41.3 nM and then to 20.67 nM. These detected concentrations can be considered extremely high compared to previously found GBCA and Gd concentrations in surface waters with maximum single-digit nM concentrations.[12,15–18] The same speciation with a decreasing concentration shows that dilution of the GBCAs is relevant, and no other significant discharge sources alter the GBCA speciation in the Lippe downstream from the sampling point Lip2. For this reason, the main discharge of GBCAs into the Lippe must be located between Lip1 and Lip2. Potential dischargers in this area are four discharge points of industrial WWTPs and the discharge of the WWTP of the town of Werne. The WWTP Werne includes Bergkamen and several smaller urban areas in the region and serves a single hospital located in Werne. The industrial dischargers include the production site of GBCAs, which might be corresponding to the increased concentration and the occurrence of the unknown species X as a potential production backlog or a new GBCA in development. The appearance of the unknown species could also be related to the previously discussed origins. These speculations cannot be further confirmed, and it has to be noted that, as no molecular conformation can be given, the detected and assigned signals of gadobutrol and gadoterate also might originate from different unknown Gd species with the same retention time on the used IC column. The overall high concentrations of Gd in the Lippe can be confirmed by the water monitoring data from the LANUV, which has been collected periodically for several years. One of their sampling locations (number 6002) is located next to the sampling point Lip4 and can be used as a comparison for that point and the general Gd concentration range in the Lippe. During the time period from 2020 to 2024, a total of 56 samples were taken, and the total Gd in the filtered fraction was analysed. An average of 37.3 nM Gd with an RSD of 85% in the range of 1.5 nM (16.10.2024) to 197.1 nM (12.10.2022) was detected. No direct comparison can be done as the most recent published sample date is 11 December 2024, but the concentration range with high fluctuations matches the detected Gd total concentrations for the Lippe samples, thus confirming the high Gd concentrations in the Lippe. The substantial and highly fluctuating concentrations highlight the necessity of monitoring the GBCA speciation.

The Emscher River springs in the southwest of Dortmund and shows a total GBCA concentration of 1.66 nM at Emr1, mostly consisting of 84% gadoterate, followed by 14% gadobutrol, and then 1% gadoteridol. These anthropogenic GBCAs mostly originate from the only major WWTP in the upstream region, discharging into the Emscher located in Dortmund Deusen, showcasing the mainly used GBCAs by clinics in the catchment area of the WWTP. At Emr2, the total GBCA concentration increases to about 3 nM with a different speciation. Here, gadobutrol is the main GBCA with 56%, followed by gadoteridol with 35%, and gadoterate and the unknown species X both with 5%. Between Emr1 and Emr2, several dischargers of GBCAs are present with major parts being the cities Essen, Bottrop, Gelsenkirchen, Gladbeck, Herne, Recklinghausen, and Bochum and smaller discharges from villages and small cities. The different GBCA speciation highlights the main use of gadobutrol in clinics in this region served by the WWTP Emschermündung located close to Emr2 and the WWTP Bottrop, especially as the absolute concentration of gadoterate decreases compared to Emr1. In particular, at this sampling point, the occurrence of the unknown species X might be linked to the potential use of the GBCA gadoquatrane in previous phase three clinical studies at the Essen University Hospital (Bayer clinical trial identifier 21 181 and 21 197 (ref. 47)) but cannot be confirmed due to limited species information. The unknown species could also have different origins, as previously discussed. The data match the total Gd data concentration range from the LANUV sampling point number 5009 located at the river mouth of the Emscher close to the sampling point Emr2, where an average Gd concentration of 2.53 nM with an RSD of 42% was determined in 59 samples from 2020 to 2025.[46]

The Ruhr at Ruh1 shows anthropogenic GBCAs with a total concentration of 0.285 nM, mainly consisting of gadoterate with 82%, then gadobutrol with 12%, and gadoteridol with 5% from upstream sources, including parts of Essen and several smaller cities and regions. Ruh2 is located directly downstream of the discharge of the WWTP Duisburg-Kaßlerfeld, responsible for major parts of Duisburg, Oberhausen, and Mülheim an der Ruhr and is the only discharge point between Ruh1 and Ruh2. Overall, the total GBCA concentration increases up to around 0.5 nM with a higher share of gadoterate at 88%. The decrease in the absolute concentration of gadobutrol indicates further dilution and no major discharge of this GBCA in this area, making gadoterate the most frequently used GBCA in this area. The data also match the total Gd data concentration range from

the LANUV sampling point number 22810 located in between Ruh1 and Ruh2, where an average Gd concentration of 0.37 nM with an RSD of 50% was determined in 56 samples from 2021 to 2025.[46]

All previously discussed rivers influx in the Rhine, which was sampled prior to and after each corresponding river mouth. At sampling point Rhi1, upriver GBCA contamination with a total concentration of around 0.19 nM with gadoteridol, gadobutrol, and gadoterate was detected, where gadoterate is the major part with 60%, followed by gadobutrol with 31%, and gadoteridol with 10%. These GBCA discharges might originate from the Düsseldorf or Cologne regions or even from the German federal states Hesse, Rhineland-Palatinate, and Baden-Württemberg, or from the nations France, Switzerland, and Austria, highlighting the vast catchment area of the Rhine. Rhi2 shows a similar GBCA concentration with the same GBCA speciation, demonstrating that the inflow of the Ruhr with a different GBCA distribution and a higher total GBCA concentration has no notable effect on the GBCA speciation in the Rhine. This effect might be due to the negligible total water volume of the Ruhr compared to the Rhine, causing a strong dilution of the Ruhr water, making the different GBCA speciation perish. Additionally, limited mixing of the Ruhr and Rhine water might occur, although this effect cannot be counteracted by GBCA speciation in the following Rhine sampling locations. Rhi3 and Rhi4 also show the same GBCA speciation, showing that the inflow of the Emscher and Lippe (both with different GBCA speciations) do not affect the GBCA speciation in the Rhine noticeably. In particular, for the Lippe, the high total GBCA concentration of above 20 nM shows no increase of the GBCA concentration in the Rhine. Here, it has to be noted that sampling was conducted on the opposing site from the inflow of the Lippe in the Rhine with only a downstream distance of roughly 4 km. For this reason, limited mixing might have occurred. Overall, no effects of the influx of the rivers Ruhr, Emscher, and Lippe could be observed. The data also match with the total Gd data concentration range from the LANUV sampling point number 449 located between Rhi2 and Rhi3, where an average Gd concentration of 0.33 nM with an RSD of 22% was determined in 8 samples from 2020 to 2025.[46]

Certain parts of the area were already previously sampled and analysed using GBCA speciation analysis by Birka *et al.*[44] in October 2014, focusing on the effect of drinking water purification from surface waters on the GBCA concentration. Here, the GBCAs gadoterate, gadopentetate, and gadobutrol have already been detected in surface waters used by a waterwork at a catchment lake near the Lippe and by several waterworks on the Ruhr with concentrations of around 88–262 pM for the total GBCAs. The main GBCA in all samples was gadopentetate with concentrations from 88 to 161 pM. Additionally, gadobutrol (<8–49 pM) and gadoterate (<11–85 pM) were detected. In comparison to these data, the recent changes in the GBCA development and regulations were reflected, as no linear GBCAs were detected anymore, while concentrations were in the same range compared to Ruh1 in the Ruhr River, showing a similar total use and discharge behaviour.

These findings highlight the necessity of Gd and GBCA monitoring in water bodies, as changes in the GBCA speciation have happened and are likely going to happen in the future due to the expected approval and increase in the use of newly developed GBCAs. Also, the detected concentrations in the Lippe severely exceed the prior findings and might have unforeseen ecotoxicological and environmental impacts. For this reason, future studies should focus on the identification of potentially found unknown species and inclusion of gadoquatrane in the chromatographic separation, once it is available as an injection solution to use as an analytical standard. In particular, regarding its expected approval, gadoquatrane might be of clinical and environmental relevance. Additionally, the excellent LODs and high matrix robustness of the developed method should allow the employment of the developed method for the analysis of drinking water and stability experiments of different GBCAs under different clinically and environmentally relevant conditions.

4 Conclusion

A fast, sensitive, robust, and automated hyphenation of anion exchange chromatography to ICP-MS was developed to allow the GBCA speciation analysis of six clinically relevant GBCAs in the European Union, including the recently approved GBCA gadopiclenol, which shows higher efficiency, a reduced Gd dose and is likely to gain increasing market share. The rapid chromatographic separation within 175 s and the fully automated sample uptake, dilution, and external calibration enable high-throughput screening and monitoring. Excellent LODs in the single-digit pM concentration range were achieved, allowing the trace contaminant analysis for a wide concentration and sample range. The method shows good robustness regarding the matrix effects of the analysed river water samples. Species assignment is straightforward, as there is no retention time shift, and complete recoveries of the macrocyclic GBCAs were achieved.

Using the developed method, river water samples from the Ruhr metropolitan area with a high population and hospital density were analysed regarding their total Gd concentration and GBCA speciation to gain further insights into the discharge of GBCAs into the aquatic environment. For all samples, almost quantitative total GBCA recoveries were achieved, indicating the stability of the GBCAs in the river water. Overall, the GBCAs gadoteridol, gadobutrol and gadoterate were detected. Changing GBCA speciations across a river course showed different discharge profiles from corresponding WWTPs and their served cities and hospitals and allowed tracing of the origin of the individual contaminants. Additionally, an unknown species X was detected, which could not be identified further but might be a GBCA under development, a potential transformation product of a GBCA under development, or a potential transformation product due to advanced water treatment or metabolic activity. Compared to previously published GBCA concentrations, extremely high total GBCA concentrations of up to 300 nM total GBCAs were found in the river Lippe. The Emscher River and Ruhr River showed increasing total GBCA concentrations over their river courses in

the range of 0.285 nM to 3.04 nM with differences in their speciation throughout the river, highlighting their different contaminated inflows. The largest river, the Rhine, where all the other rivers enter, showed a constant total GBCA concentration of about 0.19 nM and no change in its GBCA speciation due to its larger absolute water flow. These findings could be further confirmed by regularly determined Gd total metal data from the LANUV state authorities.

The detected high GBCA concentrations highlight the necessity of ongoing monitoring of the GBCA speciation in the aquatic environment. Although no gadopiclenol could be detected in the analysed river samples, the developed method shows further potential for monitoring the behaviour of this potentially newly emerging aquatic contaminant. In addition, for gadopiclenol and other clinically relevant GBCAs, speciation analysis could be conducted for stability testing, getting insights into potential transformation and metabolism, or potential tissue retention.

Data availability

Data will be made available upon reasonable request.

Author contributions

Mathis Athmer: conceptualisation, methodology, formal analysis, validation, investigation, writing – original draft, visualisation, project administration. Lina Marotz: methodology, formal analysis, validation, investigation, writing – review & editing. Uwe Karst: conceptualisation, methodology, validation, resources, writing – review & editing, supervision.

Conflicts of interest

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

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References

1 N. Iyad, M. S. Ahmad, S. G. Alkhatib and M. Hjouj, *Eur. J. Radiol. Open.*, 2023, **11**, 100503.
2 J. Lohrke, T. Frenzel, J. Endrikat, F. C. Alves, T. M. Grist, M. Law, J. M. Lee, T. Leiner, K. C. Li, K. Nikolaou, M. R. Prince, H. H. Schild, J. C. Weinreb, K. Yoshikawa and H. Pietsch, *Adv. Ther.*, 2016, **33**, 1–28.
3 H. S. Thomsen, *Acta Radiol.*, 2017, **58**, 259–263.
4 S. P. Lin and J. J. Brown, *J. Magn. Reson. Imaging*, 2007, **25**, 884–899.
5 Z. Zhang, S. Nair and T. McMurry, *Curr. Med. Chem.*, 2005, **12**, 751–778.
6 P. Caravan, J. J. Ellison, T. J. McMurry and R. B. Lauffer, *Chem. Rev.*, 1999, **99**, 2293–2352.
7 E. Kanal, *Magn. Reson. Imaging*, 2016, **34**, 1341–1345.
8 M. Bendszus, A. Laghi, J. Munuera, L. N. Tanenbaum, B. Taouli and H. C. Thoeny, *J. Magn. Reson. Imaging*, 2024, **60**, 1774–1785.
9 A. J. van der Molen, C. C. Quattrocchi, C. A. Mallio and I. A. Dekkers, *Eur. Radiol.*, 2024, **34**, 600–611.
10 European Medicines Agency, EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans, **https://www.ema.europa.eu/en/medicines/human/referrals/gadolinium-containing-contrast-agents**, accessed 28 March 2025.
11 I. E. Oluwasola, A. L. Ahmad, N. F. Shoparwe and S. Ismail, *J. Contam. Hydrol.*, 2022, **250**, 104057.
12 J. Rogowska, E. Olkowska, W. Ratajczyk and L. Wolska, *Environ. Toxicol. Chem.*, 2018, **37**, 1523–1534.
13 M. Liu, *J. Magn. Reson. Imaging*, 2021, **53**, 1295–1299.
14 L. Telgmann, C. A. Wehe, M. Birka, J. Künnemeyer, S. Nowak, M. Sperling and U. Karst, *Environ. Sci. Technol.*, 2012, **46**, 11929–11936.
15 P. Ebrahimi and M. Barbieri, *Geosciences*, 2019, **9**, 93.
16 I. Lim, C. Sun, J.-H. Lee, J. Kim, S. Lee, H. Sim, H.-M. Cho, J.-S. Ryu and T. Kim, *Estuarine, Coastal Shelf Sci.*, 2023, **288**, 108359.
17 S. Ma, G. Han, Y. Yang and X. Li, *Aquat. Ecol.*, 2023, **57**, 765–781.
18 P. Louis, D. A. L. Vignati, S. Pontvianne and M. N. Pons, *Sci. Total Environ.*, 2023, **892**, 1–11.
19 M. Le Fur and P. Caravan, *Metallomics*, 2019, **11**, 240–254.
20 R. E. Lenkinski and N. M. Rofsky, *Radiology*, 2024, **311**, 1–10.
21 I. A. Wysocka, A. M. Rogowska and P. Kostrz-Sikora, *Environ. Pollut.*, 2023, **323**, 121289.
22 Statistisches Bundesamt (Destatis), Bevölkerung nach Nationalität und Geschlecht 2024 30.09, 2024, **https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Bevoelkerungsstand/Tabellen/liste-zensus-geschlecht-staatsangehoerigkeit.html#651186**, accessed 25 March 2025.
23 OECD, Magnetic resonance imaging (MRI) exams (indicator), 2022, **https://data.oecd.org/healthcare/magnetic-resonance-imaging-mri-exams.htm**.
24 E. Lancelot, J. S. Raynaud and P. Desché, *Invest. Radiol.*, 2020, **55**, 578–588.
25 V. M. Runge and J. T. Heverhagen, *Invest. Radiol.*, 2024, **59**, 105–107.
26 B. M. Hofmann, K. Riecke, S. Klein, M. Berse, A. Rottmann, G. Sutter and W. Ebert, *Invest. Radiol.*, 2024, **59**, 140–149.
27 A. G. Bayer, Bayer files for approval of gadoquatrane in the U.S., **https://www.bayer.com/media/en-us/bayer-files-for-approval-of-gadoquatrane-in-the-us/**, accessed 02 July 2025.
28 E. Alsogati, H. Ghandourah and A. Bakhsh, *Cureus*, 2023, **15**, e43055.
29 Guerbet, Guerbet announces U.S. Food and Drug Administration (FDA) approval of EluciremTM

(Gadopiclenol), https://www.guerbet.com/news/guerbet-announces-u-s-food-and-drug-administration-fda-approval-of-elucirem-gadopiclenol, accessed 26 March 2025.
30 Bracco Imaging, FDA approves Gadopiclenol injection for the U.S. market, https://www.bracco.com/article/fda-approves-gadopiclenol-injection-us-market, accessed 25 March 2025.
31 Bracco Imaging, The EC granted Marketing Authorisation for Vueway® (gadopiclenol) in the European Union, https://www.bracco.com/de-de/article/ec-granted-marketing-authorisation-vuewayr-gadopiclenol-european-union, accessed 25 March 2025.
32 Guerbet, Guerbet announces marketing authorisation approval of EluciremTM (Gadopiclenol) in the European Union, https://www.guerbet.com/news/guerbet-announces-marketing-authorisation-approval-of-elucirem-gadopiclenol-in-the-european-union, accessed 25 March 2025.
33 A. Spinazzi, E. Lancelot, L. Vitali, C. Cot, G. Pirovano, A. Joseph, M. A. Kirchin, E. Darmon-Kern and P. Bourrinet, *Invest. Radiol.*, 2024, **60**, 423–427.
34 I. Maimouni, C. Henoumont, M.-C. De Goltstein, J.-F. Mayer, A. Dehimi, Y. Boubeguira, C. Kattenbeck, T. J. Maas, N. Decout, I. Strzeminska, G. Bazin, C. Medina, C. Factor, O. Rousseaux, U. Karst, S. Laurent and S. Catoen, *Invest. Radiol.*, 2025, **60**, 234–243.
35 D. Clases, M. Sperling and U. Karst, *TrAC, Trends Anal. Chem.*, 2018, **104**, 135–147.
36 U. Lindner, J. Lingott, S. Richter, W. Jiang, N. Jakubowski and U. Panne, *Anal. Bioanal. Chem.*, 2015, **407**, 2415–2422.
37 L. Telgmann, C. A. Wehe, M. Birka, J. Künnemeyer, S. Nowak, M. Sperling and U. Karst, *Environ. Sci. Technol.*, 2012, **46**, 11929–11936.
38 M. Horstmann, R. Gonzalez De Vega, D. P. Bishop, U. Karst, P. A. Doble and D. Clases, *J. Anal. At. Spectrom.*, 2021, **36**, 767–775.
39 M. Macke, C. D. Quarles, M. Sperling and U. Karst, *Water Res.*, 2021, **207**, 117836.
40 S. Okabayashi, L. Kawane, N. Y. Mrabawani, T. Iwai, T. Narukawa, M. Tsuboi and K. Chiba, *Talanta*, 2021, **222**, 121531.
41 S. K. I. Funke, M. Sperling and U. Karst, *Anal. Chem.*, 2021, **93**, 15720–15727.
42 L. C. Rodríguez, A. M. G. Campaña, C. J. Linares and M. R. Ceba, *Anal. Lett.*, 1993, **26**, 1243–1258.
43 B. A. Logue and E. Manandhar, *Talanta*, 2018, **189**, 527–533.
44 M. Birka, C. A. Wehe, O. Hachmöller, M. Sperling and U. Karst, *J. Chromatogr. A*, 2016, **1440**, 105–111.
45 Regionalverband Ruhr, Statistikportal Ruhr, www.statistikportal.ruhr, accessed 25 March 2025.
46 LANUV NRW, ELWAS-WEB water data, https://www.elwasweb.nrw.de/, accessed 25 March 2025.
47 Bayer AG, Bayer Clinical Trials Explorer Identifier 21197 and 21181, https://clinicaltrials.bayer.com/de, accessed 25 March 2025.