



Closing the gap: Ion chromatography coupled to high-resolution mass spectrometry to trace highly polar anionic substances in groundwater

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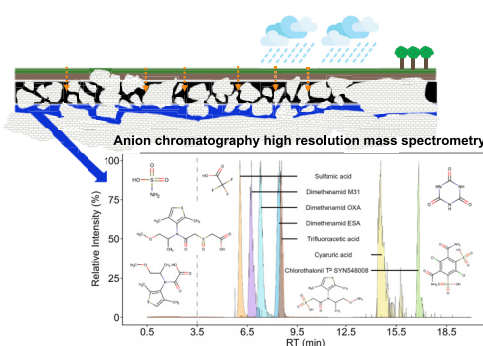
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HIGHLIGHTS

- An IC-HRMS/MS method was developed including a sample clean-up and enrichment step.
- The median matrix LOQ was 30 ng/L for 64 analytes in groundwater.
- Twelve compounds were found in concentrations higher than their matrix LOQ.
- To the author's knowledge, two were found for the first time in groundwater.
- IC-HRMS/MS was identified as a complementary method to RPLC-HRMS/MS.

GRAPHICAL ABSTRACT



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ABSTRACT

Persistent, mobile and toxic (PMT), and very persistent and very mobile (vPvM) substances pose a threat to the water cycle but are often not covered in conventional environmental monitoring programs. Within this realm of substances, one compound class of concern are pesticides and their transformation products as they are deliberately introduced into the environment. To detect very polar anionic substances, including many pesticide transformation products with log D_{OW} values ranging between -7.4 and 2.2 , an ion chromatography high-resolution mass spectrometry method was developed in this study. Since inorganic anions, such as chloride and sulfate, interfere with the analysis of organic species, their removal via precipitation with Ba/Ag/H cartridges was assessed. To improve LOQs, vacuum-assisted evaporative concentration (VEC) was evaluated. By using VEC and removing inorganic salt ions, the median LOQ improved from 100 ng/L in evian® water without sample treatment to 10 ng/L after enrichment and 30 ng/L in karst groundwater. Using this method, twelve out of 64 substances covered by the final method were found in karst groundwater in concentrations of up to 5600 ng/L, and seven exceeded 100 ng/L. To the authors' knowledge, the dimethenamid TP M31 and chlorothalonil TP SYN548008 were detected for the first time in groundwater samples. The coupling to a high-resolution mass spectrometer also allows for non-target screening and hence, this method presents a powerful tool to tackle PMT/vPvM substances.

1. Introduction

Anthropogenic, organic contaminants are ubiquitously present in the environment. Especially, compounds that can be transported away from their point of emission can be of concern. To threaten water quality, such compounds need to be **Persistent** (they are not readily degraded in the environment), **Mobile** (they are hydrophilic) and **Toxic** (PMT). Moreover,

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compounds that are prone to remain in the water cycle for a long time, are referred to as very Persistent and very Mobile (vPvM, (Neumann and Schliebner, 2017)). Analytical methods for these chemicals have not yet reached their full potential so it was proposed that many PMT substances have escaped monitoring programs until now (Reemtsma et al., 2016). Consequently, the advancement of such analytical methods and monitoring tools was identified as a top priority (Hale et al., 2022). To generate a list of vPvM/PMT compounds that are currently found in the environment, the German Environmental Agency conducted an extensive literature review (Neumann and Schliebner, 2019). Due to the extension of appropriate analytical methods in recent years, an increasing number of vPvM/PMT substances are currently being discovered in environmental compartments and even in drinking water production (Freeling et al., 2020b; Kolkman et al., 2021; Scheurer et al., 2017). These substances include for example trifluoroacetic acid (TFA) – which does not readily degrade in the environment and therefore accumulates (Scheurer et al., 2017) – and cyanuric acid, a transformation product (TP) of melamine (Neuwald et al., 2022) that was recently added to the European candidate list of substances of very high concern (ECHA, 2023).

Besides industrial and pharmaceutical chemicals that are emitted to wastewater, and if persistent further to surface water, pesticides are of high concern. Pesticides are emitted to the environment intentionally and are inherently designed to be harmful. After application, they can be mobilized by precipitation and either be transported via surface flow to reach surface waters or infiltrate and reach groundwater. Here, karst aquifers are of special concern, as they exhibit inherently high flow velocities and therefore fast transport of contaminants like pesticides and their TPs. As a proxy for mobility i.e. the tendency of substances to adsorb to soil or to dissolve in water, the partitioning coefficient between organic carbon and water (K_{OC}) is used in the regulatory context (Neumann and Schliebner, 2017). As experimental K_{OC} values are often not available, partitioning between octanol and water (K_{OW}) or corrected for the neutral fraction at a given pH, D_{OW} is used as a simplified proxy. Rather hydrophobic compounds (e.g. chlorothalonil; $\log K_{OC}$: 3.4; (Lewis et al., 2016)) tend to adsorb to the soil matrix and do not leach to groundwater but can be stored in the soil for a long time after their application. They can undergo transformation processes where often carboxyl, hydroxyl or sulfonic acid groups are introduced and the resulting transformation products (TPs) are rather hydrophilic and often anionic (Boxall et al., 2004). Continuous leaching of such TPs to groundwater is often observed. Accordingly, groundwater monitoring of pesticide TPs has revealed higher concentrations of TPs compared to their parent compounds (Kiefer et al., 2019; Kolpin et al., 2004; Reemtsma et al., 2016). Some of these TPs are compatible with reversed-phase liquid chromatography (RPLC) but others fall into the analytical gap, defined by Reemtsma et al. (2016), such as the very polar and anionic chlorothalonil TP SYN548008.

The current status of the analysis of very polar and ionic substances was summarized by Knoll et al. (2020) and Zahn et al. (2020). Major limitations in the analysis of very polar and ionic compounds are the sample preparation and chromatographic separation because such compounds do not retard well on C18 or polymeric materials such as HLB, often used for enrichment and separation in environmental analysis (Zahn et al., 2020). Instead of sample preparation, direct injection is more and more used due to increasingly sensitive mass spectrometers. Still, limits of quantification (LOQ) needed for drinking water analysis are often difficult to reach. Alternatively, vacuum-assisted evaporation or lyophilization have been demonstrated as non-selective enrichment methods (Köke et al., 2018; Mechelke et al., 2019; Montes et al., 2017). To overcome the issue of enriching unwanted matrix components in non-selective enrichment, it was proposed to extract and derivatize polar and/or zwitterionic substances via 9-fluorenylmethylchloroformate-derivatization, to subsequently enrich via solid phase extraction (SPE) and then to separate on a RPLC column (Hanke et al., 2008; Pérez-Mayán et al., 2022). However, this procedure is very selective for aminomethylphosphonic acid (AMPA) and glyphosate. In Pérez-Mayán et al. (2022), the direct injection of AMPA and glyphosate on a strong anionic exchange column did not yield sufficiently sensitive

LOQs (2800 ng/L and 1400 ng/L, respectively). Regarding chromatography, Zahn et al. (2020) concluded that a wide range of methods is available, yet sparsely used. These include e.g. hydrophilic interaction liquid chromatography (Kolkman et al., 2021; Neuwald et al., 2022), supercritical fluid chromatography (Schulze et al., 2019) or ion chromatography (IC) (Scheurer et al., 2017). Kolkman et al. (2021) reported analytes with acidic moieties (anions) to elute very early using HILIC (1.69–2.10 min). Additionally, Zahn et al. (2020) found that >75 % of the prioritized REACH data set (Arp et al., 2017) was ionic or ionizable between pH 4 and 10. Hence, anion chromatography is a more suitable separation method for many vPvM/PMT compounds including TPs, designed to retard them on an anion exchange column. Especially, the high pH value prevailing during elution in anion chromatography favors speciation towards anions. Ion chromatography has been used most frequently to analyze inorganic ions, and for example small organic acids (Bruzzoniti et al., 2019), but was also applied for the analysis of very polar anionic contaminants (Adams et al., 2017; Bauer et al., 2018; Gasparini et al., 2020; Kurz et al., 2017; Melton et al., 2019). In these studies, however, the number of analyzed compounds only ranged from 4 to 13 and mostly, tandem mass spectrometry was used. According to document N° SANTE/12682/2019 (2019) for low-resolution mass spectrometry, two mass transitions are needed for unambiguous identification while one precursor and one product ion are sufficient in HRMS/MS. This shows the advantage of high-resolution mass spectrometry, especially for small molecules where the number of available fragments might be limited. Additionally, retrospective targeted and non-targeted screenings are capable of extending the knowledge on PMT substances (Rüdel et al., 2020).

In IC-MS method development, there are some challenges to overcome (Knoll et al., 2020; Zahn et al., 2020), especially when coupled to mass spectrometry. For anion chromatography, these challenges include the need to eliminate non-volatile mobile phase components such as K^+ by ion suppressors, matrix effects in electrospray ionization like ion suppression induced by inorganic salt ions (Furey et al., 2013), and reduced ionization efficiency in buffers used for IC elution. Still, IC is very promising, covering the most polar and ionic contaminants and especially TPs so relevant for groundwater monitoring (Ngere et al., 2023).

In this study, the aim was to help close the analytical gap for highly polar, anionic contaminants, focusing on pesticides and their TPs, by developing a sensitive analytical method based on ion chromatography coupled with electrospray ionization to HRMS/MS. To reach high sensitivity (i.e. LOQs < 100 ng/L), a) matrix effects were reduced by removing unwanted inorganic anions from the samples using appropriate cartridges, b) samples were non-selectively enriched by vacuum-assisted evaporation and c) the ionization efficiency in electrospray ionization was improved by examining different make-up solvents. The developed method was validated and then applied to karst groundwater samples obtained in the Swiss Jura, as karst aquifers are especially prone towards contamination and are important drinking water resources on a Swiss national level but also worldwide (FOEN, 2019; Ford and Williams, 2007).

2. Materials and methods

2.1. Chemicals and standards

In this study, 70 substances were investigated for their compatibility to ion chromatography (SI-B 1). This substance list included 5 pesticides, 57 pesticide TPs and 8 other substances. Their m/z -ratios ranged between 96 and 354 and their predicted $\log D_{OW}$ values between -7.4 and 2.2 (pH 7.4, Marvin Sketch, ChemAxon), though predictions especially in the negative range are error-prone. The generally low $\log D_{OW}$ values suggest that the majority of the selected substances could fulfil the mobility criterion ($\log K_{OC} < 4$) defined by Neumann and Schliebner (2017). The substance palette was chosen based on their speciation (calculated pK_a values), $\log D_{OW}$ values, reports in the literature, e.g. (Hintze et al., 2021; Kiefer et al., 2020; Kiefer et al., 2019; Reemtsma et al., 2013; Reinhardt et al., 2022; Zahn et al., 2020) and availability of reference standards.

The 70 reference standards (STDs) and 19 isotopically labelled internal standards (ILIS) were of analytical grade and purchased from various manufacturers (SI-B 1). For details on preparation of standard mixes etc. refer to SI-A 2.3.

Water to produce the KOH-gradient, to regenerate the suppressor and for sample preparation was ultrapure water if not stated otherwise (Sartorius, Arium® Pro Ultrapure Water Systems). Evian® mineral water was used as a substitute groundwater matrix. It is mineralized with 3.8 mg/L nitrate, 360 mg/L bicarbonate, 15 mg/L sulfate, 14 mg/L silica and 10 mg/L chloride. Chloride and sulfate levels are similar to the baseline values of the karst groundwater analyzed here (7 and 8 mg/L, respectively), but nitrate levels are ca. 5 times lower (20 mg/L in karst groundwater). The composition of the karst groundwater analyzed here did not change considerably throughout the monitoring period as sporadic grab samples revealed (Table 2.2 in SI-A 2.2). Acetonitrile (Fisher Chemical), ethanol (absolute for analysis, Merck) and methanol (Fisher Chemical) of analytical grade were used. The KOH-gradient was automatically generated in the eluent generator compartment of the ICS 5000+ (Dionex™ EGC 500+, Thermo Scientific™).

2.2. Field sampling

From mid of April 2021 until the end of October 2021, groundwater samples were obtained with an automatic, cooled (5 °C) sampling device (TP5 C, MAXX GmbH, Germany). It collected four composite samples per week while one composite sample was produced by pooling grab samples taken every 15 min for 42 h. The sampler was placed at a groundwater outlet of a karstic catchment in the Swiss Jura, dominated by 43 % agricultural land use (Table 2.1, SI-A 2.2). Once per week, approximately 100 mL per sample was filled into polypropylene containers (125 mL, Thermo Scientific™, Nalgene™ Products), frozen at −20 °C and stored in the dark until analysis in November 2022. Further, the local precipitation regime was monitored using a CAE PG4i pluviometer that was located at the groundwater outlet.

2.3. Sample preparation

Prior analysis, groundwater samples were thawed at 5 °C and afterwards handled at room temperature. 30 mL of sample was shaken and transferred into glass bottles (125 mL, Simax) and spiked with ILIS to reach an ILIS concentration of 200 ng/L (Fig. 2.1). To determine recoveries, groundwater samples were spiked with reference standards at

concentrations of 50, 100 and 500 ng/L. Two procedural solvent blanks (no ILIS or STD added), two procedural ILIS blanks (ILIS added) and calibration samples (ILIS and STD added; 0.1, 1, 10, 20, 50, 100, 200, 500, 1000, and 5000 ng/L) were prepared in ultrapure or evian® water and then prepared analogously to groundwater samples.

Prior usage, all cartridges to remove inorganic anions (Dionex™ OnGuard™ II Ba/Ag/H Cartridges, 2.5 mL; removes alkaline earth and transition metals, bromide, chloride, iodide and sulfate) were flushed with 100 mL ultrapure water employing a SPE station with 12 ports and a vacuum pump. Afterwards, batches of 12 samples were processed simultaneously by transferring 7 mL of each sample into polypropylene syringes (20 mL, Omnifix® Solo, Braun) attached to one cartridge and passed through at a rate of 2 mL/min. The disposal of the first 7 mL allowed to condition the cartridges as stated in the manual to prevent dilution and/or contamination of the samples with washing solution. The remainder of each sample (~23 mL) was passed through and collected in amber glass vials (50 mL, Infochroma AG). 20 mL of sample was then transferred into 1 mL-appendix Büchi-vials and evaporated down to 1 mL in a Büchi Syncore evaporator (12 ports) to yield a 20-fold concentration (Mechelke et al., 2019). Subsequently, the vial walls were rinsed with the sample to re-constitute any potential residual substance precipitated at the glass walls during evaporation. Then, the sample was transferred into glass centrifuge vials and centrifuged (4000 rcf, 15 min, Megafuge 1.0R, Heraeus). The enriched sample was transferred into HPLC-vials (1.5 mL Short Thread Vial, BGB®) and stored dark at 5 °C until analysis. No significant difference was observed between glass or polypropylene containers used during sample preparation, concerning loss or enhancement of analytes.

2.4. IC-ESI-HRMS/MS

The IC-method was developed on an ICS-5000+ system (Thermo Scientific™). 100 µL of sample was injected by the autosampler and separation of the analytes was achieved on a 2 × 250 mm Dionex™ IonPac™ AS19-4 µm column (Thermo Scientific™) equipped with a 2 × 50 mm guard column of the same specifications. The IC was run in gradient mode while the KOH-gradient was continuously produced by an eluent generator (Dionex™ EGC 500+, Thermo Scientific™) at a flow rate of 0.35 mL/min. The column was equilibrated for 4 min before the start of the run at a KOH-concentration of 5 mM, held at 5 mM to 5 min, increased linearly to 20 mM at 8 min and then to 90 mM at 15 min. The KOH concentration was kept constant at 90 mM to 32.5 min and then decreased to 5 mM until the end of the run (Table 2.3, SI-A 2.5). A dynamically

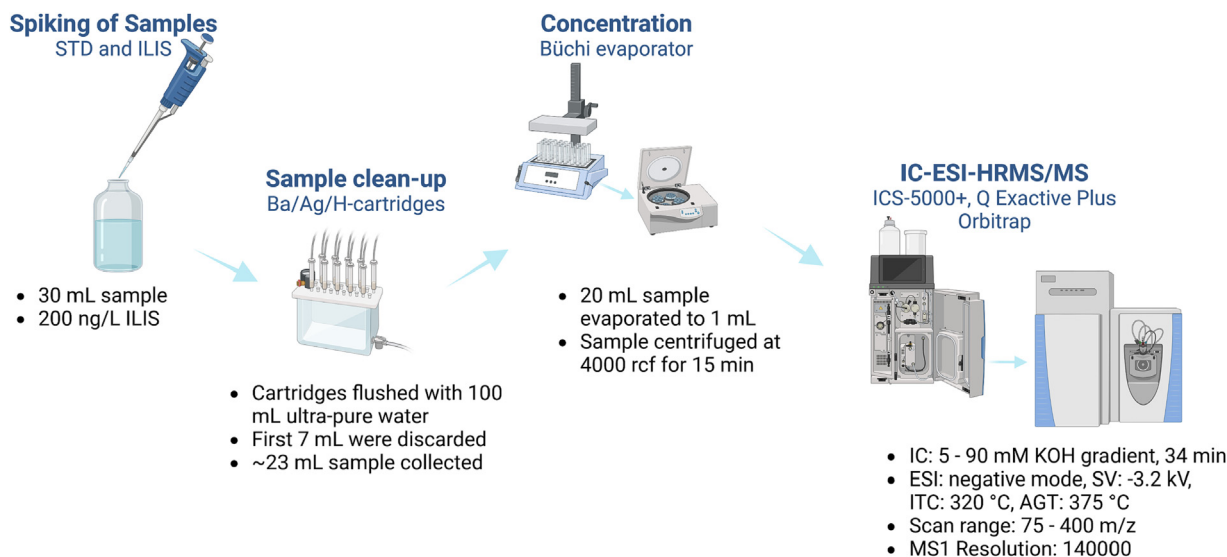


Fig. 2.1. Flow diagram of the final sample preparation and analytical method. AGT, aux gas temperature; ESI, electrospray ionization; IC, ion chromatography; ILIS, isotopically labelled internal standard; ITC, ion transfer capillary; HRMS/MS, high resolution tandem mass spectrometry; STD, reference standard.

regenerated suppressor (Dionex™ DRS 600, Thermo Scientific™) was used at appropriate values of suppressor current to exchange cations by H^+ and thereby neutralizing the basic eluent before entering the MS. The IC was run in external water mode, such that the suppressor was regenerated by a regeneration flow of 0.5 mL/min ultrapure water, delivered by an external pump (Ultimate 3000, RS Pump, Dionex™, Thermo scientific™). To protect the MS, the electrical conductivity was monitored between the suppressor and addition of the make-up flow. A trigger was programmed to stop flow to the MS in case the conductivity was higher than 10 $\mu S/cm$ for longer than 240 s. The aforementioned external pump also delivered the make-up flow of 0.2 mL/min ethanol before entering the MS, resulting in 0.55 mL/min flow to the MS.

The IC was coupled to an Orbitrap QExactive Plus mass spectrometer (Thermo Scientific™) run in negative ionization mode, a scan range from 75 to 400 m/z and a resolution of 140 k in the MS1. The aux gas flow and temperature were set to 60 AU and 375 °C, respectively and the sheath gas flow was set to 20 AU. Based on an inclusion list with individual normal collision energy values (SI-B 1), a data dependent Top5 scan experiment with a resolution of 17.5 k and a dynamic exclusion time of 3 s was conducted (Table 2.5 in SI-A 2.5).

The make-up solvent aids desolvation of the eluent in the ion-source (Kurz et al., 2017). Acetonitrile (ACN), ethanol (EtOH) and methanol (MeOH) – as well as all three solvents with ammonium-fluoride (NH_4F) as an additive – were examined for their influence on the intensity of 5 selected analytes with the previously optimized MS-parameters. The dead time of the IC column was calculated according to Eq. (2.1) (SI-A 2.5) and yielded 1.7 min for the Dionex IonPac including guard column. To prevent contamination of the ion source from matrix components not retarding on the columns, two times the dead time of each run was sent to waste.

2.5. RPLC-ESI-HRMS/MS

For comparison, a RPLC analysis was conducted which included direct injection of the same samples (100 μL) onto a RPLC column equipped with a guard column (Atlantis® T3 5 μm , 3 × 150 mm; Atlantis® T3, 5 μm VanGuard® Cartridge, 2.1 × 5 mm) according to Kiefer et al. (2019). Separation was achieved employing a gradient of MeOH/ H_2O with 0.1 % formic acid, respectively, starting at 5 % MeOH. From 1.5 min to 18.5 min MeOH increased to 95 %, held there until 28.5 min and then re-equilibrated at 5 % for 4 min until the next injection (Table 2.4, SI-A 2.5). In the RPLC analysis, the LC was coupled to the same Orbitrap MS with slightly different settings (Table 2.6 in SI-A 2.5).

Again, to protect the ion-source from early-eluting matrix components, two times the dead time for the Atlantis T3 RPLC column (2.3 min including the guard column) was sent to waste.

2.6. Quantification and method validation

All raw MS-data was first evaluated using Tracefinder 5.1 (Thermo Scientific™) and subsequently, the data was processed in R (R-Studio), i.e. calculation of matrix LOQs, matrix factors (MF) and relative recoveries (RR) (SI-B 3). Quantification of analyte concentrations was performed with the internal standard calibration method by preparing STD calibration samples of 0.1, 1, 10, 20, 50, 100, 200, 500, 1000, and 5000 ng/L with 200 ng/L ILIS in ultrapure or evian® water. The ultrapure water LOQ was determined as the lowest calibration standard still exhibiting a peak with at least 5 data points. In Section SI-A 3, extracted ion chromatograms of detected compounds in karst groundwater samples near their respective LOQs are shown. Some compounds did not prove linearity over the whole range of calibration levels hence their highest calibration level was reduced to 1000 ng/L. To correct for signal suppression and enhancement, individual MFs were determined for each compound, based on Eq. (2.2) and 2.3 (SI-A 2.6). These MFs were then used to correct the LOQs in ultrapure water to yield the matrix LOQs (Eq. (2.4), SI-A 2.6). The accuracy of the method was determined as the average RR for each compound using spiked samples (Eq. (2.5), SI-A 2.6, $n = 3$). The relative standard deviation of the

three calculated RRs for one compound was then taken as the precision for the respective compound (SI-B3). For compounds, which did not have a matching ILIS, the raw sample amounts determined in Tracefinder were corrected with the RR (Eq. (2.7) SI-A 2.6).

3. Results and discussion

3.1. Method development

3.1.1. Optimizing MS conditions

The MS parameters were optimized by testing the response of five analytes, selected for their difference in physicochemical properties (chlorothalonil TP SYN611968, fosetyl, metolachlor NOA436611, phosphorous acid, and triflusaluron-methyl IN-W6725; SI-B 1.1). The standard mixture (10 mg/L) was injected at a rate of 0.01 mL/min to a flow of 0.35 mL/min water with 0.2 mL/min of make-up solvent while changing: a) the ion transfer capillary temperature from 300 to 400 °C in steps of 20 °C, b) the aux gas temperature from 300 to 500 °C in 50 °C steps and c) the spray voltage from −2.0 to −3.4 kV in −0.2 kV steps. While two of the parameters were kept constant at recommended standard values (380 °C, 400 °C and 2.5 kV, respectively), the other one was optimized for the best response of all five analytes. Optimum average values for the ion transfer capillary temperature, the aux gas temperature and the spray voltage were 320 °C, 375 °C and −3.2 kV, respectively. For details, see Fig. 2.1–Fig. 2.5 in SI-A 2.1.

In addition to different ESI settings, six different make-up solvents were examined, acetonitrile, ethanol and methanol, each of them amended with 2 mM ammonium-fluoride as a modifier to enhance ionization in negative mode. All compounds performed best in ethanol, while acetonitrile resulted in the lowest responses. The pure make-up solvent without NH_4F performed better than with the modifier, indicating that all anions are sufficiently ionized. Kurz et al. (2017) tested acetonitrile, methanol and 2-propanol as make-up solvents and obtained the best results with 2-propanol. However, 2-propanol is more viscous than acetonitrile, methanol or ethanol and in our study created too much backpressure between the MS and the pressure-sensitive suppressor. Therefore, ethanol without NH_4F was chosen.

3.1.2. Sample preparation

3.1.2.1. Anion precipitation. When coupling ion chromatography to HRMS/MS, co-eluting inorganic anions can interfere with organic analytes during detection in the MS. These interferences can lead to blind spots in the full scan where the ion trap is filled to a large extent with inorganics instead of the analyte. As chloride and sulfate (RT: 6.9 and 11.9 min, respectively, Fig. 2.7, SI-A 2.4) are usually present in significant concentrations in groundwater, it was attempted to remove them with the H/Ba/Ag cartridges. Here, the cation exchange resins release barium and silver ions upon exchange with other cations, thereby precipitating and immobilizing sulfate and chloride, respectively. Nitrate was detected at ~25 mg/L in the karst samples but cannot be removed with these or other cartridges and hence led to the aforementioned blind spots for some analytes.

To ensure proper preconditioning of the cartridges, blank samples without any treatment were compared to blank samples treated with a cartridge with increasing flushing volumes of ultrapure water. In the total ion count (TIC) of blank samples treated with cartridges, contamination peaks were observed that decreased in intensity with increasing flushing volume until a steady intensity was reached. Therefore, diverting from the manual, the cartridges were flushed with 100 mL of ultrapure water instead of the recommended 15 mL. The leaching contaminants (presumably contributing to matrix effects) were hence prevented from entering the samples. Additionally, the absolute recovery for the cartridge treatment step was determined by spiking before and after treatment and showed that no significant co-precipitation, adsorption or enhancement of analytes occurred (data not shown).

3.1.2.2. Sample enrichment. The success of sample enrichment was examined by comparing three calibration series prepared in evian® water. The first series was not treated at all while the second was treated just with cartridges and the third with cartridges and VEC. To determine if IC had any advantage over RPLC, the three prepared calibration series were measured with both separation techniques. For each treatment and separation method, the number of compatible compounds and their LOQs for each treatment was determined (Fig. 3.1).

The number of compatible substances was substantially higher in IC than in RPLC in all three treatments. In enriched samples, 16 compounds were only detected by IC compared to RPLC while two (2,4-dichlorobenzoic acid and chlorothalonil TP R471811) were only detected with RPLC. Hence in enriched IC, 14 compounds more could be analyzed. This demonstrates the superiority of IC when analyzing small, highly polar and anionic substances. Here, compounds only compatible with IC, included: acetochlor ESA/alachlor ESA, acetochlor OXA/alachlor OXA, AMPA, AMPS, chlorothalonil TP SYN548008, cyanuric acid, dimethachlor ESA, dimethenamid ESA, fludioxonil TP CGA339833, glufosinate, glyphosate, metolachlor TP NOA413173, *N,N*-dimethylsulfamid, *N*-acetyl-AMPA, pethoxamid MET-42, sulfamic acid and trifluoroacetic acid (median log D_{OW} : -2.3).

In more detail, the median IC-LOQs in samples not treated, and samples treated with cartridges, were 100 ng/L (Fig. 3.1, Fig. 2.1). The removal of chloride and sulfate did not improve sensitivity. The same samples, determined via RPLC, led to lower median LOQs of 20 ng/L for both treatments with the cost of losing the most polar compounds as mentioned above. The 20-fold vacuum-assisted evaporative concentration step yielded excellent LOQs for both separation techniques. For IC this enrichment led to a median LOQ of 10 ng/L, i.e. a tenfold improvement for a majority of the compounds. The discrepancy to the theoretical 20-fold enrichment might be due to the undesired enrichment of interfering matrix constituents that were not removed by the cartridges and therefore led to signal suppression (discussed below). Yet, LOQs for AMPA (10 ng/L), clopyralid (10 ng/L), fosetyl (20 ng/L), glufosinate (10 ng/L) and glyphosate (10 ng/L) determined here, are well in accordance with values determined after tedious derivatization with RPLC analysis in groundwater (Hanke et al., 2008). They also agree with values determined with ion chromatography tandem MS in drinking water, bottled water and surface water (Kurz et al., 2017). RPLC limits of quantification determined here ranged lower with a median LOQ of enriched samples of 1 ng/L (i.e. 20-fold improvement). However, the higher number of compatible compounds points to IC being more suitable for highly polar, anionic contaminants.

Overall, the developed method allows reaching LOQs needed to determine whether EU groundwater standards of 100 ng/L for pesticides and

potentially toxicologically relevant TP are met (European Commission, 2006). By including not only very polar, anionic compounds but also moderately polar anionic substances (e.g. dimethenamid TPs), this method covers a large range of anionic contaminants.

3.1.2.3. Chromatographic separation. As expected, small, strongly ionic molecules were observed to be separated better in IC than in RPLC. In Fig. 3.2, extracted ion chromatograms of sulfamic acid, dimethenamid M31, dimethenamid OXA, dimethenamid ESA, TFA, cyanuric acid, and chlorothalonil TP SYN548008 in a sample, collected after heavy precipitation in July 2021, are presented. Except for dimethenamid M31 and dimethenamid OXA, these compounds were only quantifiable with IC. All compounds had stable retention times across measurements, peak widths were below 45 s and did not tail significantly, except cyanuric acid which exhibited some noisy tailing. The comparison of six small, highly polar, anionic compounds (AMPA, glufosinate, glyphosate, *n*-acetyl-AMPA, sulfamic acid and TFA in an evian® calibration sample showed that such compounds eluting in two times the dead time in RPLC, can be well separated using IC (Fig. 2.8, SI-A 2.5).

3.2. Method validation and quality assurance

3.2.1. Matrix effects of groundwater during ESI

Overall, the matrix factor for groundwater during ESI could be determined for 64 compounds and ranged from 0.1 to 2.1 with a median of 0.9 (Fig. 3.3). With a 25th percentile of 0.5, a significant number of compounds seems to be impacted by signal suppression i.e. matrix effects. They were mainly caused by interfering inorganic anions like fluoride, nitrate, and sulfate during ESI (Fig. 3.3). Sulfate was insufficiently removed by the applied cartridges while fluoride and nitrate could not be removed from the samples anyhow. Due to the 20-fold concentration step, these anions were then present in high concentrations causing matrix effects. For six compounds, no matrix factor could be determined (SI-B 3) because 2,4-dichlorobenzoic acid, chlorothalonil TP R471811, ethephon and fludioxonil TP CGA192155 co-eluted with sulfate (~12 min), fludioxonil TP CGA339833 eluted within two times the dead time together with non-retarded matrix components and metazachlor ESA co-eluted with nitrate (~9 min). Due to insufficient retention on the column, the previously well retarded peaks of 2,4-dichlorobenzoic acid, chlorothalonil TP R471811, ethephon and fludioxonil TP CGA192155 in calibration samples, deteriorated in spiked samples. Through competition with sulfate in the column, the analytes were insufficiently retarded resulting in strong tailing. Additionally, the competition in ESI and the saturation of the ion trap with sulfate (m/z of 95.9517; note lower boundary of scan range: 75 m/z) resulted in strong suppression. Similarly, due to competition with nitrate during separation and in ESI, metazachlor ESA exhibited strong tailing and significant suppression in spiked samples. For this compound, also an unidentified isobaric compound is present (double peak, also present in ultrapure water).

In more detail, matrix factors were in the generally accepted range of 0.7 to 1.3 for 34 out of 64 analytes. Hence, ~50 % of all compounds experienced either significant suppression (25) or enhancement (5). Out of the 25 compounds that were affected by suppression, 3 co-eluted with fluoride (~5 min), 8 with nitrate (~9 min) and 4 with sulfate (~12 min). This demonstrates the necessity of removing inorganic anions before IC analysis. Here, the removal of bromide and chloride, as well as the incomplete removal of sulfate were later confirmed by analyzing an anion standard passed through the cartridges (Fig. 2.7 in SI-A 2.4). Furthermore, the non-selective, evaporative enrichment led to the concentration of the remaining inorganic anions. In contrast, RP-based SPE materials do not enrich inorganic anions, but polar, anionic organic compounds often break through.

3.2.2. Relative recovery (accuracy) and precision

The relative recovery was determined for 64 compounds whenever possible with three spike levels at 50, 100 and 500 ng/L. However, not in all cases the three spiked concentrations could be quantified or did not comply

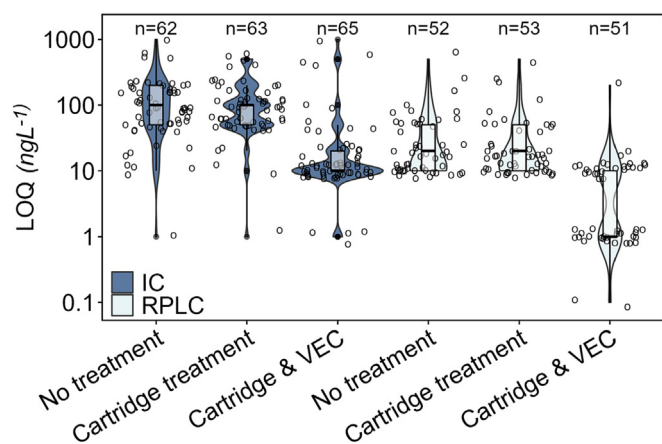


Fig. 3.1. Limits of quantification determined in three different experiments, analyzed with IC-HRMS/MS or RPLC-HRMS/MS. Calibration rows were prepared in evian® and then either: a) not treated further (No treatment), b) passed only through the cartridge (Cartridge treatment) and c) passed through the cartridge and enriched via vacuum assisted evaporative concentration (Cartridge & VEC).

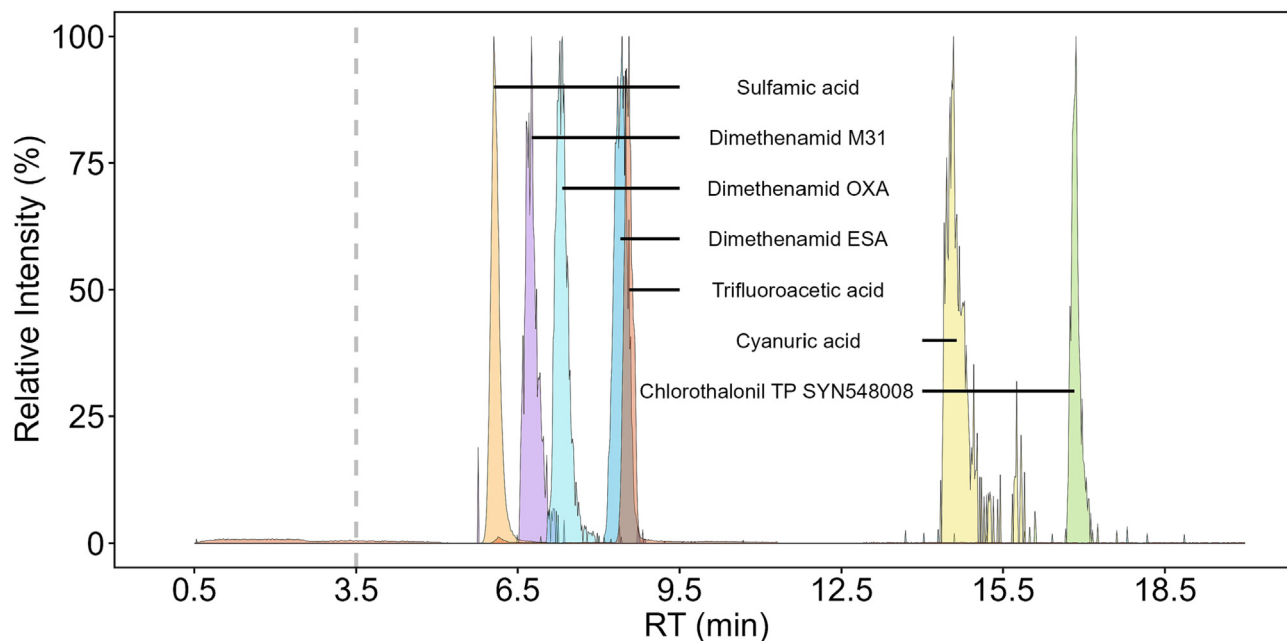


Fig. 3.2. Non-smoothed extracted ion chromatograms of seven detected compounds in an enriched groundwater sample after a rain event (sample 39). To enable a better graphical display, the peaks were normalized to their maximum intensity within this sample. The grey dashed vertical line at RT = 3.5 min denotes two times the column dead time. For demonstration purposes, this sample was scanned from 0.5 min to 33.5 min.

with the quality criterion (Eq. (2.6), SI-A 2.6). The median relative recovery of 1.0 compared to a median matrix factor of 0.9 shows that some matrix effects were accounted for by a matching ILIS, resulting in good overall accuracy. However, 16 out of 64 compounds had relative recoveries below 0.7 and ten were above 1.3. The filled symbols in Fig. 3.3 mark compounds that had a matching ILIS and all of them except two were within the acceptable range of $\pm 30\%$. For example, metolachlor TP CGA50720 had a matrix factor of 0.09, co-eluting with nitrate, but an excellent relative recovery of 0.9. This demonstrates the importance of matching ILIS as the easiest way of correcting for strong matrix effects. For six compounds (2,4-dichlorobenzoic acid (12.2 min), chlorothalonil TP R471811 (12.2 min), ethephon (12.8 min), fludioxonil TP CGA192155 (12.3 min), fludioxonil TP CGA339833 (2.9 min), metazachlor ESA (9.1 min)), no relative recovery

could be determined due to strong ion suppression in the spiked samples or elution within two times the dead time (fludioxonil TP CGA339833). Five of these compounds eluted either a) during the nitrate peak at ~ 9 min (1) or b) during the sulfate peak at ~ 12 min (4).

The low median relative standard deviation (RSD) of the RR (i.e. precision) of 0.1 demonstrates excellent repeatability despite partly strong matrix effects (Fig. 3.4). For example, the precision of AMPA, clopyralid, glufosinate and glyphosate was only slightly higher compared to values found in Kurz et al. (2017) despite the more challenging sample preparation conducted here. Fosetyl however showed a relatively high RSD (i.e. low precision) of 0.4 due to matrix effects and a non-matching ILIS. Finally, the overall precision compares well to values found in VEC-RPLC analysis (Mechelke et al., 2019).

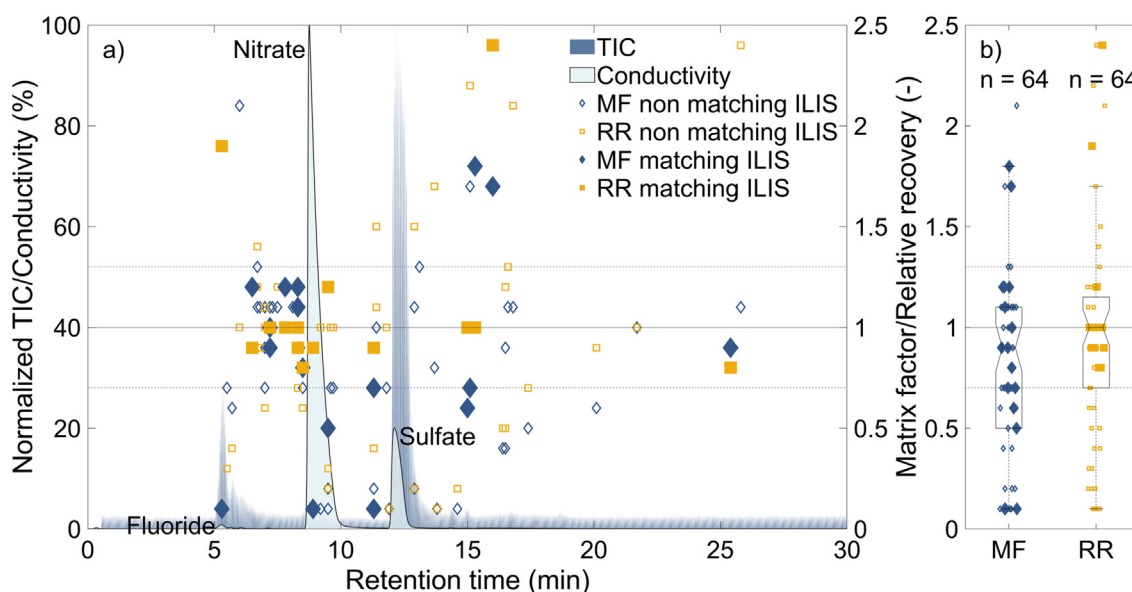


Fig. 3.3. Matrix factor (MF) and relative recovery (RR) values determined in karst groundwater are depicted at their IC retention time. They are compared to the recorded conductivity signal and the total ion current (TIC) of one of the samples. Plot b) shows boxplots of the matrix factor and the relative recovery for all analytes.

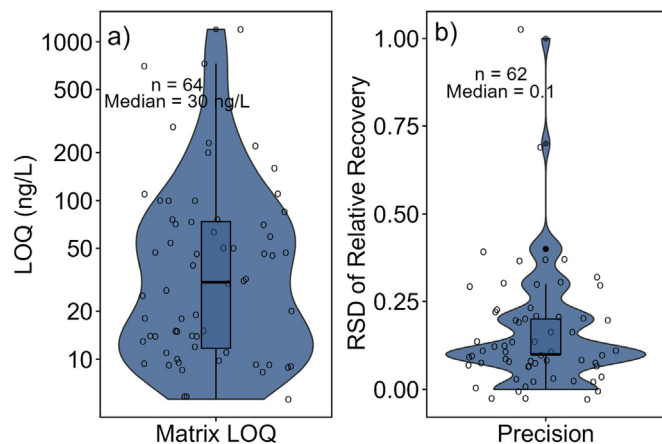


Fig. 3.4. a) Matrix LOQ, and b) analytical precision for the analysis of karst groundwater. Two precision values could not be calculated due to insufficient number of calculated RR values for these two compounds.

3.2.3. Limits of quantification in karst groundwater

Limits of quantification in ultrapure water could be determined for all 70 analytes, while matrix LOQs could be determined for 64 compounds (for which a matrix factor was determined; Fig. 3.4 and SI-B 3). Of those, 78 % had a matrix LOQ below 80 ng/L and compared to the median of 10 ng/L in ultrapure water, the median matrix LOQ of 30 ng/L again shows the effect of signal suppression by the enriched inorganic anions nitrate and sulfate. For a few compounds, blank values were found in which case the matrix LOQs were set to two times the highest blank concentration.

3.3. Occurrence of analytes in karst groundwater












In 86 karst groundwater samples taken during the pesticide application period from April to October 2021, twelve out of 64 analytes of the final method were found above their LOQ (Table 3.1). Their predicted log D_{OW} values ranged from -5.5 to -0.7 (chlorothalonil TP SYN548008 and chlorothalonil TP R417888, respectively). Eleven of those could be identified with at least one product ion, while no fragment of cyanuric acid was found (SI-B 4). The samples had already been analyzed with IC excluding VEC ca. 3 months after their collection, and highly concentrated TPs (e.g. dimethenamid TPs) were found in similar concentration indicating their stability during the storage period. Moreover, the RPLC analysis of these samples showed that six compounds could also be analyzed with the RP column Atlantis T3, while six were exclusively quantifiable using IC. The reported concentrations refer to average values over 42 h (composite samples) and hence, short concentration peaks even higher than the reported values are to be expected. Three chlorothalonil TPs, 2 dimethachlor TPs, 3 dimethenamid TPs, nicosulfuron TP UCSN, sulfamic acid and trifluoroacetic acid were detected (Table 3.1). Pesticide application data from 2021 revealed that of the detected TPs, dimethenamid, dimethachlor and nicosulfuron were applied in the catchment. However, the two dimethachlor TPs ESA and OXA were found only in a few samples and in low concentrations of up to 48 and 35 ng/L, respectively. Nicosulfuron was only detected in 7 samples with a maximum concentration of 13 ng/L. The remaining compounds are discussed below.

3.3.1. Chlorothalonil TPs

Reports of chlorothalonil TPs in surface water and agricultural soils (Hintze et al., 2021) and in different groundwaters (Kiefer et al., 2019) suggest that these are widespread in the Swiss agricultural environment, impacting drinking water resources. The sulfonic acid TP R417888 was

Table 3.1

Detected compounds in 42 h karst groundwater samples. Out of 64 analytes, twelve were found above their matrix LOQ. Log D_{OW} values and structures were predicted and drawn using Marvin Sketch (ChemAxon). Refer to SI-B for additional compound information and detailed results.

Compound		Log D_{OW}	Matrix LOQ (ng/L)	Detections (86 samples)	C_{max} (ng/L)
Chlorothalonil TP R417888		-0.7	31	4	34
Chlorothalonil TP R419492		-4.5	18	7	30
Chlorothalonil TP SYN548008 ^a		-5.5	9	86	110
Cyanuric acid ^{a,b}		-1.1	50	16	970
Dimethachlor ESA ^a		-1.1	13	13	48
Dimethachlor OXA		-1.5	9	3	35
Dimethenamid TP M31		-1.8	39	13	350
Dimethenamid ESA ^a		-0.8	9	42	320
Dimethenamid OXA		-1.1	11	30	290
Nicosulfuron TP UCSN		-2.4	8	7	13
Sulfamic acid ^{a,b}		-3.8	110	86	5600
Trifluoroacetic acid ^{a,b}		-2.6	700	85	2800

^a Not quantifiable with Atlantis T3.

^b LOQ increased due to blank value.

detected in 4 of 86 samples with a maximum concentration of 34 ng/L. The reversed-phase analysis of the same samples yielded comparable values, which demonstrates the good accuracy of the developed IC method. Moreover, in the RPLC analysis of these samples, the chlorothalonil TP R417811 was found in all samples in concentrations >100 ng/L (C_{\max} : 430 ng/L). However, in the IC analysis, the chlorothalonil TP R417811 was strongly suppressed by sulfate, rendering it not quantifiable, despite an ultrapure LOQ of 50 ng/L (see SI-B 3). In a suspect screening study of different groundwater samples in Switzerland, this TP exhibited the highest concentrations of all chlorothalonil TPs analyzed therein (Kiefer et al., 2019). In RPLC-separation with the Atlantis T3 column, the TP R419492 elutes very early at 5.1 min, barely escaping two times the column dead time of 5 min. However, because of its double negative charge at high pH values, it was well retarded in IC, eluting at 26.9 min. Chlorothalonil TP R419492 was found in 7 of 86 samples with a maximum concentration of 30 ng/L. Finally, the very polar di-sulfonic acid chlorothalonil TP SYN548008 was found in all samples in concentrations of up to 110 ng/L. Hence, this TP slightly exceeded the groundwater limit of 100 ng/L which was imposed on all chlorothalonil TPs in Switzerland in 2020 by classifying the active substance as potentially carcinogenic and therefore its TPs as toxicologically relevant (Bundesamt für Landwirtschaft et al., 2021). It is a TP of R471811 and to the author's knowledge, this was the first time, this particular TP was found in groundwater samples not only in Switzerland but also worldwide although it is certainly widespread. This might be due to the lack of an adequate analytical method to date.

3.3.2. Dimethenamid TPs

To the author's knowledge, apart from the registration dossier (EFSA, 2018), dimethenamid TP M31 has never before been reported in the literature. Previous studies commonly focused on the two TPs ESA and OXA (Huntscha et al., 2012; Reemtsma et al., 2013), but the detection of TP M31 in karst groundwater shows that this selection of TPs was incomplete.

In 2021, dimethenamid was applied for maize in the catchment for the last time on June 26th. Previously in 2021, sugar beet was also treated with dimethenamid, but in smaller quantities. RPLC-analysis of 42 h-composite samples collected in June and July 2021, showed a maximum dimethenamid concentration of 790 ng/L on June 27th during a rain event shortly after its application (data not shown). However, elevated concentrations of the toxicologically not relevant dimethenamid TPs OXA, ESA and M31 only occurred with precipitation events some two weeks later (290, 320 and 350 ng/L, respectively, Fig. 3.5) indicating their formation in soil during the two weeks ($DT_{50, \text{aerobic, soil}} = 13 \text{ d}$, (Lewis et al., 2016)). According to the registration dossier, the three TPs were expected to occur in these ranges in groundwater ($PEC_{\text{gw}} > 0.75 \mu\text{g/L}$, $> 0.75 \mu\text{g/L}$ and $> 10 \mu\text{g/L}$, respectively), being the three most abundant TPs of dimethenamid (12 %, 13 % and 10 % applied radioactivity, respectively) in an aerobic soil incubation study and being highly mobile in soil (EFSA, 2018).

3.3.3. Cyanuric acid, sulfamic acid and trifluoroacetic acid

Cyanuric acid, sulfamic acid and trifluoroacetic acid were found in concentrations of up to 970, 5600 and 2800 ng/L, respectively (Fig. 3.6). Although Kolkman et al. (2021) found one fragment of cyanuric acid (fragment $m/z = 85.00435$), no fragments could be identified here. While no fragments were found, the observed isotope pattern for ^{15}N and ^{13}C complied well with the theoretical one. Hence, only the precursor ion could be used for identification and the level of confidence for this compound is therefore lower (SANTE/12682/2019, 2019). While sulfamic acid and TFA occurred in almost all samples, cyanuric acid predominantly occurred in the precipitation-intensive periods in July in 25 of 86 samples. In a screening study using HILIC, Kolkman et al. (2021) found cyanuric acid with a maximum concentration of 240 ng/L in drinking and surface water. Neuwald et al. (2022) found cyanuric acid in different water samples, with a median concentration of 170 ng/L to 2800 ng/L. Here, the origin of cyanuric acid remains unclear, since it is a TP of melamine and cyromazine (Reemtsma et al., 2013). Recently, a study proposed the encapsulation of

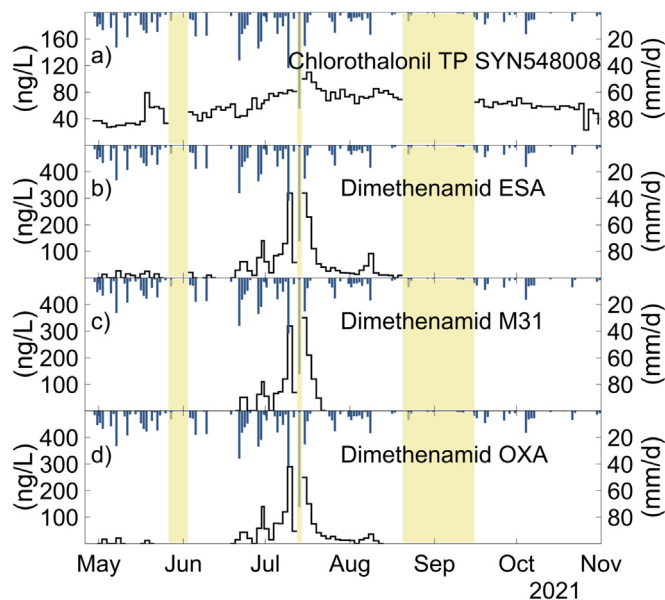


Fig. 3.5. Concentration dynamics of a) chlorothalonil TP SYN548008, b) dimethenamid ESA c) dimethenamid M31 and d) dimethenamid OXA in 42 h composite samples collected at a karst groundwater outlet in the Swiss Jura. Note the different y-scales and the data gaps marked as yellow rectangles.

pesticides in nano-spheres of melamine formaldehyde which are supposed to slowly release the active ingredient into the environment (Liu et al., 2019). However, it is unknown whether such products were applied in this catchment.

Sulfamic acid showed rather constant concentrations at a baseline value of ~1000 ng/L. Yet, concentration peaks of up to 5600 ng/L were observed in precipitation-intensive periods (i.e. May and July). The sources of sulfamic acid in the environment can be manifold. For instance, it is a degradation product of the artificial sweetener acesulfame-K (Castronovo et al., 2017). Besides, sulfamic acid is used as an acidic cleaning agent and incomplete removal in wastewater treatment plants (WWTP) resulting in high effluent concentrations of up to 1.6 mg/L have been reported in Germany

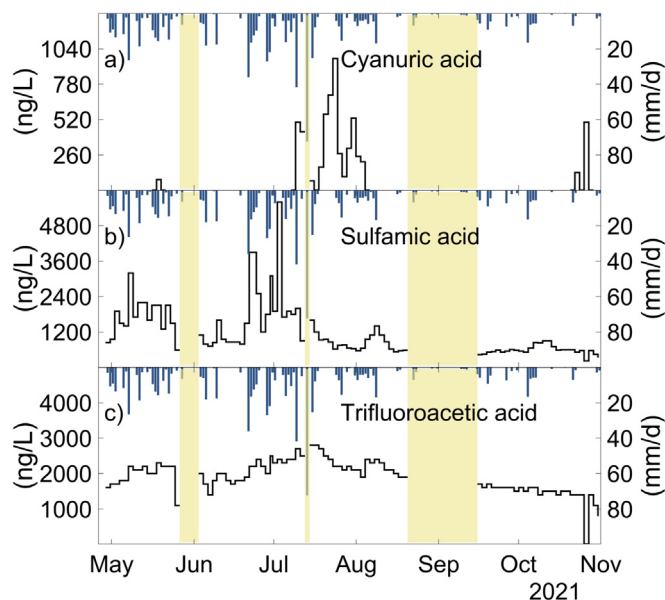


Fig. 3.6. Concentration dynamics of a) cyanuric acid, b) sulfamic acid and c) trifluoroacetic acid in 42 h composite samples collected at a karst groundwater outlet in the Swiss Jura. Note the different y-scales and the data gaps marked as yellow rectangles.

(Freeling et al., 2020b). The largest quantity of sulfamic acid found in waterbodies in the $\mu\text{g/L}$ -range therefore likely originates from WWTP discharge. For water bodies not impacted by wastewater, natural sources like precipitation were proposed as the major contributor in a Canadian study. In precipitation, they measured maximum concentrations of up to 2500 ng/L which compare well to the values determined here (Van Stempvoort et al., 2019). Another source of sulfamic acid in the environment are pesticides. Sulfamic acid could be a transformation product of sulfonylurea herbicides which have been applied in this catchment in 2021 (e.g. foramsulfuron, mesosulfuron-methyl, triflurosulfuron methyl) and presumably, during many years before. For example, a major transformation product of foramsulfuron is foramsulfuron-sulfamic acid (EFSA, 2016) which could then lead to the release of sulfamic acid.

As Freeling et al. (2020b) determined, sulfamic acid is attenuated during sufficiently long aquifer passage. Hence, in drinking water produced from sedimentary aquifers, sulfamic acid levels were significantly lower than in raw water from surface water. However, in karst aquifers, aquifer passage of infiltrating (precipitation) water towards a spring can be extraordinarily fast, not allowing for sufficient attenuation. For sulfamic acid, this hypothesis is further supported by the detected elevated concentrations after precipitation. While monitoring karst groundwater used for drinking water production seems therefore especially important, it should be stated that values reported here are probably of low concern for the consumer, even over a lifetime of drinking water consumption, as Freeling et al. (2020b) derived a guideline value for risk to human health of 6 mg/L.

Trifluoroacetic acid was found in 85 of 86 samples, however, no pronounced concentrations peaks were detected (Fig. 3.6). As discussed elsewhere (Hale et al., 2022; Scheurer et al., 2017), TFA is ubiquitously present in the environment, has even been detected in beer and tea (Scheurer and Nödler, 2021), and has many different sources including formation in the atmosphere (Freeling et al., 2020a). The observed slightly increasing trend during precipitation intense periods could be due to a seasonal trend of TFA concentration in precipitation water as it was described in Freeling et al. (2020a). However, no precipitation water samples were collected for confirmation. The median concentration of 2000 ng/L found here seems comparably high, considering Scheurer et al. (2017) found concentrations of this level only at downstream locations of the river Rhine in North Rhine-Westphalia, Germany (upstream: <1000 ng/L). Similar to sulfamic acid, TFA is difficult to eliminate during drinking water production but to present knowledge causes no harm to humans in the observed concentrations in this study (UBA, 2020).

4. Conclusion and outlook

A sensitive method for a broad range of polar, anionic substances was successfully developed. The method involves precipitating inorganic salt ions like chloride, followed by vacuum-assisted evaporative concentration, IC separation, and detection by HRMS/MS. However, the enrichment using VEC is non-selective, and matrix components such as salt ions prevalent in groundwater may interfere with IC-MS. Alternative sample clean-up approaches should be explored in the future to further reduce matrix effects and make use of the full chromatographic runtime, especially regarding sulfate, nitrate and phosphate. Despite heavy matrix effects during co-elution with sulfate and nitrate and the exhaustive sample preparation, matching ILIS could successfully compensate for this, thereby demonstrating their high importance in ESI-HRMS/MS analysis as reported elsewhere (Huntscha et al., 2012). The method achieves LOQs for 64 substances that are sufficient for sensitive water monitoring and compliance checks of the often-used threshold value of 100 ng/L in ground and drinking water.

The developed method has a wide range of applicability, as indicated by the analytes' log D_{OW} values, ranging from -7.4 to 2.2 . It can serve as a complementary screening tool to RPLC analysis to broaden the analytical space for more polar compounds ionized at basic pH applied in IC. The method's effectiveness was demonstrated by the successful detection of chlorothalonil TP SYN548008 and dimethenamid TP M31, despite long-term application and monitoring of the parent compounds. The coupling

to an Orbitrap mass spectrometer enables non-target and suspect screening, which can be useful in detecting ever-increasing numbers of vPvM/PMT substances in the environment.

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CRediT authorship contribution statement

Johannes Schorr: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Sam Therampilly:** Methodology, Validation, Formal analysis, Data curation. **Lingyi Jiao:** Methodology, Validation, Formal analysis, Data curation. **Philipp Longree:** Methodology, Writing – review & editing. **Heinz Singer:** Writing – review & editing. **Juliane Hollender:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare no competing financial interest.

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Abbreviations

ESA	ethanesulfonic acid
ESI	electrospray ionization
HILIC	hydrophilic interaction liquid chromatography
HRMS/MS	high resolution tandem mass spectrometry
IC	ion chromatography
ILIS	isotopically labelled internal standard
LOQ	limit of quantification
OXA	oxalic acid
PMT	persistent, mobile and toxic
RPLC	reversed phase liquid chromatography
SPE	solid phase extraction
STD	reference standard
TFA	trifluoroacetic acid
TP	transformation product
VEC	vacuum-assisted evaporative concentration
vPvM	very polar and very mobile
WWTP	wastewater treatment plant

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