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ANALYTICAL SCIENCE ADVANCES

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REVIEW

Combining ion chromatography with mass spectrometry and inductively coupled plasma-mass spectrometry: Annual review 2020

Cees Bruggink[1] | **Detlef Jensen**[2]

[1] InIon Chromatography, Breda, AT, The Netherlands

[2] Thermo Fisher Scientific GmbH, Dreieich, Germany

Correspondence
Email:
CEES@INION-CHROMATOGRAPHY.COM

Abstract

The demand for analyzing low molecular weight polar and ionic components in body fluids, pharmaceutical formulations, food, environmental samples, and drinking water is increasing. Ion chromatography (IC) offers significant advantages over RPLC and HILIC due to a complementary chromatographic selectivity, a different retention mechanism, and a high tolerance toward complex matrices. A continuously regenerated membrane desalter simplifies the combination of IC-applications with MS- or MS/MS-detection, improving the sensitivity and specificity. Analytical workflows are streamlined, providing higher sample throughput. Combining IC with ICP-MS simplifies the speciation analysis of inorganic and organic polar components. The knowledge about the distribution of an element among chemical species in a sample is essential due to significantly different toxicological or environmental properties. This annual review evaluates the literature published from late 2019 until November 2020.

KEYWORDS

biomarkers, carbohydrates, desalting, disinfection by-products, endocrine disruptors, environmental analysis, fluoroalkyl carboxylic acids, food safety, human body fluids, isobaric differentiation, metabolomics, pharmaceutical analysis, polar pesticides, speciation

1 | INTRODUCTION

There is an increasing interest in analyzing polar components in metabolomics, forensics, food, beverage, and the environment. The analysis of polar components using reversed-phase chromatography (RPLC), however, is complicated due to their weak retention. Consequently, RPLC often reverts to the use of ion-pair reagents or the analytes' derivatization to enhance their interaction with the stationary phase.[1]

Hydrophilic interaction liquid chromatography (HILIC) is a variant of normal phase chromatography that fills partly the gap left by RPLC. HILIC separates polar components while the mobile phase contains a high concentration of organic solvent. This high organic solvent concentration can influence the solubility of larger components like oligosaccharides, and HILIC can suffer from incompatible sample matrices and sample compositions. Stationary phases are predominantly silica-based, limiting the applicable pH-range of the mobile phase.

Ion chromatography (IC), on the other hand, offers improved retention based on ionic interaction and adsorption, as well as a wide range of chromatographic selectivity due to the variety in the composition of the ion exchange functionalities and crosslinking of the monomers used.[2] The aqueous mobile phase addresses solubility issues of polar components. The polymeric based stationary phases are compatible

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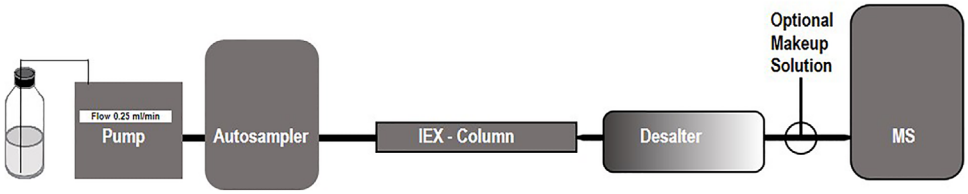

FIGURE 1 Instrumental setup of ion chromatography coupled to mass spectrometry

with eluents covering an extended pH-range compared with columns used in RPLC and HILIC. In most publications today, the term Ion Chromatography is used synonymously for ion exchange chromatography in conjunction with electrochemical detection. Some ion-pair reagents, like TFA, decrease signal intensities in electrospray ionization (ESI). The absence of an ion-pair reagent in the IC mobile phase prevents such signal losses. Combining IC with MS-detection offers significantly improved selectivity and often increased sensitivity compared to conventional detection.[3] For the separation of anionic species mostly high-pH mobile phases are used, while the separation of cationic components requires acids. Besides, many of the inorganic constituents cause corrosion and are not volatile. To prevent these issues, a continuously operated membrane-based desalter is used in-line with column and MS to convert the inorganic acids and bases to water (Figure 1). Corrosion is prevented, and the column's effluent can be directed to the MS-interface. To aid the desolvation process of the aqueous effluent and to gain detection sensitivity, organic solvents are often added before the MS (make-up solvent).[4,5] Due to the complexity of modern scientific challenges driven by the intricacy of biological and environmental sample matrices, the demand for new and additional analytical selectivity, increased sensitivity, and integrated automated analytical workflows emerge.[6–8] The necessity to determine low-level trace-components in the presence of matrix components at orders of magnitude higher concentrations adds to the analytical challenge.[3,9] Additional specificity of MS or inductively coupled plasma mass spectrometric detection (ICP/MS) is essential in this hunt. The increased detection specificity – from a chromatographer's point of view – simplifies the targeted and nontargeted analysis and contributes to increased sample throughput.[10]

In addition, high-resolution mass spectrometry (HRMS) helps to identify the eluted molecule, and the different scanning modes improve the reliability of the analytical results.[11]

The combination of IC with ICP-MS provides an element-specific detection capability used for the speciation analysis of metals and non-metals.[12,13] The pH-compatibility of the material the nebulizer is made off could prevent the use of conventional high pH IC-eluents. The desalting strategy described above can be applied, or volatile acids or aqueous ammonium salts are used in the mobile phase. Due to the high energetic environment of the plasma, inter- and intramolecular interactions are eliminated, and IC-ICP/MS proves to be less matrix dependent than IC-MS/MS.

This article's scope is to review and discuss relevant articles published from late 2019 until November 2020.

2 | LIFE SCIENCE

To better understand the complex processes in living cells, improved identification and quantitation combined with structural information and exact molecular composition are essential.[14] Ionic and zwitterionic metabolites are accessible by IC-MS. IC-MS and ICP-MS are useful diagnostic tools for the determination of specific molecules such as biomarkers. Within this review's scope, the collectively used term "Life Science" covers metabolomic, biomedical, and forensic research.

2.1 | Metabolites investigated with IC-MS

2.1.1 | Body Fluids

The metabolome consists of a collection of small molecules in cells, cellular organelles, organs, or the entire body.[15] Due to the continuous biological cycles in the different parts of the human body, the determination of glycans, nucleosides, nucleotides, proteins,[16] is demanding. Though complex in their composition, human body fluids can be used as a probe in understanding such processes. The superior separation of IC can resolve some of the isobaric metabolites, such as saccharides, that MS would not differentiate on its own.

Sun *et al*. reported non-targeted identification of gender-associated anionic metabolites in urine and serum using IC coupled with HRMS. In addition to 68 abundant metabolites, they identified 63 minor ones.[6]

There is a necessity for an efficient analytical workflow in metabolic profiling. For the chromatographic part of the workflow, Le *et al*. combined an RP-column with a strong cation exchange column in one LC-system coupled to QTOF MS detection.[17] In contrast to conventional approaches, only one sample analysis is needed due to the two combined orthogonal chromatographic selectivities. This configuration separates clinically significant polar and nonpolar compounds without derivatization or ion-pairing reagents, allowing ionization in both polarities. A single dataset is generated for a body fluid sample instead of two. The automated database analysis revealed 5445 and 4111 ion features for pooled plasma and urine samples, respectively, leading to 88 confirmed metabolite identifications for plasma and 82 for urine. This approach facilitated detecting metabolites at clinically relevant concentrations with good precision and good chromatographic separation based on the study's experimental design.

During the past decades, an increase in the concentrations of health threading thyroid disrupters, like perchlorate, nitrate, and thiocyanate,

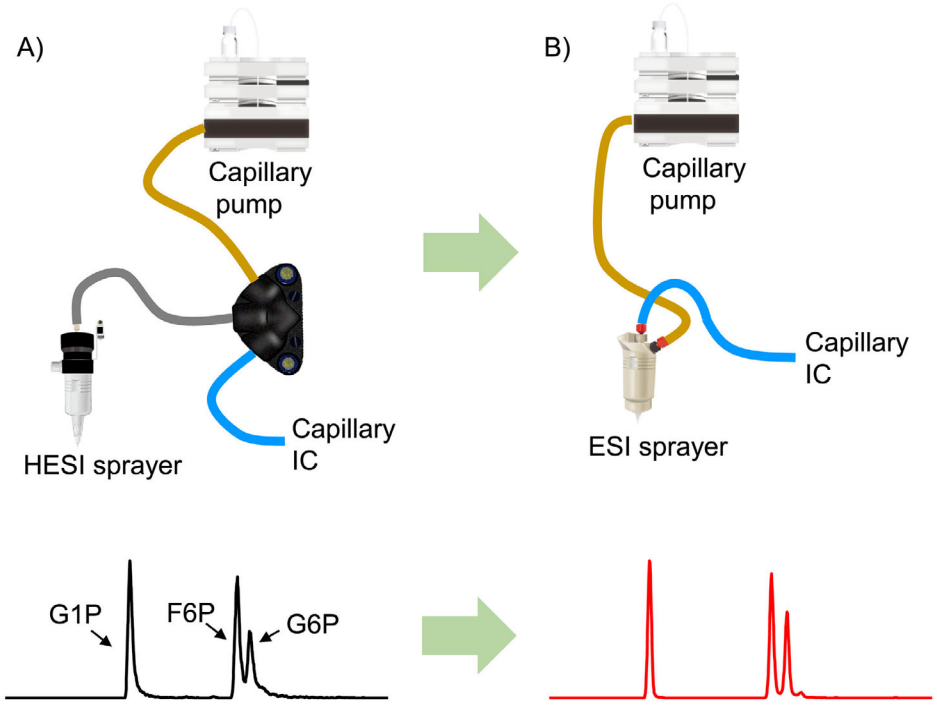

FIGURE 2 Schematic diagram of the eluent, make-up solution, and sprayer connections in capillary ion chromatography (IC)-MS. (A) Heated electrospray ionization (HESI) sprayer, and (B) electrospray ionization (ESI) sprayer. Abbreviations: F6P, fructose 6-phosphate; G1P, glucose 1-phosphate; and G6P, glucose 6-phosphate, with permission from 21 ©2020 J. Chromatogr. A

is found in food and human excretions. Their reliable quantification requires specific, selective, interference-free, sensitive, and accurate analytical approaches. Zhu and co-authors selectively determined perchlorate, nitrate, and thiocyanate in human urine combining anion-exchange chromatography with triple quadrupole mass spectrometry. The urine samples only required a ten-fold dilution with DI water before analysis, simplifying the analytical workflow. Evaluation of the samples by unsupervised principal component analysis showed excellent analytical quality.[18]

Panseri *et al.* describe the analysis of perchlorate and chlorate in baby food. Perchlorate is a pollutant present in the environment, and, as a consequence, it can incorporate into food and drinking water.[9] This work is particularly important, as perchlorate can reduce the uptake of iodide in the human thyroid, decreasing the formation of iodine hormones, which are essential for children's good mental development.

Rosado-Sousa *et al.* published analytical protocols to analyze metabolites. One of the protocols describes how to determine organic acids and unstable phosphorylated intermediates. These charged acids and intermediates are involved in the glycolytic pathway, the Calvin cycle, and the plants' Krebs cycle. The protocol covered 28 anionic metabolites. The method avoids derivatization, and MS-detection minimizes the impact of chromatographic interferences, simplifies sample analysis, and facilitates data evaluation.[19]

At times of growing international political instability, the thread of using chemical weapons by terrorist groups is increasing. Nerve agents are highly toxic chemicals; some have been used in terrorist and illegal military activities. Ion chromatography and tandem mass spectrometry allow accurate, sensitive, and simultaneous determination of nerve agent markers in urine. Baygildiev *et al.* determined nerve agents such as alkyl phosphonic acids and much less polar alkyl methyl phosphonic acids in urine samples. The separation of the non-derivatized analytes was performed on a mixed-mode column offering reversed phase and strong anion-exchange properties. Detection was carried out applying a Qtrap MS or a triple quadrupole MS. Before the analysis, the urine samples were purified using a simple solid-phase extraction with high recovery for each analyte.[20]

2.1.2 | Pharmaceuticals, biopharmaceuticals, and cells

In the case of a limited sample amount, the chromatographic setup needs to be adapted. Hirayama and coauthors used an ion chromatograph in the capillary format (inner column diameters < 1 mm) injecting 0.4 µL to analyze 44 anionic metabolites, including nucleotides, cofactors, organic acids, and sugar-phosphates in cancer cells. The publication describes the use of a double coaxial ESI sprayer for the first time separating the flow path of the eluent from that of the make-up solution, minimizing analyte dilution, peak distortion and prevents possible damage to the desalter,[21] see Figure 2.

In catabolic and anabolic functions, coenzymes, such as pyridine nucleotides, nicotinamide adenine dinucleotide (NAD), and nicotinamide adenine dinucleotide phosphate (NADP), are essential. They are involved in >200 different hydride transfer reactions. The concentrations and their ratio of oxidized to reduced forms regulate an extensive network of reactions. Røst and co-workers developed a fast

and sensitive quantitative method to determine these coenzymes in human cells and Escherichia coli bacteria. They utilized a zwitterionic HILIC column's chromatographic selectivity, with pronounced electrostatic interactions, hyphenated to an MS/MS. Røst *et al*. describe their method to be ideal for high-throughput analysis of biological extracts.[22]

Regulatory authorities require in-depth characterization and detailed quality control of charge variants in biopharmaceuticals to demonstrate the similarity of the drug substance between manufactured batches throughout the whole production process.[23] An important class of therapeutic proteins is antibody-based molecules, including recombinant monoclonal antibodies (mAb) and bispecific antibodies, antibody fragments, and Fc-fusion proteins heterogeneous in nature. Shi *et al*. used a weak cation-exchange column designed to analyze mAb and associated variants. The stationary phase comprises non-porous polymeric beads that are grafted with a highly hydrophilic, neutral polymer to reduce non-specific interactions between the surface and the biopolymer. Hydrophobic interactions with the resin are eliminated, allowing for non-denaturating chromatographic conditions. To determine modifications in charge variants, ion trap technology is applied for the MS-experiments. The different proteins collected in the trap are subsequently fragmented. The MS-evaluation of the fragments permits the top-down characterization of the protein. Shi and co-workers use a weak cation-exchange column coupled in-line to HRMS detection. The acidic charge variants components elute earlier off the column, and the basic variants were more retained, based on electrostatic interaction. As a model system, they oxidized an mAb with hydrogen peroxide. The hydrogen peroxide is introduced in a heated T-mixer situated in front of the HRMS, oxidizing the proteins, leading to additional cationic components. Overall, the chromatographic-detection setup demonstrates the advantage of the online method in providing site-specific structural information of charge modifications without fraction collection and laborious peptide mapping.[24]

One of the many challenging tasks faced by pharmaceutical companies is the determination of short-chained aliphatic and unsaturated organic acids during development and manufacturing. When assessing impurities in a starting material (educt), it is necessary to determine breakdown products in formulation stability monitoring or to control the cleaning of production lines. Because these short-chained, low molecular weight organic acids are hydrophilic and very polar, their identification and quantification are complicated at trace levels. Jensen *et al*. described a direct SAX approach for separating native, low molecular weight aliphatic and unsaturated organic acids in pharmaceutical solutions. The combination of anion exchange chromatography and mass selective detection enhances peak purity evaluations at trace levels.[25]

Lewis *et al*. followed a similar approach for the direct analysis of low-molecular-weight amines in pharmaceutical samples. Their report documents that improved amine analytics are central in pharmaceutical drug development and drug purity analysis. Their optimized design describes using a cation-exchange column hyphenated with a single quadrupole mass spectrometer for better selectivity and sensitivity. Due to the high degree of automation, including an in-situ preparation of the eluent, and by avoiding derivatization steps, the method's overall robustness increased.[26]

2.2 | Metabolites investigated with IC–ICP–MS

In contrast to MS-detection, the application of ICP-MS results in a high element-specific approach. Due to the high energy the compounds experience in the plasma, molecules, or multi-atom ions are cleaved, releasing mononuclear ions detectable by MS.

Selenium containing metabolites in cerebrospinal fluid of Parkinson patients were separated on a SAX column, and the effluent was directed to the nebulizer of an ICP-MS. The high chromatographic selectivity did not only allow the speciation of inorganic Se(IV) and Se(VI). It enabled the detection of eight additional selenium-containing metabolites yielding new insights into selenium homeostasis in Parkinson patients.[27]

3 | FOOD AND BEVERAGES

3.1 | Analysis of ions in food with IC-MS

Chloride, fluoride, and sulfur as minerals have vital functions in mammalian bodies. These anions and their counter ions are essential for balancing blood, osmotic pressure, and body water. Their conventional analysis is laborious and time consuming. Mesko and co-authors established an analytical workflow using SAX coupled with a single quadrupole mass spectrometer to analyze these minerals in egg powder, which is added to many food products. They also reported their analysis in feed and compared the results with AOAC International's recommended official chloride and fluoride methods. The new analytical flow path reduces the number of steps necessary, permits multicomponent analysis, and reduces the amount of chemicals. Simultaneously, the limits of detection and the sample throuput are improved compared to the AOAC International recommended methods.[28,29]

It is the prebiotic value of carbohydrate fibers to support mammalian intestinal microflora's growth and balance. They control the gastrointestinal peristalsis and reduce illness incidences such as colon cancer and diarrhea.[30] At high pH-values, carbohydrates, as polyalcohols, can be deprotonated and separated by SAX.[31] Consequently, Tedesco and co-workers use a high pH-anion-exchange separation and MS detection to determine saccharides in honey. The column effluent is desalted in-line with a continuously regenerated membrane-based ion exchanger before entering the MS. The coupling of ion-exchange chromatography with mass spectrometry minimizes the sample preparation steps before analysis to a simple dilution step of honey. The authors describe the confirmation of seven monosaccharides and thirteen oligosaccharides applying selected ion monitoring in the negative ionization mode. This work adds the use of MS-detection to the conventionally used pulsed amperometric detection (PAD) for carbohydrates. Additional detection selectivity facilitates the analysis of honey origins and helps to prevent food fraud.[32]

Minor-components introduced through the nectar collected by the bees influence the quality of honey. Neufang *et al*. combined a SAX column with a membrane-based desalter and a triple quadrupole MS to analyze glyphosate, glufosinate, and AMPA in honey. The diluted sample's high sugar content necessitated an inline sample preparation to prevent the carbohydrates from reaching the MS-interface. Matrix effects on the MS hardware are reduced, and the analytical instrument's uninterrupted operating time increases. According to the authors, removing the carbohydrates did not impact the analytical figures of merit and facilitated the polar pesticides' detection in the sub µg/L-range.[33]

Gasparini *et al*. extended this approach using high-resolution, accurate-mass MS detection. They analyzed an extended range of anionic pesticides and related metabolites in honey, fruits, and vegetables. As required by the European Community, this analytical procedure allows surveillance control of fruits and vegetables and monitoring the level of polar pesticides in food as environmental pollution indicators.[34]

In some countries, bromate, despite its carcinogenic properties,[35] is still allowed as a flour-additive to enhance the baking results. Therefore, it is essential to determine if all carcinogenic bromate was chemically reduced during the baking process. The method published by Aggrawal *et al*. includes sample preparation for baking goods and flour and the determination of bromate via IC-MS using a SAX-column. The high pH-eluent is continuously desalted before entering the MS-detector. With the use of a high capacity SAX column and a large-volume injection, low bromate concentrations were detected in flour and bread samples. The MS detector increased the specificity of the analysis and facilitated the interference-free bromate quantification.[36]

3.2 | Speciation of ions in food and beverages with IC-ICP-MS

Chromium (III) is an important element for humans and animals to regulate the efficacy of insulin in tissues and maintain the metabolism of carbohydrates, lipids, and proteins at healthy levels.[37] Chromium (VI), on the other hand, is allergenic, teratogenic, mutagenic, and carcinogenic; therefore, it is considered a class I human carcinogen.[38] As dietary intake of Cr(III) in most developed countries is not optimal, Cr(III)-based dietary supplements, as chromium-enriched yeast, are available. Due to the contrary properties of Cr(III) and Cr(VI), it is essential to precisely quantify Cr(VI), rather than the total Cr level, to evaluate potential risks and ensure safety for human health. Zhang *et al*. extracted Cr(III) and Cr(VI) with a pH-adjusted EDTA solution preserving the species distribution. The species were separated on two short SAX-columns (4 mm × 50 mm) and detected by inductively coupled plasma mass spectrometry (IC-ICP-MS).[39] A similar procedure was described by Mihai and co-authors to determine chromium picolinate and trace Cr(VI) in multivitamins and nutritional supplements.[40] In both publications, shorter columns yielded a shorter cycle time, increasing the sample throughput.

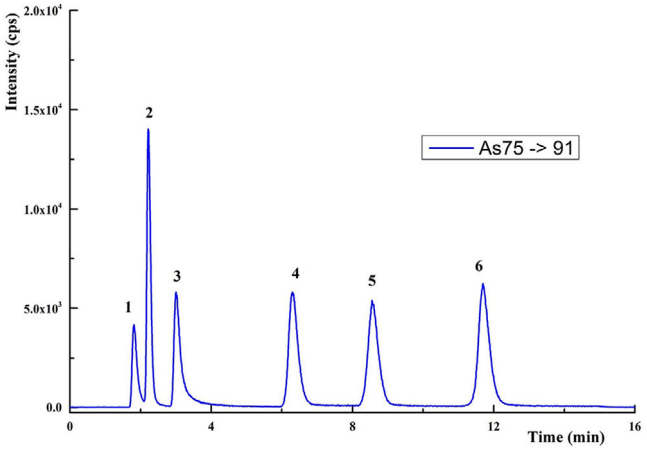

FIGURE 3 Chromatogram of arsenic species (10 µg/L) with gradient elution peak identifications: 1. AsC; 2. AsB; 3. As(III); 4. DMA; 5. MMA; 6. As(V), with permission from 43 ©2020 Food Chem

The speciation of chromium in marine life and poultry tissue is another example of anion-exchange chromatography combined with ICP-MS detection. Pechancová *et al*. focus their study on soluble Cr(III), total Cr(VI), and total bound Cr species in biological tissues. It is characterized by efficient sample preparation and fast simultaneous analysis of Cr species with parallel total Cr analysis serving for chromium balance evaluation. This work additionally focused on minimizing the impact of polyatomic interferences, known in ICP-MS.[8] Rice has been the focus of speciation analysis for many years. Chen *et al*. separated Cr(VI) from other chromium species in a simple ultrasonic rice extract by IC and applied ICP-MS detection. This methodology is utilized to determine Cr(VI) under high throughput conditions in different rice samples and can also be applied for screening rice for toxicity concerning Cr.[12]

More commonly known is the accumulation of arsenic species in rice. To assess potential health threats to the consumer, a differentiation between inorganic and organic arsenic species is essential.[41] Herath and co-authors describe the analysis of arsenite and arsenate and the less toxic dimethylarsonate and monomethylarsenate in sixteen different rice varieties. The fast isocratic separation is based on an anion-exchange separation hyphenated with ICP-MS.[42] Zou *et al*. report a similar approach for determining six arsenic species in edible mushrooms,[43] see Figure 3.

With the constant quest for new sources of "superfoods" to supplement modern society's most nutrient-deficient diets, sea cucumbers are gaining increasing popularity. Gajdosechova *et al*. describe the use of anion exchange and cation exchange separations for optimum selectivity of oppositely charged arsenic species. By coupling IC to ICP-MS, they identified and quantified inorganic arsenic, five known organic arsenic metabolites, and arsenosugars in aqueous extracts of sea cucumber.[44]

Selenium is considered to be of great importance for the human organism's proper functioning with multiple biological activities, which depend on the content of selenium and the nature of the seleno-compounds.[45] The critical issue is a very narrow safety range

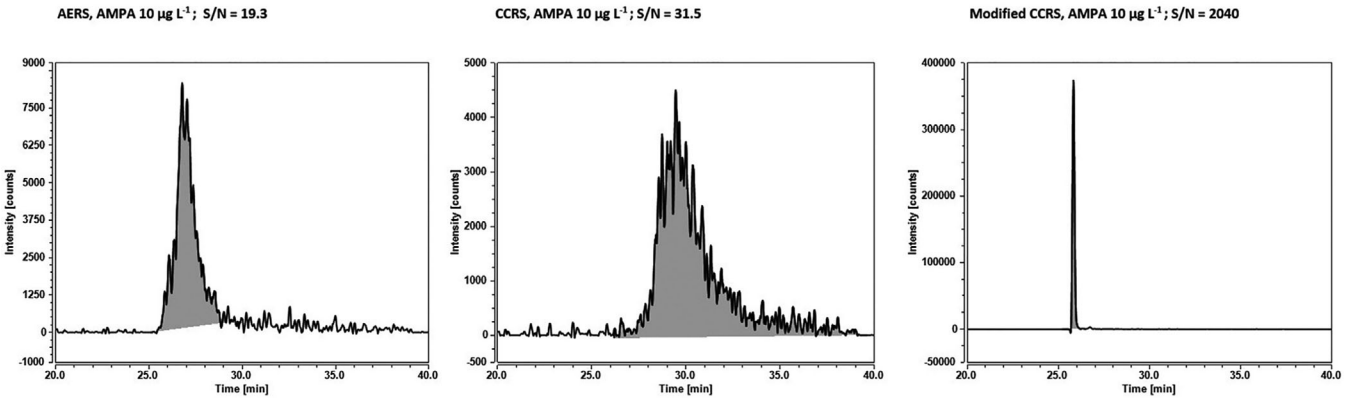

FIGURE 4 Chromatographic peak shape of AMPA analyzed using three modes of suppressors, electrolytic regenerating suppressor, AERS, with sulfuric acid regenerating suppressor, CCRS and modified chemical regenerating suppressor into ammonium form, CCRS Ammonium, with permission from 3 ©2020 Anal. Chim. Acta

between its deficiency and toxicity. Anion-exchange chromatography, combined with ICP-MS, is used to evaluate inorganic and organic seleno-compounds in onion, radish, and sunflower sprouts. In addition, Kurek *et al*. identified seleno-methylselenocysteine, selenomethionine, 5′-seleno-adenosine, 2,3-DHP-selenolanthionine, Se-S conjugate of cysteine-selenoglutathione, 2,3-DHP-selenocysteine-cysteine, 2,3-DHP-selenocysteine-cysteinealanine, glutathione-2,3-DHP-selenocysteine, gamma-Glu-MetSeCys, and glutamyl-glycinyl-N-2,3-DHP-selenocysteine. The characterization of selenium compounds was performed by ICP-MS, IC-ICP-MS, ultra-high performance liquid chromatography coupled with ESI triple quadrupole MS, or Orbitrap-MS/MS.[46]

Iodine, as its water-soluble iodide ion, is essential for the thyroid hormone synthesis.[47] Milk and dairy products are considered significant dietary sources of iodine in many countries. The bioavailability of iodine in cow milk for humans is tested by van der Reijden *et al*. analyzing iodine species in human urine by IC-ICP-MS. They found that nearly all of the iodine in cow milk is present as iodide. Although fractional iodine absorption from milk decreases with increasing dose, its bioavailability is high.[13]

The average daily intake of aluminum should not exceed a few milligrams. Despite the increasing understanding of its toxicity, human exposure to aluminum is continuously increasing. Aluminum has an active role in some neurodegenerative diseases, such as amyotrophic lateral sclerosis or Alzheimer's and Parkinson's dementia.[48] Karaś *et al*. speciated inorganic and organic aluminum complexes in white and red wine via cation-exchange chromatography hyphenated with ICP-MS.[49]

4 | ENVIRONMENTAL

4.1 | Analysis of environmental samples with IC-MS

Analytical techniques for environmental research are very often the same as used in life sciences,[8,18] food, and beverages.[9]

Geerdink and co-authors analyzed polar pesticides and their main metabolites (Glyphosate, Glufosinate, AMPA, MPPA) in 172 surface water samples from The Netherlands by IC-MS/MS. Some of the estuarine water samples show a moderately increased salinity (12.6 g/L). The high salt content limits the loadability of an ion-exchange column, thus potentially increase the method's quantification limit. The authors addressed this issue by selecting a high capacity anion exchanger. Their approach for continuously desalting the eluent uses a new tactic to regenerate the desalter's cation-exchange membranes. They use ammonium-based regenerating solutions instead of acids. Converting the cation-exchange membranes to the ammonium form and using NH_4OH in the regenerant, AMPA, as a zwitterion, stays in the anionic form. In this state, it shows negligible interaction with the membranes and the resin used in the desalter. This conversion results in a 100-fold increased sensitivity due to a much better peak shape,[3] see Figure 4.

Drinking water, often produced from surface water, requires disinfection before human consumption. During this process, disinfection by-products (DBPs) with potentially harmful properties can be formed.[50] Therefore, it is mandatory to determine the concentration of DBPs in drinking water. Zhang *et al*. published a method to analyze nine haloacetic acids (HAAs), bromate, and dalapon directly in drinking water samples by US EPA Method 557, combining a newly developed, dedicated SAX column with mass spectrometry. Due to the adapted chromatographic selectivity, the sample throughput increases by almost 40% compared to the reference method.[7]

The paper of Bruzzoniti *et al*. reports a chromatographic method complying with the Drinking Water 98/83/EC Directive revision. It allows the simultaneous determination of the requested five haloacetic acids and the three oxyhalides ions listed in the regulation. The method already includes three emerging iodinated acids, not yet considered by the revision, see Figure 5. The authors have also studied the effect of disproportionate concentrations of chlorite and chlorate on HAAs. Their new approach improves the determination of MCAA in the presence of high chlorite concentration. A new exciting option since it extends the scope of US EPA Method 557.[51]

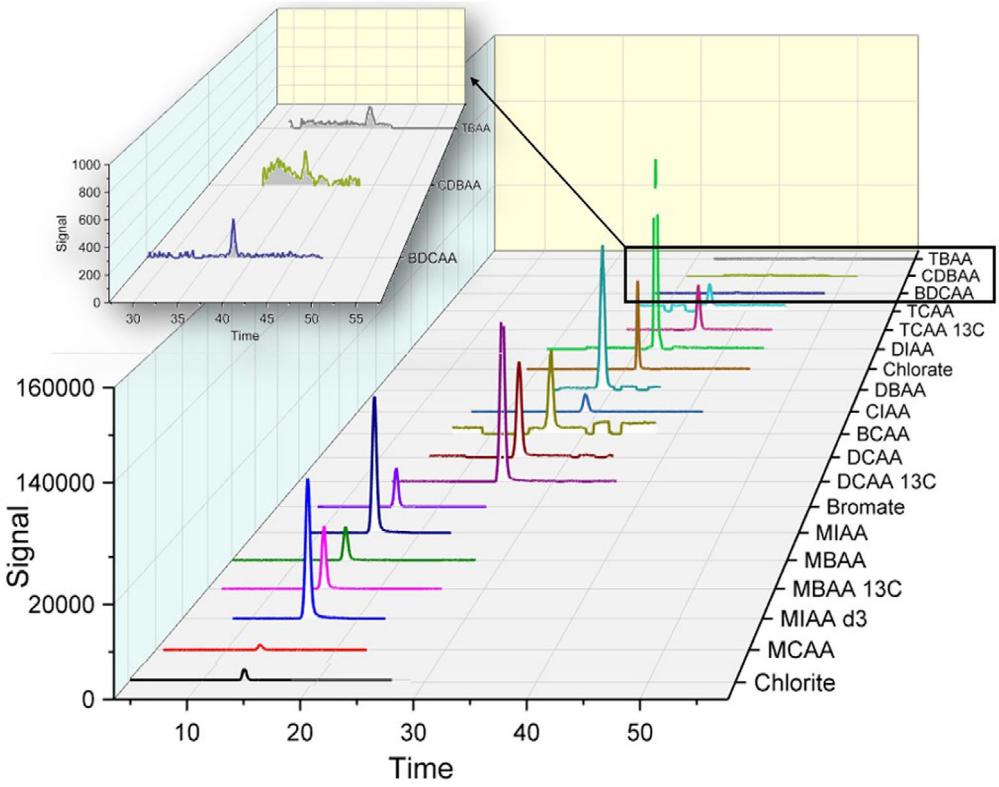

FIGURE 5 IC-MS/MS separation of fifteen DBPs and isotopically enriched internal standards (2 µg/L each), with permission from 51 ©2019 J. Chromatogr. A

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) have been produced and applied in numerous industrial and consumer products for >60 years.[52] They can be found in many environmental samples, such as soil, groundwater, and drinking water. Poly- and perfluorinated precursors to perfluoroalkyl acids (PFAAs) degrade to perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) as terminal products. Routine environmental analysis of PFASs by liquid chromatography-tandem mass spectrometry (LC-MS/MS) mainly comprises long-chain PFCAs and PFSAs. The conventionally used Reversed-Phase columns hardly retain lower molecular weight PFCAs and PFSAs. Janda *et al*. added IC-MS/MS to their analytical toolbox to access short-chained PFCAs. They included for the first time C2 and C3 PFCAs, thus improving the molar precursor balance of their soil assay.[53]

Biomass burning emissions, from both wildfires and anthropogenic burning, threaten human health. Those emissions are trackable by analyzing monosaccharide anhydrides, like levoglucosan, mannosan, and galactosan, in the air as biomass burning markers (BBMs). The BBMs can only be generated from cellulose and hemicellulose degradation when the burning temperature is in the range of 150-350 °C. In the publication of Rodriguez *et al*. the BBMs are separated at high pH by anion exchange chromatography. A membrane-based inline desalter converts the alkaline column effluent to water. A low concentrated LiCl-solution is added, and the neutral monosaccharide anhydrides form positively charged Li-adducts, being detectable with MS/MS in the positive ionization mode. The authors accurately determined the BBMs in marine and terrestrial aerosol samples from Australia, surrounding coastal waters, and remote areas of the Southern Ocean, covering a broad range of BBM concentrations.[54]

4.2 | Analysis of environmental samples with IC-ICP-MS

Oxoanions from metals can be present in various oxidation states in the environment. Different biological effects could result in contact with biological tissues, see Section 3.2. To determine the solubility and oxidation state of these oxy-metals has proven essential to human health. Hence, speciation analysis is necessary for atmospheric samples and soil. Taira *et al*. published the determination of oxoanions of arsenic, selenic, antimony, vanadium, and chromium as part of airborne particles ($PM_{2.5}$). They use anion-exchange separation combined with ICP-MS detection. The results improve the understanding of the metal behavior in airborne PM after depositing on a wet environment and biota.[55]

Hamilton and co-authors selectively determined hexavalent chromium in potentially-contaminated soil of agricultural origin in Zambia. The authors report a pH-optimized extraction method involving the addition of a complexing agent to prevent the interconversion of Cr-species. The soil extracts were analyzed for Cr(VI) with

anion-exchange chromatography coupled to ICP-MS. The additionally applied speciated isotope dilution mass spectrometry allows the accurate quantification of Cr(VI) in agricultural soils.[56]

Such accumulation can also happen for organisms living in a symbiotic relationship. Button *et al*. analyzed fungi growing on birch trees from woodland contaminated by a former mine. The samples were analyzed for arsenic species. The analysis was performed with separate anion-exchange and cation-exchange columns and instruments to address the arsenic species' different charges specifically. Detection is carried out by ICP-MS.[57]

Pollutants found in plants and body fluids can reveal environmental problems. In urine excretions from a cohort of 200 children, arsenic metabolites were analyzed with a mixed-mode ion-exchange column, with anion- and cation-exchange properties, by Bocca and co-workers. This column preceded the ICP-MS detector. They found arsenic metabolites originating from plants growing in polluted soil. This work's particular focus was on simplifying the analytical workflow since the column's selectivity allows for the simultaneous determination of anionic and cationic As-species.[58]

5 | SPECIATION ANALYSIS IN URANIUM, PLUTONIUM, ORE, AND BORIC ACID

When uranium ore is treated to enrich uranium, the concentrate will contain high levels of other elements. Rare earth elements (REEs) are difficult to remove, and their concentration needs to be determined. Bradley and co-authors use a mixed-mode column combining anion- and cation-exchange properties to separate these rare earth elements followed by ICP-MS detection. The analytes were measured by ICP-MS directly after being eluted from the column, and for comparison purposes, fractions were collected and analyzed offline. The two methods were used to compare the precision, accuracy, and processing time of the methodology. The online IC-ICP-MS method showed significant improvements regarding accuracy and uncertainty; it allowed the determination of REEs in minimally processed ore samples and permitted the determination of isobaric REEs.[59]

Wanna *et al*. used IC-ICP-MS to analyze lanthanides in spent nuclear fuel and environmental soil samples. Different nuclides are isobaric such as ^{150}Nd and ^{150}Sm or ^{142}Ce and ^{142}Nd. Therefore, chromatographic separation is essential to distinguish these nuclides. Wanna *et al*. report the application of a mixed-mode ion-exchange column to separate the lanthanides using a gradient elution protocol consisting of nitric acid and oxalic acid. Neutral plutonyl and uranyl nitrate complexes and anionic lanthanides oxalate complexes were separated and detected by ICP-MS. This sophisticated inline workflow avoids laborious manual wet chemistry.[60]

High-purity boric acid is used in the pharmacy, metallurgy, glass, ceramic, dye, textile, and nuclear industries. Wang *et al*. published a method for unsupervised analyzing trace metals in boric acid. The high concentration of boric acid in the samples causes interference in the determination of metal impurities. The analytical approach shows improved results for metal ions, Cr, Fe, Ni, Co, V, Mn, Cu, Zn, Cd, and Pb at trace level after online removal of the boric acid matrix. The transition metals are selectively trapped on two imidodiacetate-based cation exchange columns. After flushing the boric acid matrix to waste, the retained metals are eluted to a strong acid cation exchange column for separation. The selective and sensitive detection is carried out by in-line ICP-MS.[61]

6 | CONCLUSION

The analytical demand to quantify small molecular weight polar and ionic components in complex matrices drives the search for analytical methods with increased matrix-tolerance, increased selectivity and specificity, and, whenever possible, higher sensitivity. In contrast to conventional RPLC and HILIC approaches, IC offers significant advantages due to a complementary chromatographic selectivity and a different retention mechanism. Its higher matrix tolerance allows the injection of complex, often high ionic strength matrices, usually after a simple dilution, simplifying the analytical workflow. Some authors describe automated sample preparation, for example, in-line dilution, matrix elimination by Chelation, thus improving the overall reproducibility of the analytical results. In the context of this review, the term IC is used synonymously for ion-exchange chromatography. The particular challenge of combining IC with an MS is due to the composition of the respective eluents. In IC, corrosive acids or bases are used, which are often non-volatile and incompatible with MS. To prevent unwanted corrosion in the MS and to avoid ion suppression effects due to the ionic eluent components, the use of a continuously regenerated membrane desalter is described in the majority of articles related to IC-MS or IC-MS/MS. Through the capabilities of modern MS-equipment, targeted and nontargeted analytical approaches are possible, facilitating the determination of polar and ionic analytes in body fluids, pharmaceutical formulations, food samples, soil, aerosols, and drinking water. The articles review present evidence for increased sensitivity, increased selectivity, and often significantly improved analytical sensitivity.

Coupling IC with ICP, element-specific speciation is simplified. The knowledge about the distribution of an element amongst defined chemical species in a sample is essential due to the often significantly different toxicological or environmental properties of the element. IC-ICP-MS has been used to speciate chromium, arsenic, selenium, aluminum, iodide, lanthanides, and to differentiate isobaric nuclides. This speciation research concerns both inorganic and organic compounds in food, food supplements, drinks, tissues, body fluids, soil, airborne fine-particles ($PM_{2.5}$), and chemicals. All authors report about selectivity, sensitivity, specificity, and simplified workflow together with enhanced data reliability.

Table 1 summarizes all the relevant articles published between late 2019 and November 2020 used in this review.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

TABLE 1 Overview of the reviewed publications by application area

Area	Sample		Separation Mode	Column	Detection Mode	Reference	Reference Number
Life Science, Biomedical, Metabolomics, and Forensic							
Biomedical	mAb	Characterization	WCX	ProPac WCX-10	HRMS	Shi, Xao, et al.	24
Forensic	Urine	Nerve agents alkyl phosphonic acids	Mix mode RP-SAX	Own developed	Qtrap	Baygildiev, Vokuev, et al.	20
Life Science	Drugs	Organic acids	SAX	IonPac AS11-HC-4 µm	MS	Jensen and Man	25
Life Science	Drugs	Amines	SCX	IonPac CS20-4 µm	MS	Lewis, Jackson, et al.	26
Life Science	Tissues	Chromium Speciation	SAX	Hamilton PRP X-100	ICP-MS	Pechancová, Gallo, et al.	8
Life Science	Cerebrospinal fluid	Selenium Speciation	SAX	IonPac AS14	ICP-MS	Maass, Michalke, et al.	27
Metabolomics	Cancer cells	Anionic Metabolites	SAX	IonPac AS11-HC-4 µm	HRMS	Hirayama, Tabata, et al.	21
Metabolomics	Extracts human plasma cells and E. Coli	Pyridine nucleotides	HILIC Zwitterionic	AdvanceBio MS Spent	MS/MS	Røst, Shafaei, et al.	22
Metabolomics	Plants	Organic acids, phosphorylated intermediates, Calvin cycle and Krebs cycle	SAX	IonPac AS11-HC	MS/MS	Rosado-Souza, David, et al.	19
Metabolomics	Serum, Plasma, Urine	Anionic Metabolites	SAX	IonPac AS11-HC-4 µm	MS/MS	Sun, Saito, et al.	6
Metabolomics	Plasma, Urine	Profiling	Mix mode NP-SCX	HSS T3 + Intrada Amino Acid in series	QTOF	Le, Mak, et al.	17
Metabolomics	Urine	Perchlorate, nitrate, thiocyanate	SAX	IonPac AS16	MS/MS	Zhu, Huang, et al.	18
Food and Beverages							
Beverage	Wine	Alumium speciation	SCX	Hamilton PRP X-200	ICP-MS	Karaś, Zioła-Frankowska, et al.	49
Beverage	Cow milk	Iodine	SAX	IonPac AS19	ICP-MS	van der Reijden, Galetti, et al.	13
Food	Pet food	Halogens and sulfer	SAX	IonPac AS11-HC	MS	de Mello, Novo, et al.	29
Food	Egg Powder, Milk powder	Halogens and sulfer	SAX	IonPac AS11-HC	MS	Mesko, Toralles, et al.	28
Food	Honey	Carbohydrates	SAX	CarboPac PA10	MS	Tedesco, Barbaro, et al.	32
Food	Honey	Pestizides	SAX	IonPac AS19-4 µm	MS/MS	Neufang, Scheibner, et al.	33
Food	Bread, Flour	Bromate	SAX	IonPac AS31	MS	Aggrawal and Rohrer	36
Food	Fruit, vegetables, honey	Polar pesticides	SAX	IonPac AS19	HRMS	Gasparini, Angelone, et al.	34
Food	Baby food	Perchlorate, chlorate and polar herbicides	SAX	IonPac AS19-4 µm	HRMS	Panseri, Nobile, et al.	9
Food	Yeast	Chromium Speciation	Mix mode SCX-SAX	IonPac AG7	ICP-MS	Zhang, Cheng, et al.	39

(Continues)

TABLE 1 (Continued)

Area	Sample		Separation Mode	Column	Detection Mode	Reference	Reference Number
Food	Rice	Chromium Speciation	SAX	Hamilton PRP X-100	ICP-MS	Chen, Jiang, et al.	12
Food	Multivitamins, supplements	Chromium picolate, Cr(VI)	SAX	Hamilton PRP X-100	ICP-MS	Mihai, Kawamoto, et al.	40
Food	Rice	Arsenic speciation	SAX	Hamilton PRP X-100	ICP-MS	Herath, Kumarathilaka, et al.	42
Food	Edible mushrooms	Arsenic speciation	SAX	Hamilton PRP X-100	ICP-MS	Zou, Zhou, et al.	43
Food	Sea cumcumber	Arsenic speciation	SAX and WCX	Hamilton PRP X-100 and Metrosep C6	ICP-MS	Gajdosechova, Palmer, et al.	44
Food	Variety of plant sprouts	Seleno-compounds	SAX	Hamilton PRP X-100	ICP-MS	Kurek, Michalska-Kacymirow, et al.	46
Food	Tissues	Chromium Speciation	SAX	Hamilton PRP X-100	ICP-MS	Pechancová, Gallo, et al.	8
Environmental							
Atmosphere	Aerosol	Levoglucosan, mannosan, galactosan	SAX	CarboPac PA1	MS/MS	Rodriguez, Perron, et al.	54
Atmosphere	Airborne fine particles PM(2.5)	Oxy-metals of arsenic, selenic, antimony, vanadium, and chromium	SAX	IonPac AS16 and AG7	ICP-MS	Taira, Sakakibara, et al.	55
Food	Urine	Arsenic metabolites	Mix mode SCX-SAX	IonPac AS7	ICP-MS	Bocca, Pino, et al.	58
Plant	Fungus	Arsenic speciation	SAX and SCX	Hamilton PRP X-100 and Varian IonoSpher C	ICP-MS	Button, Koch, et al.	57
Soil	Soil	Short-chain perfluoroalkyl carboxylic acids	SAX	IonPac AS17C	MS/MS	Janda, Nödler, et al.	53
Soil	Agriculture soil	Hexavelent chromium	SAX	Hamilton PRP X-100	ICP-MS	Hamilton, Lark, et al.	56
Water	Surface water of low to moderate salinity	Glyphosate, AMPA, Glufosinate, MPPA	SAX	IonPac AS24A	MS/MS	Geerdink, Hassing, et al.	3
Water	Drinking water	Haloacetic acids, bromate, and dalapon	SAX	IonPac AS31	MS/MS	Zhang, Saini, et al.	7
Water	Drinking water	Haloacetic acids	SAX	IonPac AS24	MS/MS	Bruzzoniti, Rivoira, et al.	51
Miscellaneous							
Chemical	Boric acid	Trace metals	SCX	IonPac CG10	ICP-MS	Wang, Lou, et al.	61
Minerals	Uranium ore	Rare earth	Mix mode SCX-SAX	IonPac CS5A	ICP-MS	Bradley, Manard, et al.	59
Nuclear	Uranium and plutonium	Lanthanides	Mix mode SCX-SAX	IonPac CS5A	ICP-MS	Wanna, Van Hoecke, et al.	60

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