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1 **A REVIEW OF OXYHALIDE DISINFECTION BY-PRODUCTS DETERMINATION IN**
2 **WATER BY ION CHROMATOGRAPHY AND ION CHROMATOGRAPHY-MASS**
3 **SPECTROMETRY**

4

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15 by-products

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Abstract

This paper is a review of ion chromatographic (IC) separations of inorganic oxyhalide disinfection by-products (DBPs) in water and beverages. The review outlines the chemical mechanisms of formation, regulation of maximum allowable levels, chromatographic column selection and speciation. In addition, this review highlights the application of IC coupled to mass spectrometry (MS) for trace and elemental composition analysis of oxyhalides, along with the analytical considerations associated to enable sensitive analysis. Furthermore, a review of literature concerning IC determination of inorganic oxyhalide DBPs in environmental matrices, including water, published since 2005 is presented, with a focus on MS detection, and a discussion on the relative performance of the methods. Finally some prospective areas for future research, including fast, selective, multi-analyte analysis, for this application are highlighted and discussed.

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69 1. Introduction

70 Disinfection by-product (DBP) risk management is a major challenge for water
71 suppliers. Disinfectants can react with naturally-occurring materials in water to form
72 chemical by-products, which pose potential adverse health risks.

73 The primary requirements for water treatment are to remove organic matter,
74 inorganic species and micropollutants as well as to preserve the purified water for
75 human consumption. The two main options for water disinfection are chlorination and
76 ozonation. Whilst chlorination is the more historic and widely utilised of the two,
77 ozonation offers several advantages, such as destruction of a wider range of
78 organisms and the removal of tastes and odours. Even using ozonation, chlorine is
79 still required during the process for water preservation. However, elevated drinking
80 water occurrence of chlorate (ClO_3^- ; m/z 83), chlorite (ClO_2^- ; m/z 67), perchlorate
81 (ClO_4^- ; m/z 99) and also bromate (BrO_3^- ; m/z 128) have been identified as chlorine
82 dioxide or ozonation DBPs formed during water treatment, generally at the μg – mg/L
83 level [1-2]. This has resulted in significant research efforts to understand their
84 environmental occurrence, fate and risk to humans especially *via* drinking water
85 sources. In addition to this, it is also essential to monitor the quality of bottled
86 beverages, such as fruit juices, to ensure the ingredient water, as well as the finished
87 product, complies with the regulations and is safe for human consumption. The
88 presence and levels of these DBPs will depend on the disinfection process used, as
89 well as the chemicals already present within the source water. Several, more
90 detailed reviews on the disinfection of water, and formation of DBPs and their
91 potential health impacts on humans are available elsewhere and so only warrant a
92 summary discussion here [3-4].

93 Alongside other techniques, the analytes of interest, bromate, chlorate and
94 perchlorate, have been routinely and widely determined by ion chromatography (IC)
95 for over 20 years, and a review in 2005 by Michalski discussed the analysis of
96 inorganic oxyhalide DBPs using IC with conductivity, UV/Vis and mass spectrometry
97 (MS) detection [4]. The ability to speciate gives IC an obvious advantage over
98 several other analytical techniques, such as various spectroscopic methods including
99 atomic spectroscopy. Speciation can be vital when it comes to the identification and
100 characterisation of oxyhalides, such as in the differentiation of oxychloride species
101 (i.e. ClO_3^- , ClO_4^-) from the free chloride ion.

102 The aims of this review are to (a) detail the existing (IC(-MS)) methods available
103 from a perspective of inorganic DBPs analysis since 2005; and (b) discuss potential
104 directions for IC-MS technologies to further advance methods in terms of analysis
105 time, sensitivity, specificity and target analytes, for the analysis of oxyhalide DBPs.

106

107 **2. Formation and regulation of bromate, chlorate and perchlorate in water**

108 **2.1. Bromate**

109 Bromate is formed when water containing bromide is exposed to disinfection using
110 the ozonation process. This process infuses ozone into the water in order to remove
111 the organic and inorganic pollutants present *via* oxidation and
112 filtration/sedimentation.

113 A mechanism by which bromate is formed was proposed by Legube *et al.* and is
114 shown in Figure 1 [5]. The researchers state that reactions between ozone, bromide
115 and hypobromite are relatively slow at low temperatures, but they are also
116 dependent on the pH of the water and concentration of bromide (typically between
117 trace-0.5 mg/L concentrations in fresh water [6]). Bromate can also be formed when

118 disinfecting drinking water using concentrated sodium hypochlorite. Bromide is
119 present in both the chlorine and sodium hydroxide used to form hypochlorite, and is
120 quickly converted to bromate at the high pH of the solution (a 10-15 % solution of
121 hypochlorite has a pH ~13) [7]. Once formed, bromate is very stable in water, and
122 difficult to remove.

123 The International Agency for Research on Cancer (IRAC) has classified bromate in
124 group 2B as a possible carcinogen to humans. Using the available information, the
125 European Commission and the US Environmental Protection Agency (EPA) have set
126 a maximum allowable level (MAL) of 10 µg/L in drinking water. The U.S. Food and
127 Drug Administration (FDA) adopted the EPA levels for bromate and chlorite in 2001
128 as some food and beverage companies use ozonation or other disinfection
129 treatments on their products [8]. This was also the case for residual disinfectants,
130 chlorine, chlorine dioxide and chloramines. Despite these regulatory levels, in a 2005
131 study by Snyder *et al.*, the concentration of bromate exceeded this limit in three of
132 the 21 tested bottled waters in the US with the highest concentration found to be 76
133 µg/L, almost eight times the MAL [9].

134 2.2. Chlorate

135 Chlorate, and also chlorite, are DBPs either formed by the decomposition of sodium
136 hypochlorite, shown in the reaction below, or alternatively when chlorine, chlorine
137 dioxide or chloramine is used to disinfect drinking water.

138



141

142 As with bromate, these oxychlorides are more likely to occur at high pH and
143 temperatures. It is also possible for chlorate to enter water *via* environmental
144 contamination due to its occurrence in manufacturing and household items such as
145 in some weedkillers. Although not classified by IRAC due to limited toxicological
146 data, the World Health Organisation (WHO) recommends provisional guideline
147 values for both chlorate and chlorite concentrations in drinking water at 0.7 mg/L
148 based on a tolerable daily intake of 30 µg/kg/d (by body weight) [10]. In the study by
149 Snyder *et al.* chlorate was detected in 71 % of samples, although below the guideline
150 value at concentrations ≤5.8 µg/L.

151 2.3. *Perchlorate*

152 Another oxychloride anion, perchlorate, is particularly toxic to humans at much lower
153 concentrations due to interference with the uptake of iodine in the thyroid and
154 mammary glands, resulting in hypothyroid function. Due to this toxicity, the US EPA
155 established an official reference dose of 0.7 µg/kg/d (by body weight). It again is a
156 product of decomposition of sodium hypochlorite, however a large proportion of
157 perchlorate contamination is environmental through the use of propellants, fireworks
158 and explosives.

159 In the US, perchlorate is still under consideration for enforceable regulation by the
160 US EPA, and is currently only regulated in drinking water at State level in the US in
161 both Massachusetts and California at 2 and 6 µg/L respectively. In 2013, Iannece *et al.*
162 measured concentrations between <5-75 ng/L of perchlorate in 70 % of 62 bottled
163 waters tested from 15 of the 20 regions across Italy [11]. These found concentrations
164 are of similar magnitude to those previously detected by Snyder *et al.* (<0.74 µg/L)
165 and pose no immediate health concern in accordance with current recommended
166 values [9].

167

168 **3. Determination of DBPs by IC**

169 As mentioned, oxyhalide DBPs in water have been determined by IC for over two
170 decades, with the ability to speciate offering an advantage to oxyhalide analysis, as
171 previously discussed in Section 1. For this reason, alongside its robust and reliable
172 nature, and capability to achieve the required sensitivity, IC is an approved technique
173 for the monitoring of inorganic anions and oxyhalides in environmental matrices for
174 many agencies worldwide, such as the US EPA. Table 1 shows a list of existing IC
175 methods, focussing on those reported since 2005 for the analysis of inorganic DBPs
176 in environmental matrices. Relevant monitoring methods, such as those developed
177 by the US EPA, pre-dating 2005 are also included.

178 As can be seen in Table 1, the two main IC column types utilised for the
179 determination of DBPs are the Metrosep and also IonPac columns. Both of these
180 column types consist of organic polymer particulates, allowing stability at higher pH
181 compared to silica columns, with various capacities and selectivities. For example,
182 the IonPac range is based on ethylvinylbenzene-divinylbenzene (EVB-DVB) with a
183 high degree of crosslinking (<55 %) to maintain a stable structure. In general, particle
184 size in IC is larger than reversed-phase liquid chromatography (RPLC), with a
185 diameter <10 µm to prevent band broadening. However, in recent years there is a
186 trend towards a reduced particle size of 4 or 5 µm, or alternatively monolithic
187 columns, in order to increase efficiency and capacity whilst retaining the required
188 selectivity. Functional groups are then either surface functionalised, agglomerated or
189 grafted to the surface. Column capacity is an important factor for DBP analysis as
190 the ions in the sample matrix can overwhelm the trace amounts of the DBP

191 oxyhalides present. Typically for this application a moderately high capacity (~40-60
192 μ equivalents/column for 2 mm I.D. columns) is used, as highlighted throughout this
193 review. The selectivity of the stationary phase must also be considered, especially
194 when used with conductivity detection, to enable the analytes of interest to be
195 sufficiently resolved from the sample matrix.

196 These days the column formats are typically micro-bore (2.0 mm I.D., occasionally
197 1.0 mm I.D.) or standard bore (4.0 mm I.D.), with the IonPac recently expanding into
198 capillary format (0.25 or 0.4 mm I.D.). With regards to column length, the IonPac
199 favour a standard 250 mm, whereas the Metrosep is available in 100, 150 or 250
200 mm for most of their resins. The majority of columns discussed in this review are 250
201 x 2.0 mm I.D. unless stated otherwise.

202 One of the few columns demonstrated to simultaneously analyse a wide range of
203 both oxyhalides and common anions found in water and beverages is the IonPac
204 AS20. This micro-bore column has a comparatively high capacity of 77.5
205 μ equivalents/column (2.0 mm I.D.), due to hyperbranched functional groups, and
206 also displays very low hydrophobicity making it ideal for the analysis of perchlorate in
207 environmental samples. This hyperbranched column arises as instead of coating the
208 polymer substrate with latex particles, the first layer of stationary phase is
209 electrostatically attached to the surface. Diepoxide monomers and primary amines
210 added layer by layer in a polycondensation reaction which creates chains along the
211 polymer backbone. Johns *et al.* used this column for the separation of 18 anions,
212 potentially present in explosive residues in soil using a hydroxide gradient [12]. This
213 was achieved in 18 min with only a minor sacrifice of resolution, as highlighted in
214 Figure 2, showing potential for detecting trace concentrations of these analytes in
215 water. Whilst conductivity detection was used in this case, a similar method has

216 been utilised with MS detection [13]. However, the authors' experience has shown
217 that the resin will display increasingly reduced capacity and require careful
218 monitoring with regular replacement (approximately every 6 months) when used for
219 high through-put work, such as water monitoring, or with complex sample matrices.
220 Another hyperbranched column frequently used in the monitoring of water quality is
221 the IonPac AS19, designed for the trace detection of bromate in drinking water [14].
222 Cengiz and Bilgin was reported as the first study to analyse perchlorate, nitrate and
223 thiocyanate, as inhibitors of iodide uptake in the thyroid, with six common anions
224 present in drinking water in a single run [15]. Using a standard 4 mm I.D. AS19
225 column with flow rate of 1 mL/min enabled a separation of the nine analytes in 17.5
226 min, a very similar separation time to that achieved on the AS20 by Johns *et al.*
227 Retention time repeatability for all analytes was <1 %, however, long term
228 robustness or repeatability does not seem to have been reported.

229 Very few IC methods utilise UV/Vis detection as a large proportion of small ions are
230 non-absorbing species. Therefore indirect detection with a strongly absorbing eluent,
231 such as phthalate, is often used [16]. Alternatively a post-column reaction reagent is
232 added [17]. US EPA methods 300.1 and 317 measure oxyhalide DBPs in drinking
233 water using IC coupled to conductivity and UV/Vis detection respectively with o-
234 dianisidine added as the post-column reagent for bromate detection [18]. These
235 methods employ an IonPac AS9-HC column and 9 mM carbonate eluent, with the
236 2.0 mm I.D. column having a capacity of 47.5 μ equivalents/column [18-19]. Gandhi
237 recently combined the two US EPA 300.1 methods (Part A for common inorganic
238 ions, while B focuses on the analysis of DBPs) in order to reduce analysis time [20].
239 Instead of the AS9-HC, this approach utilised a Metrosep A Supp 7-250 (4.0 mm
240 I.D.) with 3.6 mM sodium carbonate for the analysis of seven common anions as well

241 as chlorite, chlorate and bromate with a separation time of 30 min. The column is
242 designed for highly efficient separation of these analytes down to low $\mu\text{g/L}$
243 concentrations, based upon chemical modification of a polyvinyl alcohol substrate,
244 with a carbonate eluent preferred, which can allow the ionic strength of the eluent to
245 be varied [21]. Using conductivity detection analytes were detected at single digit
246 ppb levels; however direct coupling to MS would be possible with the conditions
247 used, to lower detection limits for trace analysis. Drinking water matrices can pose
248 problems for trace DBPs determinations due to high concentrations of interferent
249 ions such as chloride, which can co-elute with trace oxyhalides. In order to overcome
250 this analyte specific detection modes, such as MS, are increasingly favoured,
251 particularly where full resolution is not achieved.

252 3.1. 2D-IC

253 Two-dimensional (2D) chromatographic configurations have also become more
254 popular in the past decade to improve resolution, as shown in Table 2. There are
255 several advantages to this approach including enhancement of the signal and also
256 improved selectivity, with the possibility of resolving peaks of interest from matrix
257 analytes due to the combination of the two different stationary phase chemistries.

258 A 2D-IC method for the detection of perchlorate in water using suppressed
259 conductivity detection was developed in 2006 by Wagner and colleagues [22]. In the
260 first dimension, a large sample volume (<4 mL) was injected onto an IonPac AS20 (4
261 mm I.D.), diverting the separated matrix ions to waste while the analyte(s) of interest
262 were cut, trapped and concentrated in a concentrator column, which offers greater
263 sensitivity over using an injector loop. These analytes were then separated on a
264 second column, in this case an IonPac AS16 (2 mm I.D.), and detected using

265 conductivity, shown in Figure 3. This method is included in the US EPA's
266 publications (Method 314.2) and has since been run with a capillary column (0.4 mm
267 I.D.) in the second dimension, marginally enhancing the lower concentration
268 minimum reporting level (LCMRL) from 55 ng/L to 50 ng/L [23]. A similar method,
269 which could arguably be considered multidimensional, to remove interference from
270 high salt matrices is a cycling-column-switching mode. To enable sensitive detection
271 of nitrate and chlorate in a high chloride matrix, Wang and colleagues trapped
272 analytes on a concentrator column using just a single pump, analytical column
273 (IonPac AS19) and detector, and two valves [24]. For the concentration step an
274 IonPac AG16 was actually used. With the first part of the separation going to waste,
275 the analytes of interest were concentrated on the concentrator column before being
276 separated on the analytical column; these steps were repeated until the matrix was
277 eliminated. After just two elimination steps the LOD for chlorate was 2.2 µg/L.

278 Zakaria *et al.* actually went a step further in terms of multidimensional separations
279 and used a third dimension to improve the detection of bromate in seawater [25].
280 This extra dimension, which utilised the same phase as the second (IonPac AS24 (2
281 mm I.D.)), allowed the interference from sulphate present in the second dimension to
282 be removed from the third, similarly to that of chloride between the first and second,
283 improving the LOD greatly from 1050 µg/L to 60 µg/L.

284 Another, arguably simpler, 2D-IC setup used two columns with different selectivities
285 (IonPac's AS19 (2 mm I.D.) and AS20 (4 mm I.D.)) coupled in series *via* a tee-piece
286 to allow independent control and modification of the eluent between the two
287 columns, and only one suppressor and conductivity detector [26]. This approach
288 separated 18 inorganic anions within 28 min including chlorite, chlorate, perchlorate
289 and bromate. Significantly, it improved resolution (>1.3) compared to the previous

290 single column method just utilising the AS20 [12], showing the potential of 2D-IC
291 analysis for a larger range of inorganic anions and oxyhalides, without necessarily
292 the need for MS detection.

293

294 **4. Determination of DBPs by IC-MS and IC-ICP-MS**

295 Michalski's 2005 review showed that the majority of IC methods were comparable,
296 with low- $\mu\text{g/L}$ levels reported for the analytes of interest regardless of detection
297 mode. However, with MS detection it was possible to improve sensitivity by up to an
298 order of magnitude, highlighting one of the advantages in its use [4]. Additionally, the
299 ability to gather information about the elemental composition and structure of the
300 analytes offers a more confident identification, particularly for complex matrices. The
301 obvious disadvantages of MS-based detection techniques are that they add
302 considerable complexity and significant cost to the analysis. Despite this, MS
303 techniques have been utilised more routinely in recent years in conjunction with IC.

304 US EPA Method 321.8 is one of the earliest (1997) approved monitoring method
305 using IC coupled to MS, detecting bromate in water using IC-inductively coupled
306 plasma (ICP)-MS with a detection limit down to $0.3 \mu\text{g/L}$, well below the MAL [27].

307 ICP-MS has proved to be a very useful analytical technique for the monitoring of
308 water quality. However, there has been very little advancement in IC-ICP-MS for
309 oxyhalide analysis since 2005, with the rapid, sensitive detection of bromate being
310 the focus of these developments [28]. Whilst the analysis time is fast ($<10 \text{ min}$), it
311 does mean a sacrifice in the number of analytes analysed, with methods typically
312 focussing on only one or two analytes, as highlighted in Table 3. An interesting paper
313 by Schwan *et al.* looked at low mg/L concentrations for both chlorate and chlorite in
314 blood samples, with the potential to look at other biological samples such a tissue

315 and urine [29]. The presence of chlorate salts in animals for human consumption
316 could be an alternative route to the ingestion of these oxyhalides and so should be
317 regulated in much the same way as drinking water. The authors found that while
318 chlorate is stable over several hours in whole blood, chlorite degrades very quickly
319 (to below the LOD within 18 min). The authors also attempted to improve the
320 detection of chlorine using a triple quadrupole mass analyser after ICP ionisation.
321 Unfortunately chlorine contamination potentially coming from the plasma flame was
322 an issue here. The technique can be very sensitive to isotopic interference produced
323 by polyatomic species arising from the plasma, and therefore the development of IC-
324 electrospray ionisation (ESI)-MS maybe considered more promising [30]. EPA
325 method 557 (2009) is another method which will analyse bromate, along with
326 haloacetic acids (HAAs), another group of DBPs, and dalapon, which is a herbicide,
327 although instead of ICP-MS utilises ESI with a triple quadrupole mass analyser.
328 Table 3 shows a comprehensive list of existing IC-MS methods for the analysis of
329 relevant inorganic anions and oxyhalides since 2005 in a range of matrices.
330 As with ICP-MS, the range of chromatographic methods for trace multi-analyte IC-
331 ESI-MS is still somewhat limited, with several methods focussing on analysis specific
332 to perchlorate. An example of which is US EPA Method 331.0 published in 2005 [31].
333 This approach uses a weakly conducting eluent of 200 mM methylamine allowing it
334 to be unsuppressed and coupled directly to a quadrupole MS due to its volatility.
335 Wilkin *et al.* used a similar method for the analysis of perchlorate in surface water,
336 however added acetonitrile post-column to the eluate to promote analyte
337 volatilisation and improve the sensitivity [32]. Due to the potential for interference
338 with a common isotope of bisulphate ($^1\text{H}^{34}\text{S}^{16}\text{O}_4^-$; m/z 99), multiple reaction
339 monitoring (MRM) detection is recommended for perchlorate with the transition of

340 [M]⁻ to [M-O]⁻ monitored. The AS21 column has also been used for a wider range of
341 analytes, namely perchlorate, bromate, bromide, nitrate, chlorate, chlorite and iodide
342 in tap, ground, surface and bottled water collected in China by Wu *et al* [33]. Again
343 this method uses methylamine in the eluent with limits of quantitation (LOQs) at 0.02,
344 0.17 and 0.35 µg/L for perchlorate, chlorate and bromate respectively, all below their
345 MALs in water, using a 100 µL injection volume. This is a lower capacity version (45
346 µequivalents/column compared to 77.5 (2.0 mm I.D. x 250 mm)) of the AS20, and is
347 specifically developed for MS compatibility [34].

348 The addition of organic solvent to the eluent can lead to changes in the column
349 selectivity and retention behaviour, which could be considered advantageous when
350 optimising separations for a large range of analytes. Gilchrist *et al.* showed a
351 complete reversal in selectivity of the IonPac AS18 column with the addition of 80 %
352 acetonitrile [35]. For the optimised separation, as well as practical coupling of IC to
353 high resolution accurate mass (HRAM) MS, 30 mM hydroxide in 35 % acetonitrile
354 was used to separate 11 anions of interest, including bromate, chlorate in
355 perchlorate in <30 min. One of the two chromatographic methods specified in the US
356 EPA Method 332.0 uses a standard-bore Metrosep A Supp 5-100 with an eluent of
357 30 mM hydroxide in 30 % methanol, for the specific detection of perchlorate [36].
358 This column has a particle size of 5 µm, smaller than most of the IonPac series, and
359 the column used in this method (4.0 mm I.D. x 100 mm) has a capacity of 56
360 µequivalents/column, allowing the rapid and highly efficient separation of strongly
361 retained anions, such as perchlorate. Although membrane suppressors can be used
362 with <40 % organic solvent, this method uses a packed bed suppressor to guarantee
363 compatibility with the eluent and backpressure limitations. It was possible to achieve
364 detection limits for perchlorate in water at 0.02 µg/L using 100 µL injection volumes

365 and a quadrupole mass analyser. However, as organic solvent in the eluent pre-
366 separation can lead to unusual retention behaviour due to changes in the packing
367 bed volume [35], naturally occurring perchlorate present in the samples was
368 measured relative to an ^{18}O -enriched $^{35}\text{Cl}^{18}\text{O}_4^-$ internal standard to ensure reliable
369 identification, as well as quantitation due to varying ionisation efficiencies. Figure 4
370 highlights the trace detection of perchlorate in a high matrix sample (1 $\mu\text{g/L}$ in 1000
371 mg/L matrix) using an almost identical method (flow rate increased from 0.7 to 0.8
372 mL/min and MS conditions adjusted for the method), emphasising the attraction in
373 employing MS detection over non-specific options to limit interferences and avoid
374 false positives [37]. The alternative 332.0 method utilises the IonPac AS16 with 65
375 mM hydroxide, a membrane suppressor and a post-suppressor addition of
376 acetonitrile. The detection limit for this method was again 0.02 $\mu\text{g/L}$. The AS16 is
377 arguably the most popular column for IC analysis of perchlorate, being used by
378 several researchers, as highlighted in Tables 1 and 3 [38-41]. Differing from the
379 newer hyperbranched resins, the core polymer substrate is coated with
380 functionalised 80 nm MicroBeadTM latex particles, which does lower the capacity
381 comparatively (42.5 $\mu\text{equivalents/column}$ (2.0 mm I.D. x 250 mm)), however could
382 potentially be considered more robust. As mentioned, most of these methods focus
383 primarily on perchlorate in biological or environmental samples [42-44], using simple
384 isocratic hydroxide eluents. However, Barron and Paull used this column to
385 determine a range of analytes including inorganic anions, oxyhalides and HAAs in
386 soil and water matrices shown in Figure 5 [2]. This method uses a hydroxide gradient
387 with supplementary flow of methanol post-suppressor in order to improve the
388 ionisation efficiency at the ESI source. Addition of organic solvent *via* a tee-piece
389 post-column/suppressor is common as membrane suppressors have low

390 compatibility (<40 %) with organic solvents. However, sensitivity can be affected due
391 to dilution of the analytes. In this case, LODs were reported at 39, 9 and 10 µg/L for
392 bromate, chlorate and perchlorate respectively with no sample pre-treatment, which
393 falls above the MAL for bromate. An alternative approach to IC-MS is to utilise a
394 paired-ion electrospray ionisation (PIESI) method forming ion association complexes
395 post-column to enhance sensitivity and selectivity of these low molecular weight
396 molecules [45-46]. This approach was recently reviewed by Breitbach *et al.* and
397 Barron and Gilchrist and so will not be discussed extensively here [47-48]. Though,
398 focussing on perchlorate, Martinelango and colleagues added di-cationic reagents
399 after the IonPac AS16 resin to form ion association complexes. This not only allows
400 detection in positive ESI mode, which generally produces a better signal, but also
401 raises the *m/z* offset, decreasing potential for background interference. This is
402 especially useful for improving selectivity of perchlorate against bisulphate, as
403 bisulphate is not as amenable to forming ion-pairs as perchlorate.

404 As mentioned previously, the AS20 column has been utilised with both conductivity
405 [12] and MS detection [13, 49], and frequently so. Again both IC-MS method
406 focussed primarily on perchlorate, although one was analysing snow samples and
407 the other infant formula. This enabled the groups to achieve fast separations (< 15
408 min) as resolution of a large range of other analytes was not required. Using a larger
409 750 µL injector loop Furdui *et al.* were able to achieve 0.3 ng/L for perchlorate in
410 snow, rising to 1.5 ng/L for iodate. Both methods used MRM to monitor the loss of an
411 oxygen from perchlorate.

412

413 **5. Future perspectives for IC-MS analysis of DBPs**

414 An ideal method for the analysis of DBPs would be fast to enable high through-put
415 and cost minimisation whilst being selective for a large range of both common anions
416 and oxyhalides. Preferably there would be limited matrix interferences without the
417 need for sample pre-treatment. It is essential that the method be sensitive with a
418 requirement to be down to 1 µg/L for bromate in particular.

419 For this particular application, higher capacity columns are generally preferred. This
420 enables larger injection volumes (can be <5 mL) to be utilised, improving sensitivity
421 for trace analytes in high matrix samples while maintaining a good peak elution
422 profile. The IonPac AS27 is one of the latest columns released for the analysis of
423 trace oxyhalides and inorganic anions in drinking water matrices [50]. It has a similar
424 selectivity to the AS19 (also designed for this purpose); however the IonPac AS27
425 has a bead diameter of 6.5 µm instead of 7.5 µm, which would offer more efficient
426 and resolved separations. The IonPac AS19 has also recently been released in a 4
427 µm version, increasing the capacity from 55 to 60 µequivalents/column (2.0 mm I.D.
428 x 250 mm). Again peak efficiency and resolution would be further improved, however
429 due to the standard dimensions of the column, when run at typical flow rates (~0.25
430 mL/min for micro-bore columns) the back pressure can exceed the instrumental limit,
431 unless the instrument is specifically designed for high pressure applications [14].

432 As previously mentioned, due to the need for fast and efficient separations, there is
433 an increased interest in monolithic columns, leading to a recent expansion in
434 commercially available columns. Monoliths offer faster separations at high resolution
435 as they consist of a single rod of solid stationary phase often with a bimodal structure
436 of macropores (1-6 µm) and mesopores (10-20 nm) for higher through-flow and

437 mass transfer. Due to the high pH of the hydroxide eluent, polymeric columns are
438 preferred for their stability in alkaline conditions. Commercial polymer monoliths
439 functionalised for anion exchange, such as the IonSwift MAX columns, have recently
440 become available; however generally have a lower peak efficiency compared to their
441 silica-based counterparts. The majority of these commercially available monoliths
442 are offered in capillary-scale, again requiring specialist instrumentation.

443 Capillary-scale IC is another area that has garnered some attention in recent years,
444 although a consideration for coupling to MS is analytical flow rate. To be compatible
445 with ESI, lower flow rates are generally required, whereas band broadening
446 increases with too low a flow rate for the separation and also source fluidics are no
447 longer sufficiently optimised. Typically, micro-bore analytical columns (2.0 mm I.D.)
448 are employed at flow rates between 0.1-0.7 mL/min. Capillary IC differs to other
449 types of capillary-scale separation technologies, operating at higher flow rates (~5-10
450 $\mu\text{L}/\text{min}$) than typical for coupling to current nano-spray ionisation technologies (20-50
451 nL/min). These may also be arguably considered slightly low for ESI-MS at the
452 micro-bore scale (~100 $\mu\text{L}/\text{min}$ -1 mL/min), and therefore, coupling micro-bore IC to
453 MS at flow rates between 0.2-0.5 mL/min is likely to still offer better performance at
454 this time. However, it is highly likely that IC-MS will increasingly move towards
455 capillary-scale in the future. To the best of the authors' knowledge, the IonSwift
456 MAX-100 is the only commercially available polymer monolith at the micro-bore
457 scale (1.0 mm I.D.). Whilst designed for the fast analysis of organic acids and
458 inorganic anions, it's potential for the analysis of inorganic DBPs has been
459 demonstrated with the separation of perchlorate, chlorate and several common
460 anions in <20 min as shown in Figure 6, although this work did utilise the capillary-
461 scale version (0.25 mm I.D.) [51].

462 Shorter column lengths could also be considered for faster separations. Tyrrell *et al.*
463 separated seven anions, including chloride, chlorate, nitrate, sulphate and
464 perchlorate in under 3 min [52] using an hydroxide ramp (Figure 7(b)) and 50 mm
465 length column with 4 mm I.D. compared to 11 min for standard length IonPac AS20
466 (250 mm). Whilst the analytes of interest were not all baseline resolved, it does show
467 the great potential shorter columns have where high throughput, fast analysis are
468 required, such as for multidimensional chromatography.

469 As discussed earlier 2D-IC configurations is another area increasing in popularity. To
470 the best of the authors' knowledge there are no existing 2D-IC-MS methods for
471 inorganic compounds, such as oxyhalides. However, there is an example of 2D-IC-
472 MS for small organic acids in seawater, with the first dimension used to separate the
473 organic acids from inorganic ions, and separating these acids in the second
474 dimension [53]. In this case the advantage of using MS was the added sensitivity it
475 offers (LODs were ~2-5x lower than with conductivity), as well as a less ambiguous
476 identification, offering an alternative way to achieve the selectivity and sensitivity
477 required for the analysis of DBPs.

478

479 **6. Conclusions**

480 IC-MS technologies make a strong contribution to the analysis and monitoring of ion
481 concentrations in drinking water and beverages. This review has highlighted the
482 recent developments to further enhance methods for the application of oxyhalide
483 DBPs analysis. IC-MS offers advantages over other analytical techniques in terms of
484 its ability to speciate, which is essential in the identification of oxyhalides, as well as
485 offering selectivity and sensitivity over traditional, non-specific detection modes such
486 as conductivity and UV/Vis. While existing methods comply with the requirements set

487 by regulatory agencies, predominately these will focus on a limited number of
488 analytes. There is still opportunity to develop the use of IC-MS further not only with
489 regards to range of analytes related to water analysis, but to improve sensitivity also
490 with a number of exciting technological developments.

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701

Table 1. Comparison of ion-exchange chromatography methods for the determination of DBP related anions and oxyhalides

Analytes	Sample type	Column(s)	Eluent	Flow rate (mL/min)	Analysis time (min)	Suppressor	Detector	Post-column	LOD ($\mu\text{g/L}$)	Ref.
BrO_3^- , ClO_3^- , Cl^- , Br^- , NO_3^- , SO_4^{2-}	Water	Metrosep A Dual 1 (3x150 mm)	1 mM ortho-phthalic acid, 2 % MeCN	1	15	-	UV/Vis	-	2000-5000	[16]
F^- , ClO_2^- , BrO_3^- , Cl^- , NO_2^- , ClO_3^- , NO_3^- , SO_4^{2-} , PO_4^{3-} , ClO_4^- , CNO^- , $\text{S}_2\text{O}_3^{2-}$, SCN^- , organic acids	Soils/residues	IonPac AS20 + AG20 (2x250 mm)	5-100 mM KOH grad.	0.375	18 + equil.	ASRS	Conductivity	-	2-27	[12]
BrO_3^- , ClO_2^- , ClO_3^- , Br^-	Water	IonPac AS9-HC + AG9-HC (4x250 mm)	9 mM Na_2CO_3	1.3	25	ASRS	Conductivity/UV/Vis	0.7 mL/min o-dianisidine	$\mu\text{g/L}$ levels	[18]
ClO_2^- , ClO_3^- , BrO_3^- , Cl^- , Br^- , NO_3^- , PO_4^{3-} , SO_4^{2-}	Water	Metrosep A Supp 5 + 1 (4x250 mm)	3.2 mmol/L Na_2CO_3 / 1 mmol/L NaHCO_3	0.7	32	MSM	Conductivity	-	-	[54]
Part A: F^- , Cl^- , NO_2^- , Br^- , NO_3^- , PO_4^{3-} , SO_4^{2-}	Water	IonPac AS9-HC + AG9-HC (2x250 mm)	9 mM Na_2CO_3	0.4	25	ASRS	Conductivity	-	mg/L	[19]
Part B: BrO_3^- , ClO_2^- , ClO_3^- , Br^-	Water	IonPac AS9-HC + AG9-HC (2x250 mm)	9 mM Na_2CO_3	0.4	25	ASRS	Conductivity	-	1.32-2.55	[19]
F^- , Cl^- , NO_2^- , Br^- , NO_3^- , PO_4^{3-} , SO_4^{2-} , ClO_2^- , ClO_3^- , BrO_3^-	Water	Metrosep A Supp 7 (4x250 mm)	3.6 mM Na_2CO_3	0.7	-	833 MSM-II	Conductivity	-	-	[20]

Analytes	Sample type	Column(s)	Eluent	Flow rate (mL/min)	Analysis time (min)	Suppressor	Detector	Post-column	LOD ($\mu\text{g/L}$)	Ref.
Cl^- , NO_3^- , SO_4^{2-} , SCN^- , CrO_4^{2-} , ClO_3^- , ClO_4^-	Standard	IonPac AS20 (4x50 mm)	KOH grad.	1	3	ASRS	Conductivity	-	-	[52]
ClO_3^- , NO_2^-	High salt matrices	IonPac AS19 + AG19 (4x250 mm)	10 mM KOH	1	70	electrochemical self-generation	Conductivity	AG16 (4 mm) concentrator	2.2	[24]
ClO_4^-	Atmospheric aerosol	IonPac AS16 + AG16 (2x250 mm)	120 mM NaOH	0.25	-	ASRS	Conductivity	Concentrator	0.35 ng/m^3	[55]
BrO_3^- , ClO_2^- , I^-	Water	IonPac AS9-HC (4x250 mm)	9 mM Na_2CO_3	1.1	6.5	AMMS	UV/Vis	0.4 mL/min 0.26 M KI, 43 μM $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$	$\mu\text{g/L}$ levels	[17]
ClO_4^-	Dust	IonPac AS16 + AG16 (4x250 mm)	25 mM NaOH	0.8	~20	Chemical mode	Conductivity	-	2	[56]
ClO_4^-	Soil leachate	IonPac AS16 + AG16 (4x250 mm)	35 mM KOH	1.25	-	ASRS	Conductivity	-	1	[57]
ClO_2^- , ClO_3^-	Soil leachate	IonPac AS18 + AG18 (4x250 mm)	23 mM KOH	1	-	ASRS	Conductivity	-	5	[57]
NO_3^- , ClO_4^- , SCN^-	Water	IonPac AS19 + AG19 (4x250 mm)	20-50 KOH grad	1	30	ASRS	Conductivity	-	3-25	[15]

Table 2. Comparison of two-dimensional ion-exchange chromatography (2D-IC) methods for the determination of DBP related anions and oxyhalides

Analytes	Sample type	Column(s)	Eluent	Flow rate (mL/min)	Analysis time (min)	Suppressor	Detector	1st-2nd dimension	LOD ($\mu\text{g/L}$)	Ref.
ClO_4^-	Water	IonPac AS20 (4x250 mm) + AG20	35-100 mM KOH grad.	1	45	ASRS	Conductivity	2 mL in concentrator column	ng/L levels	[22]
		IonPac AS16 (2x250 mm) + AG16	65 mM KOH	0.25	45	ASRS	Conductivity			
F^- , ClO_2^- , BrO_3^- , Cl^- , NO_2^- , ClO_3^- , NO_3^- , SO_4^{2-} , PO_4^{3-} , ClO_4^- , CNO^- , $\text{S}_2\text{O}_3^{2-}$, SCN^- , organic acids	Standard	IonPac AS19 (2x250 mm) +AS19	9-100 mM KOH grad.	0.25	28	-	-	tee-piece	3-80	[26]
		IonPac AS20 (4x250 mm) + AG20	69.33-99.67 mM KOH grad.	1		ASRS	Conductivity			
BrO_3^-	Water	IonPac AS19 (4x250 mm) +AG19	10-65 mM KOH	1	35	ASRS	Conductivity	~2 mL in concentrator column	0.12	[58]
		IonPac AS24 (2x250 mm) + AG24	10-65 mM KOH	0.25	35	ASRS	Conductivity			

Analytes	Sample type	Column(s)	Eluent	Flow rate (mL/min)	Analysis time (min)	Suppressor	Detector	1st-2nd dimension	LOD (µg/L)	Ref.
ClO ₄ ⁻	Water	IonPac AS20 (2x250 mm) + AG20	35-60 mM KOH grad.	0.25	45	ASRS	Conductivity	1 mL in concentrator column	0.005	[23]
		IonPac AS16 (0.4x250 mm) + AG16	65 mM KOH	0.01	45	ASRS	Conductivity			
BrO ₃ ⁻	Water	IonPac AS19 (4x250 mm) +AS19	5 mM KOH	1	40	ASRS	Conductivity	AC15 concentrator or UTAC trap column	1050	[25]
		1x or 2x IonPac AS24 (2x250 mm) + AG24	20 mM KOH	0.25		ASRS	Conductivity			
ClO ₂ ⁻ , BrO ₃ ⁻ , HAAs	Water	IonPac AS19 (4x250 mm) +AS19	10-45 mM KOH grad.	1	65	ASRS	Conductivity	IonSwift MAC200 trap column	0.3-0.64	[59]
		IonPac AS26 (0.4x250 mm) + AG26	6-70 mM KOH grad.	0.01		ACES	Conductivity			

HAAs – haloacetic acids

Table 3. Comparison of ion chromatography-mass spectrometry configurations for the determination of anions and oxyhalide species related to DBPs

Analytes	Sample type	Column(s)	Eluent	Flow rate (mL/min)	Analysis time (min)	Suppressor	Detector	Post-column	LOD ($\mu\text{g/L}$)	Ref.
BrO_3^-	Water	Dionex PA100	5 mM HNO_3 + 25 mM NH_4NO_3	1	7	-	ICP-MS	-	0.3	[27]
BrO_3^- , Br^-	Water	Selfmade polymethacrylate (4.6x150 mm)	20 mM NH_4NO_3 , pH 5.8	1	7	-	ICP-MS	-	2-3	[60]
BrO_3^- , Br^- , IO_3^- , I^- , HAAs	Water	IonPac AS11-HC + AG11	30-200 mM NH_4NO_3 grad.	1	43	-	ICP-MS	-	BrO_3^- -1.65	[61]
BrO_3^-	Water	IonPac AS19 + AG19 (4x250 mm)	40 mM KOH	1	6	-	ICP-MS	-	0.013	[28]
ClO_2^- , ClO_3^-	Blood	IonPac AS15 + AG15 (2x250 mm)	10-90 mM KOH	0.25	15	ASRS	ICP-MS/ICP-TQ-MS	-	500-1000	[29]
Cl^- , SO_4^{2-} , ClO_2^- , BrO_3^- , ClO_3^- , F^- , ClO_4^- , NO_3^- , IO_3^-	Water/ soil	IonPac AS16 + AG16 (2x250 mm)	1-20 mM NaOH grad.	0.3	71 + 16 equilb.	AEES	ESI-LIT-MS	0.12 mL/min MeOH	2-138	[2]
ClO_4^-	Infant formula	IonPac AS20 + AG20 (2x250 mm)	55 mM KOH	-	20	ASRS	ESI-TQ-MS	-	0.4	[49]
ClO_4^- , Cl^- , Br^- , BrO_3^- , ClO_3^- , ClO_2^- , IO_3^- , I^-	Snow	IonPac AS20 + AG20 (2x250 mm)	45-80 mM OH^- grad.	0.3	10.2 + equilb.	-	ESI-TQ-MS	0.3 mL/min MeCN	0.0003 - 0.0015	[13]

Analytes	Sample type	Column(s)	Eluent	Flow rate (mL/min)	Analysis time (min)	Suppressor	Detector	Post-column	LOD (µg/L)	Ref.
ClO ₄ ⁻ , Br ⁻ , NO ₃ ⁻ , BrO ₃ ⁻ , ClO ₃ ⁻ , ClO ₂ ⁻ , I ⁻	Water	IonPac AS21 + AG21 (2x250 mm)	231 methylamine	0.3	10	None	ESI-TQ-MS	-	0.02-25*	[33]
ClO ₃ ⁻ , ClO ₂ ⁻ , BrO ₃ ⁻ , Br ⁻ , F ⁻ , Cl ⁻ , NO ₂ ⁻ , NO ₃ ⁻ , PO ₄ ³⁻ , SO ₄ ²⁻ , HAAs	Water	Metrosep A Supp 1 HS + A Supp 5 (4x250 mm)	16 mM Na ₂ CO ₃ / 5 mM NaHCO ₃ grad.	0.7	70	Sequential chem.	Conductivity/ ESI-trap-MS	-	µg/L levels	[62]
BrO ₃ ⁻ , ClO ₄ ⁻	Water	IonPac AS21 + AG21 (2x250 mm)	200 mM methylamine	0.5	~10	None	Qtrap-MS	-	0.01-0.04	[63]
ClO ₄ ⁻	Water	IonPac AS16 + AG16 (2x250 mm)	65 mM KOH (75 mM)	0.3	~9	ASRS	ESI-SQ-MS (conductivity)	0.3 mL/min 50 % MeCN	0.02	[36]
ClO ₄ ⁻	Beverages, soil, water	IonPac AS16 + AG16/ AS20 + AG20 (2x250 mm)	45 mM OH ⁻	0.3	~13	ASRS-MS	ESI-TQ-MS	0.3 mL/min 50 % MeCN	0.005, 0.04 mg/kg	[64-65]
ClO ₄ ⁻	Water	Metrosep A Supp 4/5 + A Supp 5-100 (4x100 mm)	30 mM NaOH, 30 % MeOH	0.7	~9	Yes	ESI-SQ-MS	-	0.02	[36]
ClO ₄ ⁻	Water/ lettuce	Metrosep A Supp 5 (4x100 mm)	30 mM NaOH, 30 % MeOH	0.8	~14	Sequential chem..	ESI-SQ-MS	-	Sub µg/L	[37]

Analytes	Sample type	Column(s)	Eluent	Flow rate (mL/min)	Analysis time (min)	Suppressor	Detector	Post-column	LOD (µg/L)	Ref.
ClO_3^-	Soil/plant leachates	IonPac AS20 (2x250 mm)	H_2O -45 mM OH^- grad.	0.3	25.5	-	ESI-TQ-MS	0.3 mL/min 50 % MeCN	0.002	[66]
ClO_4^-	Ice	IonPac AS16 + AG16 (2x250 mm)	45 mM NaOH	0.3	-	ASRS	ESI-TQ-MS	0.3 mL/min 90 % MeCN	0.0002	[43]
ClO_4^-	Snow, ice	IonPac AS16 + AG16 (2x250 mm)	40 mM KOH	0.25	20	ASRS	ESI-TQ-MS	-	0.002	[42]
ClO_4^-	Milk, seaweed	IonPac AS21 + AG21 (2x250 mm)	15 mM KOH	0.35	-	ASRS	ESI-TQ-MS	-	0.12*	[67-68]
ClO_3^- , ClO_2^- , BrO_3^- , HAAs	Water	IonPac AS19 (2x250 mm)	5-37 mM KOH grad.	0.25	-	ASRS	ESI-SQ-MS	-	1-20	[69]
BrO_3^- , Br^- , NO_3^- , ClO_3^- , ClO_4^- , SCN^- , I^- , organic acids	GSR	IonPac AS18 (2x250 mm)	30 mM NaOH, 35 % MeCN	0.18	30	ASRS	ESI-Orbitrap	-	<10	[35]
ClO_4^- , (NO_3^- , SCN^- , I^-)	Urine	IonPac AS16 (2x250 mm)	50 mM NaOH	0.5	10	ASRS	ESI-TQ-MS	-	0.03	[38-41]
ClO_4^-	Water	IonPac AS21 + AG21 (2x250 mm)	200 mM methylamine	0.35	-	None	Qtrap-MS	0.3 mL/min MeCN	0.003-0.2	[31-32, 70]
ClO_4^-	Urine/ milk/ water	IonPac AS16 + AG16 (4x250 mm)	100 mM NaOH	1	10	ASRS	ESI-SQ-MS	dicationic reagent	0.06-3	[46, 71-73]

Analytes	Sample type	Column(s)	Eluent	Flow rate (mL/min)	Analysis time (min)	Suppressor	Detector	Post-column	LOD ($\mu\text{g/L}$)	Ref.
ClO_4^-	Dust	IonPac AS21 (2x250 mm)	20 mM methylamine	0.3	-	None	ESI-TQ-MS	-	0.02 $\mu\text{g/g}^*$	[74]
ClO_4^-	Ice core	IonPac AS16 (2x250 mm)	60 mM NaOH	0.3	15	AERS	ESI-Qtrap-MS	0.3 mL/min 90 % MeCN	0.0001	[44]

* LOQ; HAAs – haloacetic acids; ICP- inductively coupled plasma; ESI – electrospray ionisation; API – atmospheric pressure ionisation ; LIT - linear ion trap; TQ – triple quadrupole; SQ – single quadrupole; GSR – gunshot residues

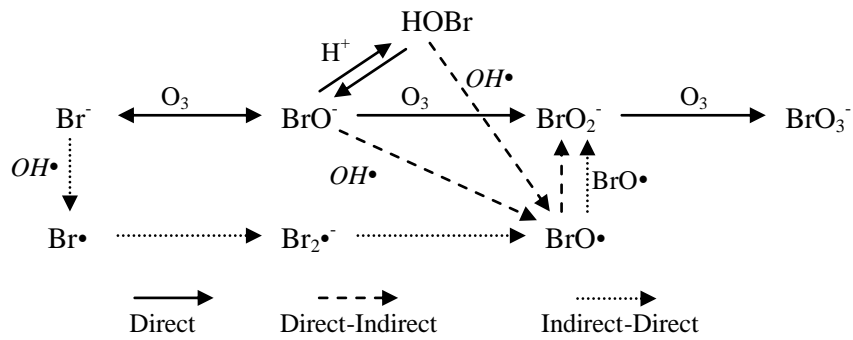


Figure 1. Bromate formation pathways during ozonation. Adapted from [5]

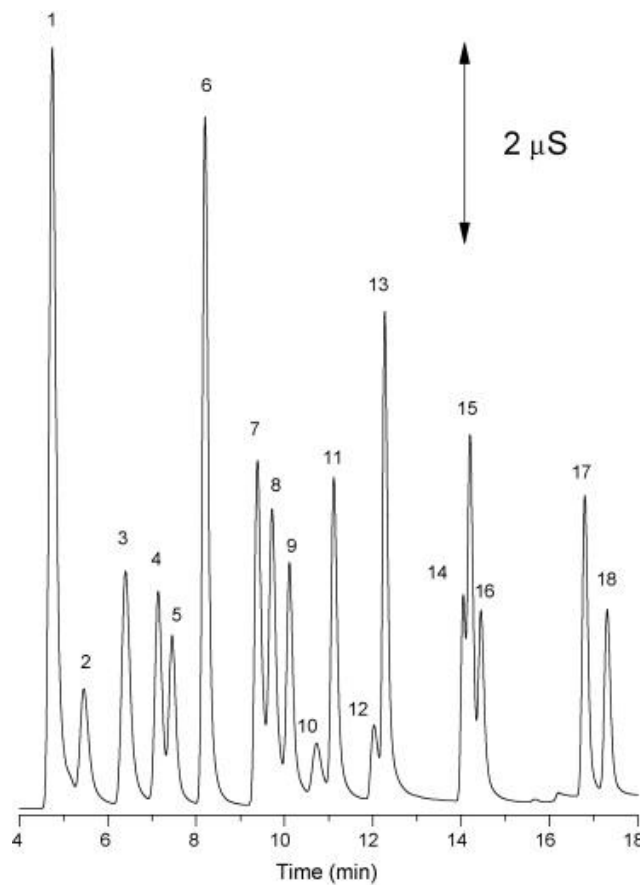


Figure 2. Separation of 5 ppm anion standards on an IonPac AS20 column with hydroxide gradient. Elution order: 1 = fluoride, 2 = acetate, 3 = formate, 4 = chlorite, 5 = bromate, 6 = chloride, 7 = nitrite, 8 = cyanate, 9 = chlorate, 10 = benzoate, 11 = nitrate, 12 = carbonate, 13 = sulphate, 14 = phosphate, 15 = chromate, 16 =

thiosulphate, 17 = thiocyanate, 18 = perchlorate. (Reprinted from [12]. Copyright 2008 with permission from Elsevier.)

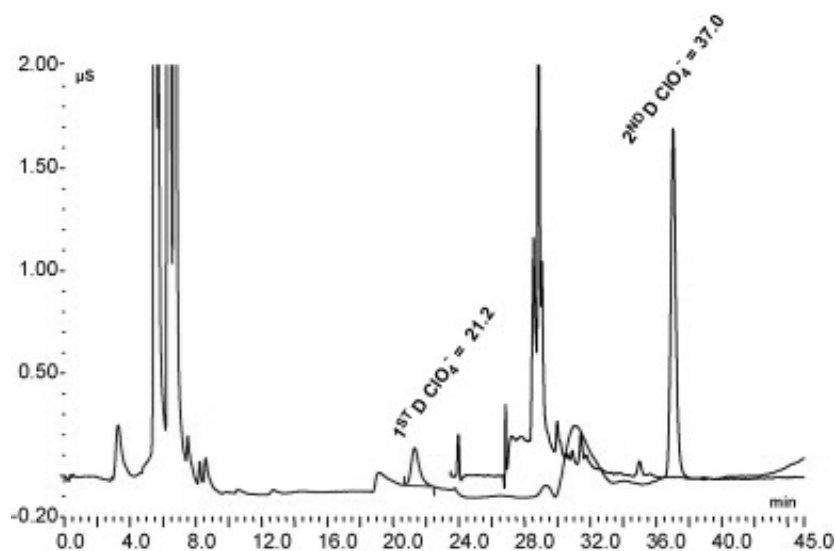


Figure 3. First- and second-dimension chromatogram using a 2.0 mL injection volume of a 25 $\mu\text{g/L}$ perchlorate fortification in purified reagent water. (Reprinted from [22]. Copyright 2007 with permission from Elsevier.)

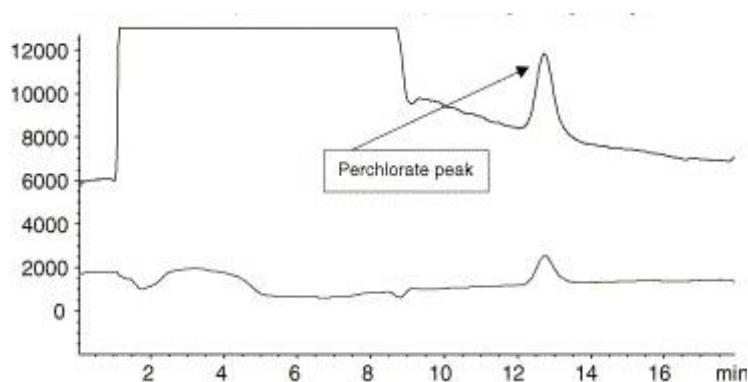


Figure 4. m/z 99 (top chromatogram) and 101 traces for 1 $\mu\text{g/L}$ perchlorate in a 1000 ppm matrix of sulphate, chloride, and carbonate using a Metrosep A Supp 5 column. (Reprinted from [37]. Copyright 2005 with permission from Elsevier.)

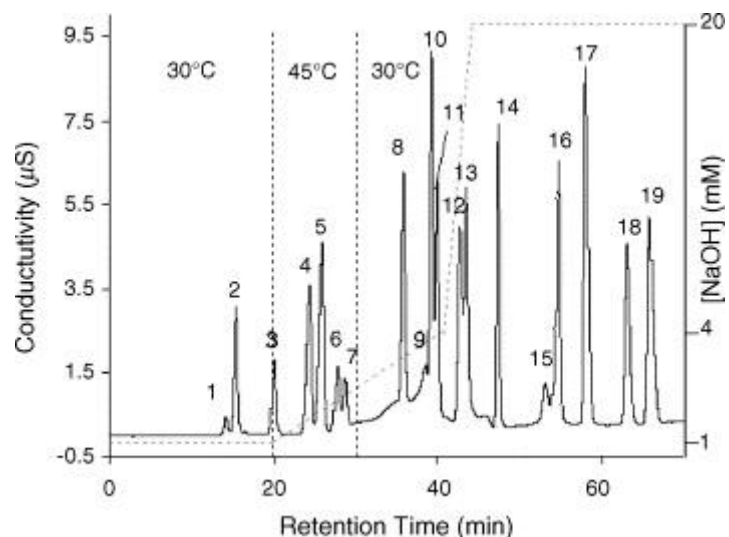


Figure 5. Optimised IC method for use with conductivity and ESI-MS detection for oxyhalides and HAAs using an IonPac AS16. Elution order: 1 = acetate, 2 = iodate, 3 = chlorite, 4 = MCA, 5 = bromate, 6 = chloride, 7 = MBA, 8 = TFA, 9 = nitrate/bromide, 10 = chlorate, 11 = DCA, 12 = CDFA, 13 = BCA, 14 = DBA, 15 = carbonate, 16 = TCA, 17 = DCBA, 18 = CDBA, 19 = perchlorate. (Reprinted from [2]. Copyright 2006 with permission from Elsevier.)

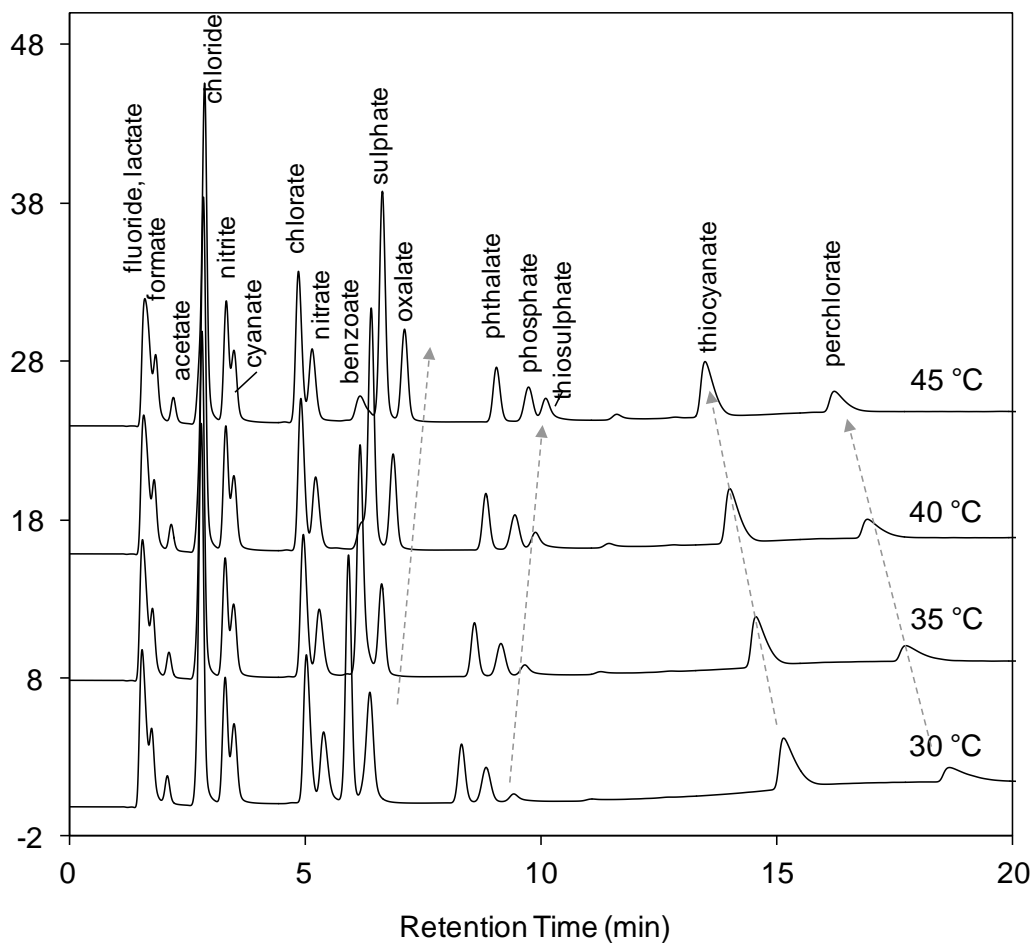


Figure 6. Fast separation of common inorganic anions, organic acids and oxyhalides on an IonSwift MAX-100 polymer monolith (0.25 x 250 mm). Reproduced from [51] with permission from the Royal Society of Chemistry.

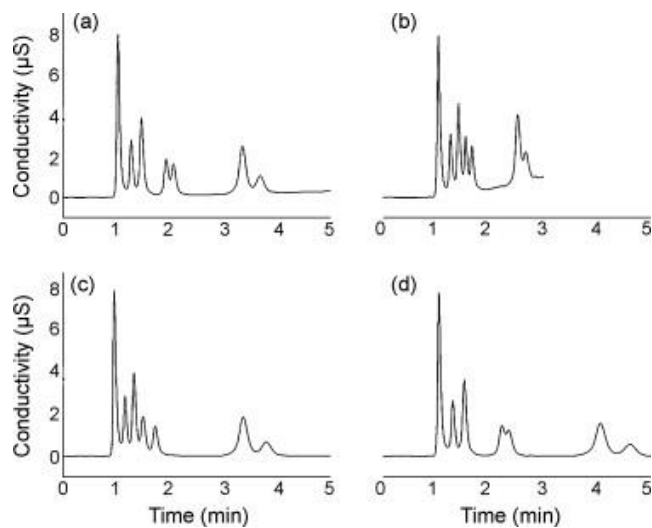


Figure 7. Optimised gradient separations of seven target anions carried out on a 4 mm × 50 mm AS20 column using (a) a ramp rate of 5 mM/ t_0 (6.92 mM/min) for maximum efficiency (effective peak capacity), (b) a ramp rate of 30 mM/ t_0 (41.49 mM/min) for fastest separation, (c) isocratic conditions of 31.5 mM and (d) isocratic conditions of 25 mM for approximation of most efficient gradient separation. Peak: 1 = chloride, 2 = chlorate, 3 = nitrate, 4 = chromate, 5 = sulphate, 6 = thiocyanate, 7 = perchlorate. (Reprinted from [52]. Copyright 2009 with permission from Elsevier.)