Inductively coupled plasma - tandem mass spectrometry (ICP-MS/MS): a powerful and universal tool for the interference-free determination of (ultra)trace elements – a tutorial review.

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Abstract

This paper is intended as a tutorial review on the use of inductively coupled plasma - tandem mass spectrometry (ICP-MS/MS) for the interference-free quantitative determination and isotope ratio analysis of metals and metalloids in different sample types. Attention is devoted both to the instrumentation and to some specific tools and procedures available for advanced method development. Next to the more typical reaction gases, e.g., H_2, O_2 and NH_3, also the use of promising alternative gases, such as CH_3F, is covered, and the possible reaction pathways with those reactive gases are discussed. A variety of published applications relying on the use of ICP-MS/MS are described, to illustrate the added value of tandem mass spectrometry in (ultra)trace analysis.

Keywords: inductively coupled plasma - mass spectrometry; tandem mass spectrometry; reaction gas; ultratrace analysis; isotopic analysis.

1. Introduction

Inductively coupled plasma - mass spectrometry (ICP-MS) can be seen as one of the leading techniques in the field of elemental analysis, focusing on the determination of ultratrace levels of metals and metalloids in a large variety of sample types. However, next to a long list of advantages (e.g., high sensitivity, a pronounced multi-element character, a wide linear dynamic range and the possibility to obtain isotopic information) the technique is also characterized by some drawbacks – the occurrence of spectral interferences being the most important one [1, 2]. Ever since the commercial introduction of the first quadrupole-based ICP-MS instrument in 1983, the search for ways to deal with spectral overlap has dominated the research in this area. Several approaches for coping with spectral overlap have been suggested, such as (matrix-matched) blank subtraction, mathematical correction, cold plasma conditions [3], trace/matrix separation, alternative methods for sample introduction, or aerosol desolvation [4]. Although the application of one of these procedures, or a combination thereof, can lead to accurate results for a wide range of analyte elements and sample types, more straightforward and universal approaches have been developed over the last 20 years, including high resolution sector-field (SF) ICP-MS instruments [5] and quadrupole (Q)-based instruments equipped with a collision/reaction cell (CRC) [6-8].

Sector-field ICP-MS aims at avoiding spectral overlap by operating the instrument at a higher mass resolution (up to R~10000 with present-day instrumentation) [9]. In this way, analyte and interfering ions that have the same nominal mass, but exhibit a small difference in their exact masses (e.g., $^{56}Fe^{+}$ and $^{40}Ar^{16}O^{+}$), can still be separated from one another, such that the analyte of interest can be measured interference-free. By means of ICP-SFMS the majority of interferences caused by spectral overlap of the signal of an analyte ion with that of a polyatomic ion with the same nominal mass can be resolved. Nonetheless, drawbacks of SF-instruments such as the higher purchase price, the higher technical complexicity and lower robustness, compared to ICP-QMS, in combination with its inability of resolving isobaric overlap, have prompted scientists to continue with improvements in the field of quadrupole-based ICP-MS as well. In line with the collision cells used for fragmentation of complex organic molecular ions in mass spectrometry [10], multipole arrangements in gas-pressurized collision/reaction cells were also introduced in ICP-MS as a straightforward means to deal with the problem of spectral interferences. Already in the late 1980s, Douglas [11] has shown that ion-molecule chemistry (gas phase reactions) should be seen as a much more adequate tool for the removal of interfering polyatomic ions than collision-induced dissociation. In the last 15 years, several companies have developed quadrupole-based ICP-MS instruments equipped with an extra quadrupole-, hexapole- or octopole-containing cell that can be pressurized with a gas. Depending on the type of instrument, interferences can

be removed by either (i) selective reaction of the analyte and/or interfering ion(s) with a reactive gas (e.g., H_2, O_2, NH_3) [6, 7] or (ii) collisions of the ions with a non-reactive gas (e.g., He), in combination with kinetic energy discrimination [8, 12]. For kinetic energy discrimination, a decelerating potential is applied in order to discriminate against the polyatomic ions, as they have a larger collision cross-section and therefore, collide more often and thus, lose more energy in the collision process than the analyte ions. With both approaches, a substantial reduction of the spectral overlap and an improvement in the limits of detection can be obtained for many applications, (i) provided that the formation of new interferences in the cell can be controlled when a reactive gas is used and (ii) taking into account that, with a non-reactive gas, only polyatomic interferences can be overcome.

Very recently (2012), the gamut of quadrupole-based ICP-MS instruments has been further extended with a new type of instrument, i.e., an ICP-tandem mass spectrometer (MS/MS) [13, 14], often also referred to as triple quadrupole ICP-MS (or ICP-QQQ). The main difference with the traditional ICP-CRC-QMS systems is the introduction of an additional quadrupole (Q1) in front of the CRC, which can be operated as a mass filter, thereby only allowing ions with one m/z-ratio to enter the cell. This leads to a better control over the reactions taking place in the cell and more insight into the reaction mechanisms and the origin of the reaction product ions observed.

At present, ICP-MS/MS instrumentation is available from one manufacturer only. However, the frequency at which new and very promising results have been published since the commercial introduction of this technique clearly indicates that this is a rapidly emerging field. It may be expected that in the near future, many more applications in which the additional benefits of tandem mass spectrometry will become apparent, will be described.

This tutorial review aims at a description of the operating principle and potential of this new technology, as well as an overview of usage, based on applications that have been described in the literature until now.

2. ICP-tandem mass spectrometry: theoretical background

2.1. Instrumentation

The first (and so far only) commercially available ICP-MS/MS instrument, launched in January 2012, is the Agilent 8800 ICP-MS system (Agilent Technologies) (Fig. 1). Although it is by no means the intention to provide the reader of this review with a manual on the use of this specific system, it is worthwhile to offer some information on the instrumental set-up, as this is crucial for a good understanding of the operating principle and some specific benefits of this approach. The instrument can be seen as a traditional quadrupole-based system,

equipped with an octopole reaction cell, but preceded by an additional quadrupole mass filter. Therefore, the abbreviation ICP-QQQ, often used to refer to this type of instrumentation, is not entirely correct, as the system consists of only two quadrupoles (and one octopole in-between). The instrument can be used in different modes of operation, depending on the nature of the analyte, the matrix elements found in the samples and the requirements of the analysis in terms of, among other, detection limits and sensitivity.

First of all, the instrument can be used as if it was a conventional ICP-QMS instrument with the first quadrupole Q1 operated as an ion guide and the cell under vented conditions.

For the determination of those elements that are hindered by spectral overlap, the collision/reaction cell can be pressurized with a (reactive or non-reactive) gas and Q1 can be used as an ion guide or bandpass ("single quad" mode – comparable to a typical ICP-CRC-MS system) or as a mass filter ("MS/MS" mode). While the addition of a non-reactive gas (e.g., He) in the cell, in combination with kinetic energy discrimination, can lead to a strong reduction of many polyatomic interferences, it is widely accepted that the reaction mode is often more efficient than the collision mode, especially for some key elements (e.g., S, P, Se) and when aiming at ng.L^{-1}-level analysis [15]. Moreover, with a non-reactive gas, only polyatomic ions can be banned from the quadrupole mass spectrometer, while the use of reactive gases also allows for a reduction of isobaric overlap.

With a reactive gas, spectral overlap can be reduced in two different ways. Reactions can be induced in order to:

- convert the interfering species into a new species that does not longer interfere with the determination of the analyte ion at its 'natural' isotopic mass (on-mass mode), or
- convert the analyte ion into a reaction product ion which can be determined free from interference at another mass–to-charge ratio than that of the original analyte ion (mass-shift mode)

It has to be pointed out that, with a conventional ICP-CRC-MS system, the higher reactivity of the gases typically used (e.g., H_2, O_2, NH_3) should not only be considered as a strong, but also as a weak point of the method, because of the in-cell formation of unwanted product ions that can lead to new interferences [15]. Moreover, in the mass-shift mode, one should always take into account the risk of spectral overlap at the new mass-to-charge ratio. These problems have been partially met by using quadrupole [15] or flatapole [16] reaction cells, where – provided a good selection of instrumental parameters – the in-cell chemistry can be controlled to some extent by the rejection of intermediate product ions [17]. Nevertheless, these systems do not operate as a real mass filter, but rather provide a dynamic mass bandpass or a low mass cut-off, such that for situations of spectral overlap where the

precursor ion is close in mass to the analyte ion, it may not be possible to efficiently suppress the formation of the interfering ion. It is at this point that the introduction of the additional quadrupole mass filter and operation of the instrument in MS/MS mode clearly provides added value, because it can exclude all plasma-based sample and matrix ions with a mass that differs from that of the analyte ion from the cell, thus enabling accurate analysis regardless of sample type. An example of such a situation has been described by Balcaen *et al*. [14] for the determination of S in organic matrices. By an appropriate selection of instrumental parameters, the same instrument could be operated in two different reaction modes: (i) 'bandpass' mode (first quadrupole operated as a bandpass, but with a mass range sufficiently wide to allow both S^+ and SO^+ ions to enter the cell) and (ii) MS/MS mode (first quadrupole operated as a real mass filter, set at the mass of the analyte ion of interest). Although the bandpass mode clearly provided better results than those obtained with a standard ICP-QMS instrument (without reaction cell), the authors concluded that there was still a considerable contribution of interfering ions at the mass-to-charge ratios of interest when the instrument was operated in bandpass mode. Only in MS/MS mode, accurate results were obtained.

In Fig. 2, another example – the determination of As in the presence of different matrix elements (*i.e.*, Ca, Cl, Nd, Sm, Zr) that could lead to spectral interferences – is shown. It may illustrate the added value of the tandem mass spectrometer set-up over the more traditional approaches (*i.e.*, (i) on-mass determination of $^{75}As^+$ after introduction of a non-reactive cell gas and using KED, or (ii) measuring on the mass of a product ion formed in a mass-shift reaction with a reactive gas in the cell, whether or not operated as a bandpass). It is clear that with a non-reactive gas and KED, only the contribution of the polyatomic ions can be reduced, while the overlap with doubly charged Nd^{2+} and Sm^{2+} ions cannot be removed. Conversion of As^+ into AsO^+ and detection at m/z=91 can solve the problems of both polyatomic and doubly charged ions, but if Zr is present in the samples, erroneous results could be obtained. Even if the reaction cell can be operated as a bandpass window, the problem cannot be solved in a straightforward way, because typically the bandpass covers a rather broad range of masses and it will not be possible to exclude the Zr ions from the cell in this way. On the other hand, in MS/MS mode, with the first quadrupole operated as a real mass filter, interference-free determination can be performed, regardless of the matrix composition.

2.2. Method development

2.2.1. Selection of the collision/reaction gas and quadrupole mass settings

As described before, the only ICP-MS/MS-instrument that is presently commercially available provides different options to deal with spectral interferences. In its standard configuration, this instrument can be equipped with up to four gas inlets and the standard set of gases available is He, H_2, NH_3/He (a mixture of 10% NH_3 in He for safety reasons, as NH_3 is a corrosive gas) and O_2. In literature, very promising results have also been presented with other reaction gases, such as CH_3F or N_2O. It is important to note that each mass flow controller (MFC) used for carefully regulating the gas flow is calibrated for a specific gas. Whenever a non-standard gas is connected to those channels, one has to take into account this difference in calibration of the mass flow controllers (MFCs) and, based on the correction factors for thermal-based MFCs, the actual flow rate for the employed gas can be derived.

As this review focuses on the figures of merit of the double mass selection (MS/MS) and this option pays off most when working with reactive gases, the discussion will be limited to this situation.

The first step in method development is the selection of the most appropriate reaction gas. For several elements and matrices, suitable methods have been described in the literature or in an application handbook provided by the instrument manufacturer [18]. However, from a more fundamental point of view and for totally new applications, access to information about the mechanisms and efficiencies of reactions between analyte and/or interfering elements and possible reaction gases is very valuable. Several systematic studies of reactions between different gases and (transition) metal ions with an inductively coupled plasma/selected-ion flow tube (ICP/SIFT) tandem mass spectrometer have led to an extensive database of reaction rate constants for ion-molecule reactions [19-21]. Based on this information, one can design a strategy for the use of a specific gas and the conditions needed to enable interference-free determination. However, with the introduction of the additional quadrupole in the tandem mass spectrometer ICP-MS instrument, there are also more straightforward ways to obtain information on the reactivity of certain ions with a specific gas, under the actual conditions present in the triple quadrupole instrument, i.e. product ion scans, precursor ion scans and neutral gain scans, which will be explained below.

2.2.2. Tandem mass spectrometry: different scanning modes for advanced method development

product ion scan

A product ion scan is typically performed to obtain insight into the reaction mechanism of a given analyte ion (or interfering ion) with a reaction gas. With the first quadrupole set at a fixed mass-to-charge ratio (of the ion under investigation) and the CRC pressurized with the

reaction gas, the second quadrupole can be scanned over (nearly) the entire mass range. In this way, only ions with a specific m/z-value can enter the cell and undergo reactions, of which the products are "visualized" via the Q2-mass scan. The choice of the best suited reaction gas and preferred product ion can be made based on the signal intensity of the different product ions. While normally the product ions with the highest signal intensity will be selected, it has to be stressed that also the matrix of the samples that have to be analyzed should be taken into account, as a similar reaction behavior of the analyte ions and ions with the same nominal mass as the analyte ion (which will both pass through Q1) in the CRC could also lead to overlap, thus hampering the use of the corresponding product ions. Therefore, it is recommended to perform product ion scans for both a standard solution of the element under investigation and a matrix-matched blank/standard solution. As an example, Fig. 3 shows the results of a product ion scan for Ti, using ICP-MS/MS with O_2 and NH_3 as reaction gases. At first sight, the most favorable situation (maximum sensitivity) for Ti is the conversion to and monitoring of TiO^+ ions, as the signals obtained for TiO^+ are ~ 10 times higher than the most intense signals obtained after reaction with NH_3 ($Ti(NH_3)_6^+$). However, from the product ion scans of the matrix-matched standards, it could be concluded that one of the major matrix elements in clinical samples, Ca, also reacts with O_2. Based on the mass of the product ions, the reaction products were identified as CaO^+ (m/z=64) and $CaOH^+$ (m/z=65) ions (the latter most probably originate from H-impurities in the cell). But even if the exact identity of the reaction product ions would be unclear, it can be directly seen from the product ion scan that the isobaric overlap could not be entirely solved by using O_2 as a reaction gas. In contrast, an interference-free and very sensitive determination of Ti with NH_3 as reaction gas was feasible (as $Ti(NH_3)_6^+$) for clinical samples [22].

Another important point to stress is that, depending on the reaction gas used, it may be worthwhile to perform product ion scans at different gas flow rates, as the reaction mechanisms (and the intensity of the corresponding analyte signals) may vary with the gas pressure or concentration in the cell. Fig. 4 shows the situation for the reaction of different trace elements with CH_3F. Product ion scans were performed at CH_3F flow rate settings of 0.25, 0.50, 0.75 and 1.00 mL min^{-1}. In order not to overload the figures, only the most prominent peaks are shown instead of the entire mass range. The results clearly illustrate the influence of the gas flow rate on the reaction processes taking place in the CRC. Identification of the different reaction product ions may be possible on the basis of their nominal mass, in combination with information on typical ion-molecule reactions, available from literature. But it is important to note that – from a practical point of view – identification of the ions is not strictly required, as mainly the m/z where the signals appear is of importance.

precursor ion scan

Opposite to the product ion scan, a precursor ion scan can be performed to clarify the origin of a specific reaction product ion. For this purpose, Q2 is fixed at the mass-to-charge ratio of the product ion, while Q1 is scanned over (nearly) the entire mass range to elucidate the mass of the precursor ion. This information can be useful to identify the source of an unexpected signal at a mass-to-charge ratio of interest, which could hinder the determination of an analyte ion at this mass, if the instrument would be operated in the single quad mode. An example of this has been described in the paper of Balcaen *et al.* [22] where a precursor ion scan was used to identify the origin of the rather high background signals found in the m/z-range = 148-152, for a HNO_3 blank solution analyzed with the tandem mass spectrometer ICP-MS instrument in single quad mode and with introduction of NH_3 in the reaction cell. It was seen that O^+ and Ar^+ ions were the precursors of product ions at the m/z ratios of interest.

neutral gain scan

This scan type allows the user to scan both quadrupoles with a fixed mass difference between Q1 and Q2, e.g., Q1: m/z – Q2: m/z + 16 for reactions with O_2 where O-atom transfer is the main reaction. A neutral gain scan is perfectly suited to illustrate the strength of the ICP-MS instrumentation, operated in MS/MS mode, for interference-free isotopic analysis. When using a reactive gas in a normal (single quadrupole) ICP-MS instrument, equipped with a CRC, for analyte elements that consist of more than one isotope, the isotopic pattern of the reaction product ions may be disturbed, especially when using gases that lead to complex cluster formation, e.g., NH_3. Under these circumstances, cluster ions with only one unit difference in mass could lead to overlapping signals for different isotopes of the same element, e.g., for the reaction between Ti and NH_3, spectral overlap of $^{m}Ti(NH_3)_6^+$ and $^{m+1}TiNH_2(NH_3)_5^+$ could lead to erroneous results when aiming at isotopic analysis. However, when using the tandem mass spectrometer, it can be ensured that all reaction product ions originate from precursor ions with the same mass, and – if interference-free measurement conditions can be obtained – the isotopic pattern of the original analyte ions is preserved for the reaction product ions. This is illustrated in the neutral gain scan performed for Ti with NH_3, presented in Fig. 5.

2.2.3. An additional advantage of ICP-MS/MS: enhanced abundance sensitivity

While at first sight, the benefit of using the MS/MS mode for non-interfered elements may be unclear, it can be advantageous for those cases where the abundance sensitivity (AS) is too low under normal (single quad) operating conditions.

According to IUPAC, abundance sensitivity in mass spectrometry is defined as the ratio of the maximum ion current recorded at mass m (I_1, or ion transmission T_1) to the ion current arising from the same species recorded at an adjacent mass m ± 1 (I_0 or ion transmission T_0) [23].

While for many applications, abundance sensitivity is not a real issue, it becomes crucial when low-abundance isotopes have to be measured in the presence of neighboring high-abundance isotope (e.g., for ultratrace analysis of high purity materials). Quadrupoles typically used in present-day ICP-MS instrumentation are characterized by abundance sensitivities of 10^6 to 10^7 (following the IUPAC definition) [24]. As for the tandem mass spectrometer ICP-MS instrument, operated in MS/MS mode, a double mass selection is performed by means of two quadrupole mass spectrometers, which both act as unit mass filters, the final abundance sensitivity can be calculated as the product of their corresponding abundance sensitivities, i.e. $I_m/I_{m\pm1} = (T_{1,Q1}/T_{0,Q1}) \times (T_{1,Q2}/T_{0,Q2})$, with $T_{1,Q1}$ and $T_{1,Q2}$ the transmission of an ion $^mX^+$ through Q1 and Q2, both set at m/z=m, respectively; and $T_{0,Q1}$ and $T_{0,Q2}$ the transmission of the ion $^mX^+$ through Q1 and Q2, both set at m/z=m ± 1, respectively. Taking into account that – for the instrumentation available at present - both Q1 and Q2 are research-grade, high-frequency, hyperbolic quadrupoles, each operating with a typical abundance sensitivity of 10^6 to 10^7, the combined AS is theoretically in the order of 10^{12} to 10^{14} [25]. This means that for a signal of 10^{12} / 10^{14} counts, there would be a contribution of ~1 count only at the adjacent mass, which is, however, difficult to verify in practice, as this large difference in signal intensity exceeds the dynamic range of the detector. An illustrative example of this advantage of tandem mass spectrometry can be found in the paper of Diez Fernandez *et al*. [26], who report the use of the technique for determination of the B/Ca (and P/Ca and S/Ca) ratios in natural biogenic carbonates in the context of geological applications, such as research in ocean acidification. The main challenges are (i) the very low B/Ca ratio, and (ii) the occurrence of spectral interferences. While addition of O_2 in the reaction cell allowed for a strong reduction of the spectral overlap for Ca, P and S, the overlap of the tail of the massive ^{12}C signal with the low signal of ^{11}B, was strongly reduced owing to the higher abundance sensitivity of the instrument. Detection limits as low as 0.4 mmol mol^{-1} were achieved for the B/Ca ratio (based on the detection of ^{11}B and ^{46}Ca), which is better than the limits of detection obtained with other instruments in this type of analysis.

3. Applications of ICP-MS/MS

The ICP-MS/MS technique is still in its infancy, as it has only been commercially introduced in 2012. Nevertheless, many papers describing both fundamental and more applied research by means of ICP-MS/MS have been published in the international literature already and show very promising results.

As this review is intended as a tutorial review rather than as a full review of the research in this area, a brief summary of some important findings will be presented, with the aims of highlighting the actual status and evolutions in the field of ICP-MS/MS in a clear and concise manner and providing the reader with some references to dedicated research papers. In order to structure this discussion, the applications have been divided in subcategories, based on the reaction gas used.

Additionally, a full overview of the literature on ICP-MS/MS, which is currently available (to the best of the authors' knowledge), is presented in Table 1.

3.1. O_2 as a reaction gas

3.1.1. O-atom transfer

With O_2 as a reaction gas, the most common ion-molecule reaction is O-atom transfer, i.e., $M^+ + O_2 \rightarrow MO^+ + O$.

Typically, the most favorable reactions that take place in a reaction cell are those that do not require additional energy, i.e. exothermic reactions ($\Delta H_r < 0$), or more accurately those that are thermodynamically allowed ($\Delta G < 0$) [27]. Therefore, it can be predicted that those elements that show a greater affinity towards O than does another O atom, will tend to form MO^+ product ions upon collision with O_2 molecules [27]. This approach can be used, both for the selective removal of interfering ions in combination with on-mass measurement of the analyte ions, and for mass-shift reactions where the original analyte ion $^mM^+$ is converted into an $^mMO^+$ ion which can be measured at m/z= m+16. In the literature, several applications with O_2 as the reaction gas, have been described.

The very first publications in this research field dealt with the determination of S and P in organic matrices [13, 14], whereby S^+ and P^+ ions were converted into their corresponding oxide ions SO^+ (m/z=48, 49 and 50) and PO^+ (m/z=47). While with a single quad ICP-MS approach, ions such as $^{47,48,49,50}Ti^+$, $^{48}Ca^+$, $^{36}Ar^{12}C^+$ and $^{32,33}S^{16,17,18}O(^1H)^+$ could give rise to spectral overlap in the targeted mass range, operating the tandem mass spectrometer instrument in MS/MS mode allowed for an interference-free measurement of S and P as their respective oxides. In both studies, it was shown that excellent limits of detection (LODs) could be obtained for S in organic matrices. Diez Fernández *et al.* [13] showed that both S

and P could be detected as their respective oxides, with an enhanced sensitivity and selectivity compared to other techniques. These authors clearly demonstrated the potential of this approach for use in proteomics studies, as it was shown that HPLC-ICP-MS/MS enabled simultaneous absolute quantification of different S-containing peptides and phosphopeptides with limits of detection of 11 and 6.6 fmol for S- and P-containing species, respectively. More recently, Amaral *et al.* [28] also contributed to the work in this research field by describing the possibility for simultaneous measurement of S (as SO^+) and C (as CO^+) in amino acids and peptides and thereby indicating the accessibility to C as an extra target element in speciation analysis. Balcaen *et al.* [14] focused on the quantitative determination of S in ethanol and biodiesel by means of isotope dilution, which requires an interference-free determination of at least two S isotopes. Instrumental LODs, calculated based on the standard deviation for repeated measurements of a calibration blank, were found to be 0.4, 1.6 and 5 µg L^{-1} for $^{32}S^{16}O^+$, $^{33}S^{16}O^+$ and $^{34}S^{16}O^+$, respectively. As a proof-of-concept, the method developed was successfully applied to the S determination in a biodiesel reference material.

A similar approach was used to deal with the Ar-based interferences that typically hinder the determination of Se (severe spectral overlap of the more abundant isotopes $^{78}Se^+$ and $^{80}Se^+$ with $^{38}Ar^{40}Ar^+$ and $^{40}Ar^{40}Ar^+$, respectively). Anan *et al.* [29] studied the chromatographic behavior of selenoproteins in rat serum. They proved that conversion of Se^+ into SeO^+ provides superior results when compared to the more traditional approach of using H_2 or D_2 as a reaction gas. Menendez-Miranda *et al.* [30] combined the mass-shift reactions of S^+ and Se^+ to SO^+ and SeO^+, respectively, with the on-mass determination of Zn and Cd to develop a multi-elemental method for assessing the chemical composition of CdSe/ZnS quantum-dots populations in complex mixtures. Therefore, they combined an asymmetrical flow field-flow fractionation system with an ICP-MS/MS-system as a very sensitive detector to allow for an interference-free detection of Cd, S, Se and Zn in different types of species formed during nanoparticle synthesis. For some sample types, the accurate determination of Se is not only hindered by spectral overlap with Ar-based interfering ions, but also with doubly charged ions from the rare earth elements. Jackson *et al.* [31] and Bishop *et al.* [32] showed that O-atom transfer can also be a useful approach in this context. Bolea-Fernandez *et al.* [33] evaluated the performance of different cell gases and conditions (e.g., use of the instrument in “vented mode”, use of He as a collision gas and use of O_2 and CH_3F as reaction gases) for Se determination and came to the conclusion that O_2 does not seem to be the preferred reaction gas, which may be due to a reduced signal stability and a low reaction efficiency of Se with O_2. From a theoretical point of view, this can be explained by the fact that the reaction between Se and O_2 is a slightly endothermic process ($\Delta H_r > 0$). Those reactions are typically

not very efficient in a reaction cell, but nevertheless they can proceed to some extent, owing to the kinetic energy of the reactant ion that is released upon collision. Addition of CH_3F in the reaction cell and subsequent measurement of Se as $SeCH_2^+$ was shown to be a better alternative for Se determination. (cf. 3.4.).

The determination of As by means of ICP-MS is hindered by the occurrence of several types of spectral interferences, such as overlap of the signal of $^{75}As^+$ with those of $^{40}Ar^{35}Cl^+$, $^{40}Ca^{35}Cl^+$, $^{150}Nd^{2+}$, $^{150}Sm^{2+}$ and $^{59}Co^{16}O^+$. While polyatomic interferences typically may be removed by using a non-reactive gas (e.g., He) in combination with kinetic energy discrimination, alleviation of the problem caused by doubly charged ions is less straightforward. Therefore, several authors have described the use of O_2 gas for conversion of As^+ into AsO^+ and subsequent determination at m/z=91. By means of the double mass selection in the tandem MS set-up, other ions with a mass of 91 (e.g., Zr) present in the sample, are excluded by the first quadrupole (set at m/z=75), such that interference-free determination of As can be achieved. This method has been successfully applied for the determination of As in high-purity 20% HCl [34], in food samples [31] [35], drinking water [36] and different types of complex matrices (synthetic sample solutions) [37, 38].

Amais *et al.* [39] described the determination of Cd and Mo in milk, where Cd determination is typically compromised by the relatively high concentration of Mo in this matrix. In order to avoid the spectral overlap of several Cd isotopes with Mo oxide ions, O_2 was added into the reaction cell for conversion of the MoO^+ ions into MoO_2^+ ions. In this way, a simultaneous determination of Cd and Mo was possible as Cd^+ ions (on-mass measurement) and MoO_2^+ ions (mass shift reaction: O-atom transfer), respectively.

Tanimizu *et al.* [40] applied ICP-MS/MS for determination of the $^{236}U/^{238}U$ isotope ratio in seawater samples and evaluation of its use as an environmental indicator for radioactive contamination. Two main problems related to this type of analysis are the spectral interference from $^{235}UH^+$ on $^{236}U^+$ and the ultra-low $^{236}U/^{238}U$-ratios. A product ion scan obtained for a 1 $\mu g.g^{-1}$ solution of U with the first quadrupole m/z set to 239 ($^{238}U^1H$) and addition of O_2 in the reaction cell, revealed that only ~1% of the UH^+ ions was transformed to UOH^+, while U^+ ions are readily converted to UO^+. Therefore, it was assumed that the $^{236}U/^{238}U$-ratio could be measured (almost) interference-free as $^{236}U^{16}O/^{238}U^{16}O$. However, it is important to note that O has different stable isotopes, such that with a conventional collision/reaction cell ICP-MS unit, where all ions enter the cell simultaneously, new problems arise, e.g., spectral overlap of the signals of $^{235}U^{17}O^+$ and $^{236}U^{16}O^+$. This issue could be avoided by operating the tandem mass spectrometer in the double mass selection mode, where a synchronized scan of Q1 (m/z=x for $^xU^+$) and Q2 (m/z=x+16 for $^xU^+$) allowed for

accurate measurements of $^{236}U/^{238}U$ ratios in the range between 10^{-9} and 10^{-7}, for a natural seawater sample and different synthetic mixtures of this sample with a U standard solution.

3.1.2. Charge transfer reaction

Next to oxygen atom transfer, also charge transfer reactions have been found a possible reaction mechanism in the reaction cell: $X^+ + O_2 \rightarrow X + O_2^+ + \Delta E$ [41]. The most obvious application field of this type of reaction, is the conversion of interfering ions into neutral ions, such that the corresponding analyte ions can be measured interference-free (provided that they do not react with oxygen). Ohno *et al.* [42] have used this approach for the determination of ultra-low $^{129}I/^{127}I$ ratios in radioactively contaminated soil samples. These analyses are typically hindered by the presence of Xe as an impurity in Ar plasma gas and the formation of IH_2^+ ions, which leads to spectral overlap of the signals of $^{127}IH_2^+$ and $^{129}I^+$ (although the amount of IH_2^+ produced in the cell by reactions with cell gas impurities is low, its contribution may be significant at the very low level of ^{129}I present in the samples). It was shown that the interference by $^{129}Xe^+$ can be minimized by using O_2 as a reaction gas without significantly affecting the I intensity, while operation of the instrument in the MS/MS mode allowed for a strong reduction of the overlap of $^{127}IH_2^+$ and $^{129}I^+$ ions, because the in-cell formation of $^{127}IH_2^+$ can be eliminated as $^{127}I^+$ is not allowed to enter the cell when Q1 and Q2 are both set at m/z=129.

As was the case for the O-atom transfer reactions, theoretically only those charge-transfer reactions whereby energy is released ($\Delta E > 0$) are likely to occur. However, Böting et al [41] performed a more extensive study of the charge transfer reactions in oxygen mode and they concluded that some elements that undergo this type of reaction in the cell, are characterized by ionization energies lower than that of O_2 (IE (O_2): 12.07 eV), and they are therefore expected to lead to endothermic charge transfer reactions that should not proceed in the reaction cell. According to the authors, a possible explanation for this unexpected behavior could be the existence of metastable ionic states of the elements under consideration that would render charge transfer towards the oxygen gas exothermic. However, as not all results of the investigations were consistent, more research is required in this area to fully understand the processes responsible for the charge transfer reactions in the cell and their utility for tackling the problem of spectral interferences.

In general, it can be stated that O_2 is a very useful reaction gas, with a rather simple and predictable reaction behavior. Although so far, only a few elements and applications have been described in the literature – definitely more elements can benefit from this approach for tackling the problem of spectral interferences. As a result, the approach is not limited to

mono-elemental determination, but can be applied in simultaneous multi-elemental analysis as well. One example of this is the work of Amaral *et al.*, where As, Cr, Hg and V were determined in drinking water [36]. While the Cl-based spectral interferences affecting As, Cr and V determination could be circumvented by means of oxygen transfer reactions and the monitoring of AsO^+, CrO^+ and VO^+ ions, respectively, Hg could be determined on-mass (as no spectral interferences were hindering its determination and its reactivity towards O_2 is limited).

3.2. NH_3 as a reaction gas

Several years ago, with the introduction of reaction cell chemistry in ICP-MS, NH_3 was already recognized as an efficient reaction gas for dealing with many spectral interferences, including the Ar-based interferences, which are one of the most cumbersome problems in ICP-MS [27]. The effect of NH_3 was mainly attributed to charge transfer reactions and based on differences in ionization energy between NH_3 and analyte and interfering species. A typical example is the resolution of the isobaric overlap of the signals of Ar^+ and Ca^+ at m/z=40 by means of NH_3. Under the (near) thermal conditions in a reaction cell, the exothermic charge transfer reaction between NH_3 and Ar^+ (IE (NH_3): 10.16 eV < IE (Ar): 15.76 eV) will proceed, while the endothermic reaction with Ca^+ (IE(Ca): 6.11 eV < IE (NH_3): 10.16 eV) will not and hence, an (almost) interference-free on-mass determination of Ca is possible.

Next to charge transfer, also other reaction patterns have been described for NH_3, such as clustering reactions, e.g. $M^+ + nNH_3 \rightarrow M^+.(NH_3)_n$. As an electron donor molecule, ammonia forms these adducts readily. For a single-quad instrument equipped with a reaction cell, ions with different masses enter the cell simultaneously, and unwanted/unexpected reactions with plasma or matrix elements may lead to product ions, the signals of which coincide with those of the analyte ions. Due to this complex reaction behavior, for some applications, the high reactivity of NH_3 can be seen as a nuisance rather than an advantage, and reaction chemistry may be difficult to control. However, with a tandem mass spectrometer, this issue becomes less of a problem, as the first quadrupole can select ions with one specific m/z-ratio only, which simplifies the interpretation of the mass spectra obtained. In fact, the rather complex ion-molecule reaction pathways of NH_3 can be even used to one's advantage for dealing with spectral interferences that may be hard to resolve with other reaction gases. An example of this is described by Balcaen *et al.* for the determination of ultra-trace levels of Ti in blood serum [22]. In this work, the figures of merit of two reaction gases, O_2 and NH_3, were compared and from Fig. 3, it can be clearly seen that NH_3 gives rise to a more complex

cluster ion formation than O_2. As discussed before, although higher signal intensities were obtained for TiO^+ than for the Ti-ammonia clusters, only with addition of NH_3 in the cell, all spectral interferences could be circumvented and the isotopic pattern of Ti could be preserved by measuring Ti as a $Ti(NH_3)_6^+$-cluster ion in MS/MS-mode (Fig. 5).

Other applications that make use of the charge transfer and/or the strong clustering capacity of NH_3 as a reaction gas, in combination with tandem mass spectrometry, have been described in the Agilent 8800 ICP-MS/MS application handbook. V and Ge could be accurately determined in hydrochloric acid, via the on-mass determination of $^{51}V^+$, after removal of ClO^+ with NH_3 and mass-shift reaction of $^{74}Ge^+$ to $^{74}Ge^{14}NH_2^+$ [34]. Also for a group of 8 noble metals (Ru, Rh, Pd, Ag, Os, Ir, Pt and Au), accurate results could be obtained in synthetic samples with a challenging matrix, which was not possible at all in the 'no gas' mode [43]. Spectral overlap of the signals of Ru, Rh, Pd, Ag and Pt with those of interfering ions could be resolved by removal of the latter and subsequent on-mass determination of the analyte ions, while Os, Ir and Au were determined via their product ions $OsNH^+$, $IrNH^+$ and $Au(NH_3)_2^+$, respectively.

3.3. H_2 as a reaction gas

While H_2 (mostly in combination with He) is very often used in single quad systems equipped with a collision cell, to the best of the authors' knowledge the added value of using this gas in the tandem mass spectrometer instrument, operated in MS/MS mode, has only been very rarely described in the specialized literature until now.

An application note by Sugiyama [44] reports on the use of H_2 as a reaction gas for the accurate and sensitive determination of Cl and Si in a water-soluble organic solvent, which can be seen as a challenging application due to the high ionization energy of these elements, in combination with spectral overlap of the analyte signals with those of C-, N-, and O-based molecular ions. It is shown by the author that for both elements, the background-equivalent concentrations (BEC-values) can be drastically reduced by using H_2 in MS/MS-mode, even though the reaction pathways are different. Si was determined on-mass (Q1=Q2=28), while the $^{35}Cl^+$-ions were converted in a mass-shift reaction into $^{35}ClH_2^+$ and measured at Q2=37 (for Q1=35). This difference in reaction behavior can be understood from the thermodynamic data presented below:

Si:

$^{28}Si^+ + H_2 \rightarrow SiH^+ + H$ $\quad \Delta H_r$ = 1.30 eV (endothermic reaction - does not proceed)

$^{14}N_2^+ + H_2 \rightarrow HN_2^+ + H$ $\quad \Delta H_r$ = - 0.60 eV (exothermic reaction - proceeds)

$^{12}C^{16}O^+ + H_2 \rightarrow COH^+ + H$ ΔH_r = - 1.63 eV (exothermic reaction - proceeds)

Cl:

$Cl^+ + H_2 \rightarrow HCl^+ + H$ ΔH_r = - 0.17 eV (exothermic reaction - proceeds)

$HCl^+ + H_2 \rightarrow H_2Cl^+ + H$ ΔH_r = - 0.39 eV (exothermic reaction - proceeds)

Very recently, the H_2-addition mass shift reaction for Cl was also used by Nelson *et al.* [45] in the development of a GC-ICP-MS/MS method for the detection of organochlorine pesticides in food matrices, where extremely low detection limits are desirable.

3.4. Alternative reaction gases, e.g., N_2O, CH_3F

As mentioned before, besides the standard set of gases recommended for use in the reaction cell of the tandem mass spectrometer instrument, also other – less common – gases or gas mixtures are the subject of investigation. To the best of our knowledge, only N_2O and CH_3F have been described as alternative reaction gases in ICP-MS/MS until now.

N_2O

Ohno and Muramatsu [46], and Zheng *et al.* [47] described a method for the determination of Cs isotope ratios ($^{134}Cs/^{137}Cs$ and $^{135}Cs/^{137}Cs$) as a geochemical tracer in environmental samples. Radioactive Cs isotopes can be released in the environment in nuclear events. While ^{134}Cs and ^{137}Cs can be easily measured by radiometric counting techniques, this is less straightforward for ^{135}Cs, due to its long half-life. ICP-MS can be seen as a good alternative, but spectral overlap of the Cs^+ signals with those of Ba^+ ions and molecular ions, such as SnO^+, SbO^+ and $ArMo^+$, hinders the determination. Both research groups investigated the possibilities of ICP-MS/MS with N_2O as a reaction gas and concluded that this approach allowed for a strong, but not entirely sufficient reduction of the interfering species. Ohno and Muramatsu opted for a mathematical correction of the remaining interferences (correction for Ba^+-interferences based on the measurement of the $^{138}Ba^+$ intensity, while the contribution of SnO^+ and SbO^+ ions was estimated via determination of the oxide production ratio and the signal intensities of $^{118}Sn^+$ and $^{121}Sb^+$, respectively) [46]. For the environmental samples investigated in the work of Zheng *et al.*, a chemical separation of Cs from the interfering matrix elements was found to be an essential step in the

sample preparation process, in order to allow for an accurate and sensitive Cs determination [47].

CH_3F

Facing the fact that for some specific and challenging applications, the standard set of reaction gases may be inadequate, Bolea-Fernandez *et al.* evaluated the potential of using the highly reactive CH_3F as an alternative gas in the CRC [48]. This choice was based on the outcome of earlier work, describing the reaction behavior of CH_3F with different elements (ICP-SIFT) [21]. To date, CH_3F has been hardly used as a reaction gas in CRC-Q-ICP-MS, most probably due to its complex reaction chemistry and the large variety of reaction mechanisms that can take place. Yet, exactly this characteristic makes the gas an attractive candidate for a strong and universal reaction gas in an ICP-MS/MS instrument, where extensive control over the reaction chemistry is possible.

For highly reactive gases, prediction of the reaction mechanisms with different elements, in varying matrices and under different instrumental conditions is often difficult. Therefore, Bolea-Fernandez *et al.* systematically studied the reaction behavior of different target analyte elements with CH_3F (introduced as a mixture of 10% CH_3F and 90% He) in the CRC and the influence of the matrix and the gas flow rate, by means of product ion scans [48]. For a first set of 7 clinically relevant target elements (Al, Co, Cr, Mn, Ni, Ti and V), it was concluded that lower gas flow rates typically lead to products which are the result of fluorine addition (XF_a^+), while at higher gas flow rates, methyl fluoride addition or the formation of higher order reaction products, such as $XF_a(CH_3F)_b^+$ is more common (Fig. 4). Despite the differences in reaction behavior, it was possible to develop a multi-element method for the simultaneous interference-free determination of ultratrace levels of the seven elements in biofluids with instrumental detection limits below 10 $ng.L^{-1}$.

As indicated before, over the years, the determination of As and Se by means of ICP-CRC-QMS, has been the subject of many investigations. Based on the promising results of the first study with CH_3F/He as a reaction gas, in combination with MS/MS, Bolea-Fernandez *et al.* investigated whether this approach could offer some benefits over the other methods described in the literature [33]. They illustrated that the reaction behavior of As and Se with CH_3F is different than that of the analyte elements described before, i.e. the main reaction products are $AsCH_2^+$ and $SeCH_2^+$, respectively. As can be seen from Table 2, instrumental LoDs as low as 0.2 $ng.L^{-1}$ and 4 $ng.L^{-1}$ were obtained for ^{75}As (determined at m/z=89) and ^{80}Se (determined at m/z=94) respectively, which is a significant improvement compared to the ICP-SF-MS and ICP-CRC-QMS methods that have been described before. The highly

accurate and precise results obtained for the As and Se concentration in a set of reference materials of plant, animal and environmental origin, covering a wide range of both matrices and concentrations, proved the potential of the method.

ICP-MS/MS with the introduction of CH_3F/He has not only shown its merits for quantification of trace elements, but also for isotopic analysis of spectrally interfered elements [49]. Isotopic analysis of Sr in geological materials was selected as an example because of the relatively pronounced natural variation in the Sr isotopic composition and its relevance in a wide application range. In this work, it has been demonstrated that the introduction of CH_3F as a reaction gas in the tandem mass spectrometer, allowed for an efficient removal of the spectral overlap of the signals of Sr^+, Rb^+ and Ca-based molecular ions (by measuring Sr interference-free at the mass of the corresponding SrF^+ ions). Moreover, the double mass selection strongly reduced the influence of matrix effects on the final results of the isotopic analysis, such that the use of matrix-matched standards (which was considered necessary in previous work [50]) was no longer required. Accurate $^{87}Sr/^{86}Sr$ isotope ratio results were obtained for geological reference materials, without prior Rb/Sr separation, and after correction for mass discrimination based on the combination of internal and external correction in a sample-standard bracketing approach. An external precision of 0.05% RSD was feasible.

Based on those promising first results obtained with methylfluoride addition in the reaction cell, it may be stated that CH_3F can be seen as a valuable alternative for the more common reaction gases used nowadays.

4. Conclusion and outlook

From the above it is clear that, with the introduction of ICP-MS/MS, the use of collision/reaction chemistry for reducing spectral interferences in quadrupole-based ICP-MS has been elevated to a higher level. Next to the inherent advantage of ICP-QMS systems equipped with a collision/reaction cell (*i.e.* the possibility of dealing with spectral overlap, including several cases of isobaric overlap), the presence of the first quadrupole allows for a better control of the reactions taking place in the following cell. In this way, interfering plasma-based ions can often be removed and many unwanted reactions with matrix ions can be prevented. The possibility of scanning one of the quadrupoles over the entire mass range, while the other quadrupole is held at a fixed m/z-ratio (product and precursor ion scans) provides an excellent means for method development and selection of the most appropriate reaction gases and gas flow settings. Moreover, based on the results of these scans, more information can be obtained on the mechanism of the reactions taking place in the reaction cell, which in turn could lead to a better insight into ion-molecule reaction chemistry.

The technology of ICP-MS/MS has been introduced onto the market only recently, but since then the frequency at which new applications have been described in the international specialized literature is high. It may therefore be assumed that in the upcoming years, ICP-MS/MS will be increasingly used, as it provides an elegant response to the shortcomings of single-quadrupole ICP-MS (and maybe even sector-field ICP-MS in some cases) for several applications, where (ultra)trace elements have to be determined in complex matrices.

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Figure captions

Fig. 1 Schematic representation of the operating principle of the tandem mass spectrometer system, functioning in MS/MS mode, leading to an interference-free determination of $^{x}A^{+}$ (at the mass of a reaction product ion). A stands for analyte element, I for interference.

Fig. 2 Example of the added value of the double mass selection mode (MS/MS) for the determination of As in complex matrices. With Q1 used as an ion guide only, spectral interferences are remaining, while operation in MS/MS-mode allows for an interference-free determination of As when using O_2 as a reaction gas

Fig. 3 Product ion scans (Q1: 48 – Q2: scanned) for a solution containing 1 µg L^{-1} Ti and a solution containing 1 µg L^{-1} Ti + 10 mg L^{-1} Ca, with (A) 0.2 mL min^{-1} O_2 and (B) 2 mL min^{-1} NH_3/He as reaction gas. Adapted from [22], with permission from Elsevier.

Fig. 4 Example of the most important information extracted from product ion scans (PIS) for (A) ^{48}Ti and (B) ^{55}Mn, performed at different methylfluoride flow rate settings. Only the most prominent peaks are shown in these graphs and the most intense peaks have been marked in red and were identified. Adapted with permission from [48] - Copyright 2014 American Chemical Society.

Fig. 5 Example of a neutral gain scan, obtained for Ti, measured as $Ti(NH_3)_6^+$ ions (NH_3/He as reaction gas). Q1 and Q2 are scanned with a fixed mass difference of 102 (mass of 6 NH_3-molecules). Despite of the complex reaction chemistry of NH_3, the isotopic pattern of Ti is conserved when using ICP-MS/MS.

Table 1: Overview of research papers, reporting on the use of ICP-MS/MS.

Ref.	Analyte nuclides (isotope mass)	Reaction gas	Reaction type	Application field
[39]	Cd (110, 111, 112, 113, 114) Mo (92, 95, 96, 98)	O_2	on-mass mass shift: $Mo^+ \rightarrow MoO_2^+$	determination of Cd, Mo in milk
[51]	P (31) S (32, 34) Si (28, 29)	O_2	mass shift: $P^+ \rightarrow PO^+$ mass shift: $S^+ \rightarrow SO^+$ mass shift: $Si^+ \rightarrow SiO^+$	determination of P, S and Si in (bio)diesel, oil
[36]	As (75) Cr (52) Hg (202) V (51)	O_2	mass shift: $As^+ \rightarrow AsO^+$ mass shift: $Cr^+ \rightarrow CrO^+$ on-mass mass shift: $V^+ \rightarrow VO^+$	determination of As, Cr, Hg and V in drinking water
[28]	C (12, 13) S (32)	O_2	mass shift: $C^+ \rightarrow CO^+$ mass shift: $S^+ \rightarrow SO^+$	determination of C (and S) in digested organic material and aminoacids
[29]	Se (78, 80, 82)	O_2	mass shift: $Se^+ \rightarrow SeO^+$	speciation of selenoproteins
[52]	Si (28, 29, 30)	O_2	mass shift: $Si^+ \rightarrow SiO^+$	characterization of silica nanoparticles
[14]	S (32, 33, 34)	O_2	mass shift: $S^+ \rightarrow SO^+$	determination of S in organic matrices (e.g., biodiesel)
[32]	Se (77, 78, 80, 82)	O_2	mass shift: $Se^+ \rightarrow SeO^+$	determination of Se in human serum in the presence of Gd-based MRI contrasting agents
[41]	As, Au, B, Be, Br, Cl, I, P, Se	O_2	charge transfer: $X^+ + O_2 \rightarrow O_2^+ + X$	fundamental study
[13]	P (31) S (32, 34)	O_2	mass shift: $P^+ \rightarrow PO^+$ mass shift: $S^+ \rightarrow SO^+$	determination of P and S in proteins
[26]	B (11) P (31) S (32) Ca (46) Ti (46)	O_2	on-mass mass shift: $P^+ \rightarrow PO^+$ mass shift: $S^+ \rightarrow SO^+$ on-mass mass shift: $Ti^+ \rightarrow TiO^+$	B/Ca, P/Ca and S/Ca ratio determination in coccoliths
[53]	P (31) S (32)	O_2 O_2	mass shift: $P^+ \rightarrow PO^+$ mass shift: $S^+ \rightarrow SO^+$	study of DNA-protein conjugates (in combination with chromatographic separation techniques)
[54]	As (75)	O_2	mass shift: $As^+ \rightarrow AsO^+$	arsenic speciation by means of ion chromatography-ICP-QQQ
[30]	S (32) Se (80) Zn (66) Cd (111)	O_2	mass shift: $S^+ \rightarrow SO^+$ mass shift: $Se^+ \rightarrow SeO^+$ on-mass on-mass	determination of S, Se, Cd and Zn in CdSe/ZnS quantum dots
[42]	I (127, 129)	O_2	on-mass (reduction of Xe-interference with O_2)	determination of ^{129}I in Fukushima soil samples
[35]	As (75)	O_2	mass shift: $As^+ \rightarrow AsO^+$	determination of inorganic As in rice
[40]	U (236, 238)	O_2	mass shift: $U^+ \rightarrow UO^+$	isotope ratios for monitoring of radioactive contamination
[55]	S (32, 34)	O_2	mass shift: $S^+ \rightarrow SO^+$	determination of SO_2 in wine
[31]	As (75) Se (78, 80)	O_2 O_2/H_2	mass shift: $As^+ \rightarrow AsO^+$ mass shift: $Se^+ \rightarrow SeO^+$	determination of As and Se in food products

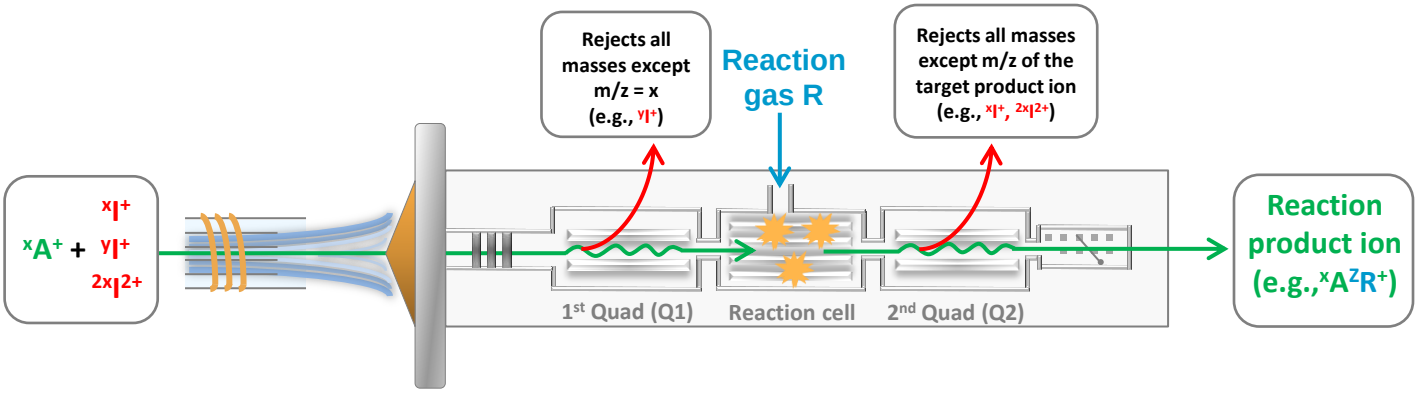
[45]	P (31) S (32) Cl (35)	O_2 O_2 H_2	mass shift: $P^+ \rightarrow PO^+$ mass shift: $S^+ \rightarrow SO^+$ mass shift: $Cl^+ \rightarrow ClH_2^+$	GC-ICP-MS/MS for detection of heteroatom-containing pesticides in food
[22]	Ti (46, 47, 48, 49, 50)	NH_3	mass shift: $Ti^+ \rightarrow Ti(NH_3)_6^+$	determination of Ti in clinical samples
[46]	Cs (134, 135, 137)	N_2O	on-mass (reduction of Xe & Ba interference with N_2O)	determination of $^{134}Cs/^{137}Cs$ and $^{135}Cs/^{137}Cs$ in Fukushima rainwater
[47]	Cs (135, 137)	N_2O	on-mass	isotope ratios for monitoring of radioactive contamination
[48]	Al (27) Ti (46, 47, 48, 49, 50) V (51) Cr (52, 53) Mn (55) Ni (58, 60) Co (59)	CH_3F	mass shift: $Al^+ \rightarrow AlCH_3F^+$ mass shift: $Ti^+ \rightarrow TiF_2(CH_3F)_3^+$ mass shift: $V^+ \rightarrow VF_2(CH_3F)_3^+$ mass shift: $Cr^+ \rightarrow Cr(CH_3F)_2^+$ mass shift: $Mn^+ \rightarrow MnCH_3F^+$ mass shift: $Ni^+ \rightarrow Ni(CH_3F)_2^+$ mass shift: $Co^+ \rightarrow Co(CH_3F)_2^+$	simultaneous determination of trace elements in biofluids (serum, urine)
[33]	As (75) Se (77, 78, 80)	CH_3F	mass shift: $As^+ \rightarrow AsCH_2^+$ mass shift: $Se^+ \rightarrow SeCH_2^+$	determination of As and Se in set of diverse matrices
[49]	Sr (86, 87, 88)	CH_3F	mass shift: $Sr^+ \rightarrow SrF^+$	Sr isotopic analysis without prior Rb/Sr separation

Table 2: Comparison of instrumental limits of detection obtained for As and Se via ICP-MS/MS using CH_3F/He with those obtained by other approaches (reproduced from [33], with permission from Springer Science and Business Media).

		Limits of detection (ng L^{-1})[a]			
ICP-MS/MS Cell conditions	**Scan type**	**^{75}As**	**^{77}Se**	**^{78}Se**	**^{80}Se**
"*Vented mode*"	SQ[b]	0.8	30	---[c]	---[c]
	MS/MS	0.9	50	---[c]	---[c]
He	SQ	1	20	40	----[c]
	MS/MS	2	40	60	---[c]
O_2	SQ	9	500	200	30
	MS/MS	7	500	9	30
CH_3F/He	SQ	1	200	20	10
	MS/MS	0.2	10	7	4
ICP-SF-MS	EScan[d]	10	50	500	---[c]

[a]LoDs calculated as 3 times the standard deviation on 10 consecutive measurements of a blank solution (0.14 M HNO_3), divided by the slope of the calibration curve
[b]SQ stands for single quadrupole mode
[c]Not measured (Ar-based interference was not resolved)
[d]High mass resolution (R ~ 10000) was used for all As and Se measurements

ICP-MS/MS


Rejects all masses except m/z = x (e.g., $^{y}I^{+}$)
Reaction gas R
Rejects all masses except m/z of the target product ion (e.g., $^{x}I^{+}$, $^{2x}I^{2+}$)
$^{x}I^{+}$
$^{x}A^{+}$ + $^{y}I^{+}$
$^{2x}I^{2+}$
1st Quad (Q1)
Reaction cell
2nd Quad (Q2)
Reaction product ion (e.g., $^{x}A^{Z}R^{+}$)

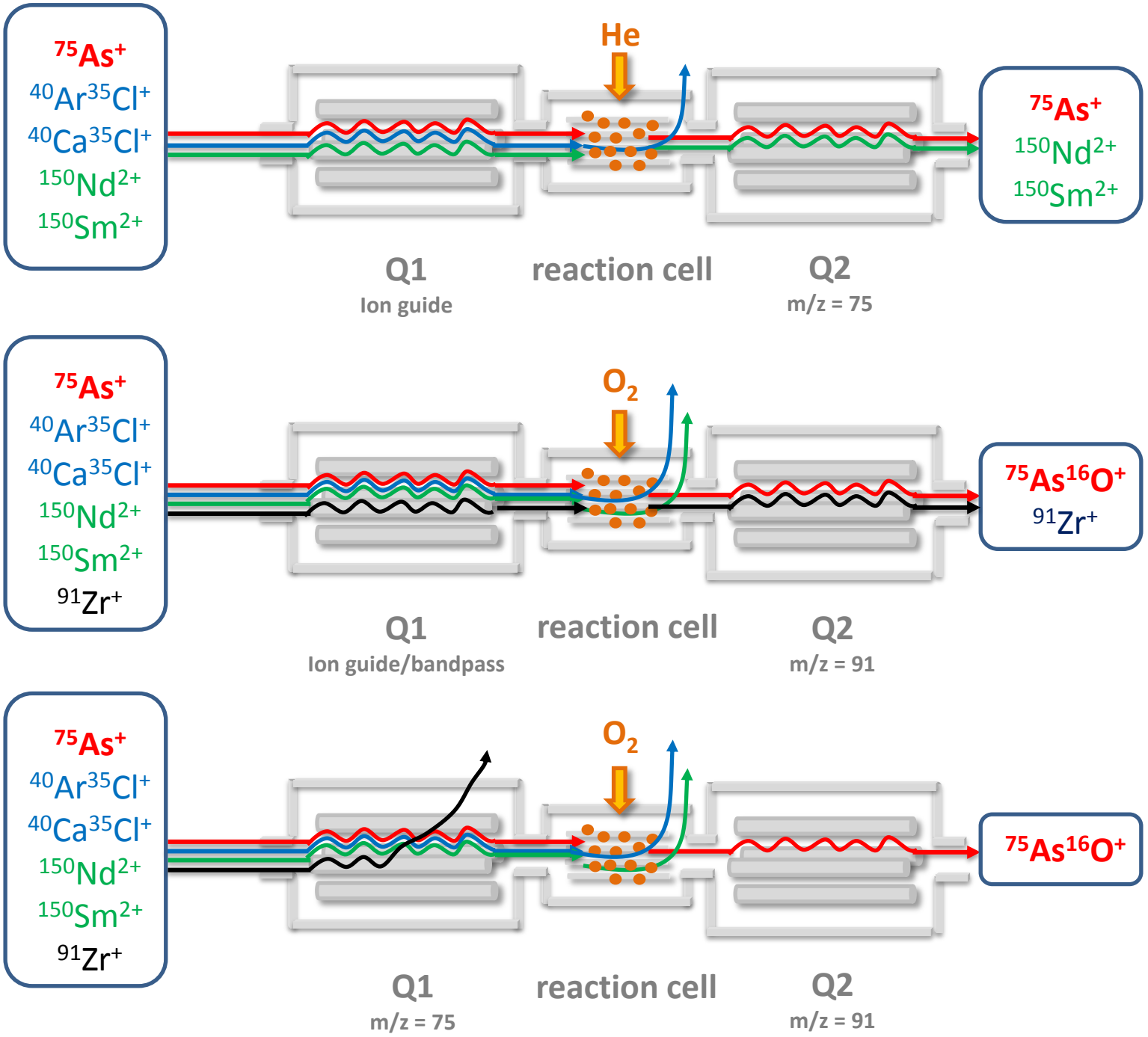
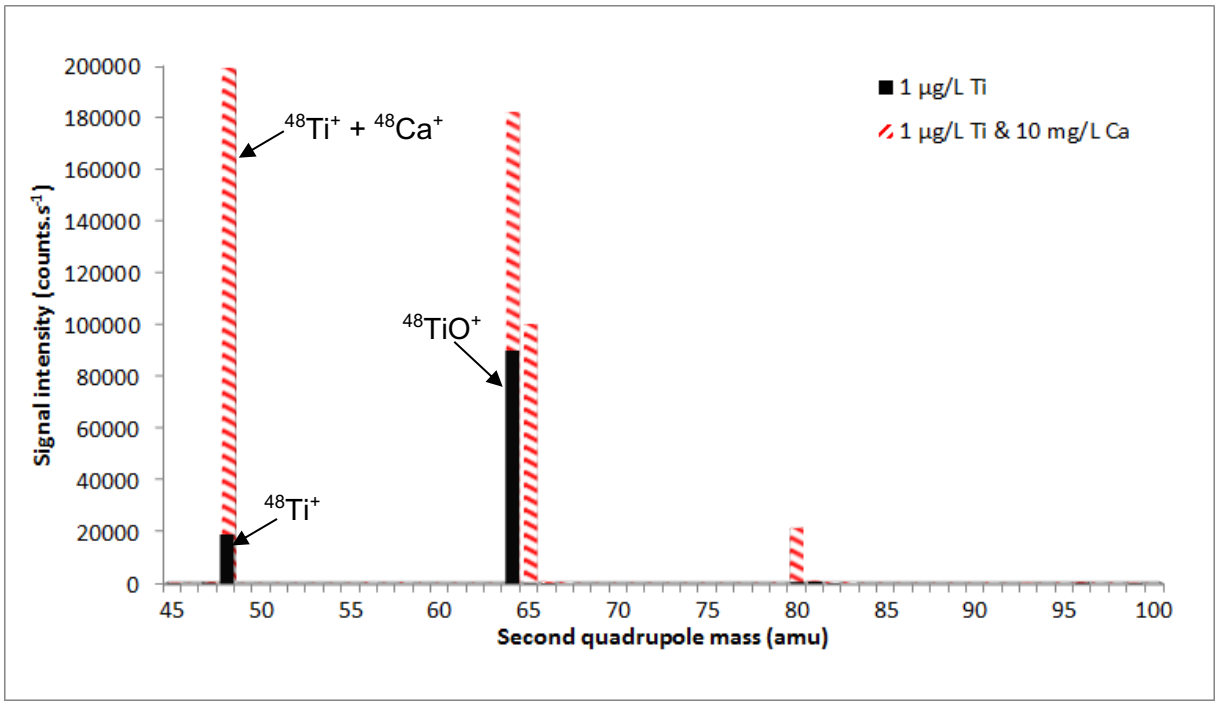

75As+
40Ar35Cl+
40Ca35Cl+
150Nd2+
150Sm2+
He
75As+
150Nd2+
150Sm2+
Q1
Ion guide
reaction cell
Q2
m/z = 75
75As+
40Ar35Cl+
40Ca35Cl+
150Nd2+
150Sm2+
91Zr+
O2
75As16O+
91Zr+
Q1
Ion guide/bandpass
reaction cell
Q2
m/z = 91
75As+
40Ar35Cl+
40Ca35Cl+
150Nd2+
150Sm2+
91Zr+
O2
75As16O+
Q1
m/z = 75
reaction cell
Q2
m/z = 91

Figure 3

A


200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
Signal intensity (counts.s-1)
48Ti+ + 48Ca+
48TiO+
48Ti+
1 µg/L Ti
1 µg/L Ti & 10 mg/L Ca
45
50
55
60
65
70
75
80
85
90
95
100
Second quadrupole mass (amu)

B

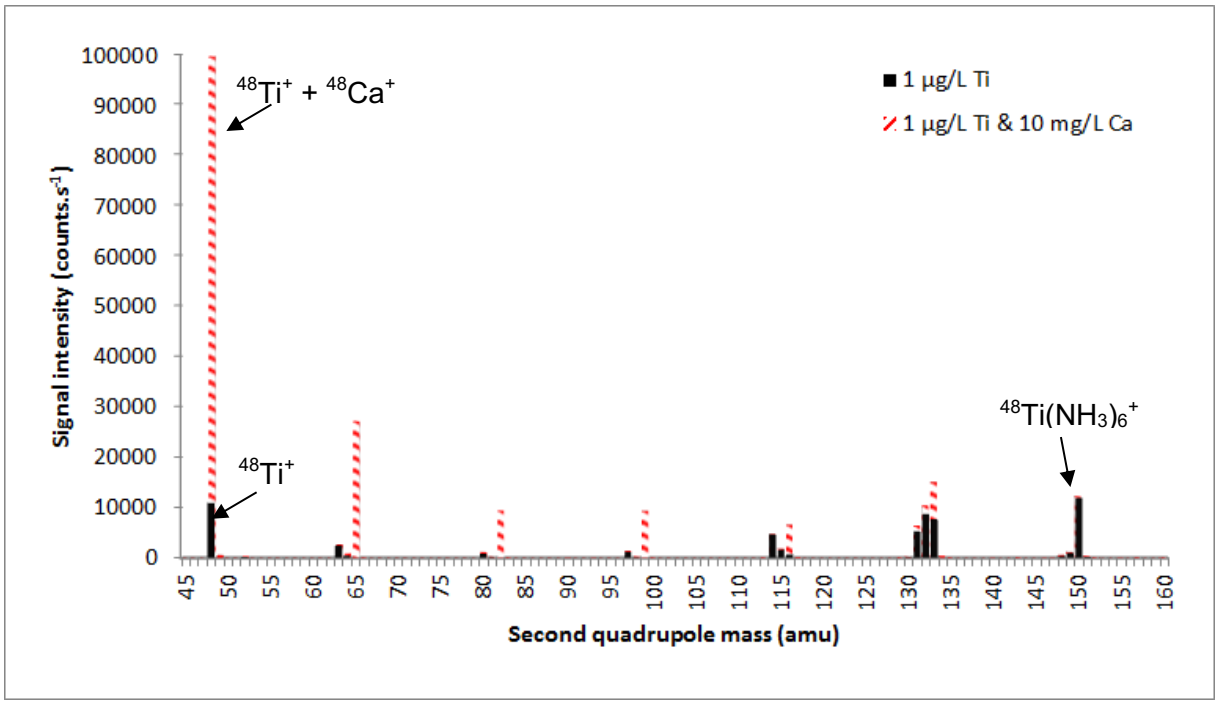
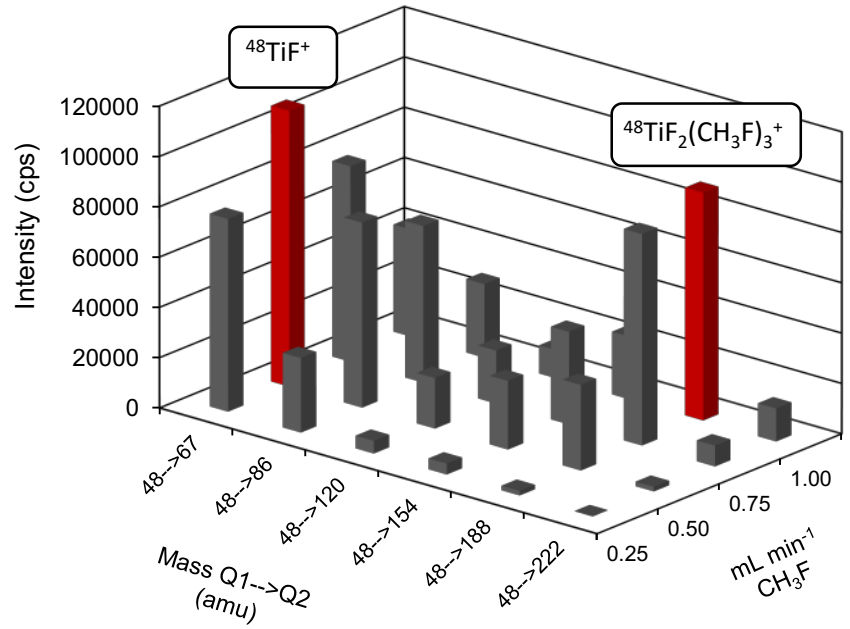

100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
Signal intensity (counts.s-1)
48Ti+ + 48Ca+
48Ti+
48Ti(NH3)6+
1 µg/L Ti
1 µg/L Ti & 10 mg/L Ca
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
Second quadrupole mass (amu)

Figure 4

A


$^{48}TiF^+$
$^{48}TiF_2(CH_3F)_3^+$
Intensity (cps)
120000
100000
80000
60000
40000
20000
0
48-->67
48-->86
48-->120
48-->154
48-->188
48-->222
Mass Q1-->Q2 (amu)
0.25
0.50
0.75
1.00
mL min^{-1} CH_3F

B

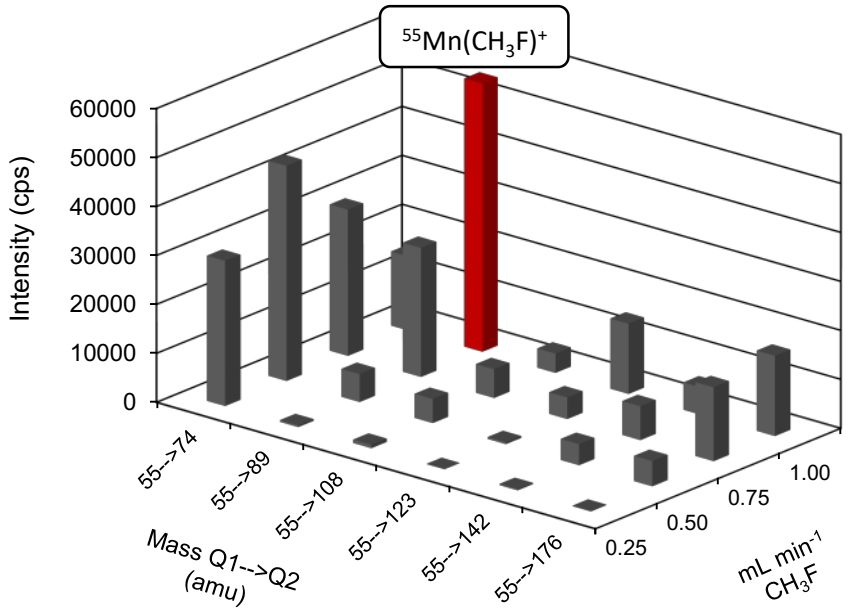
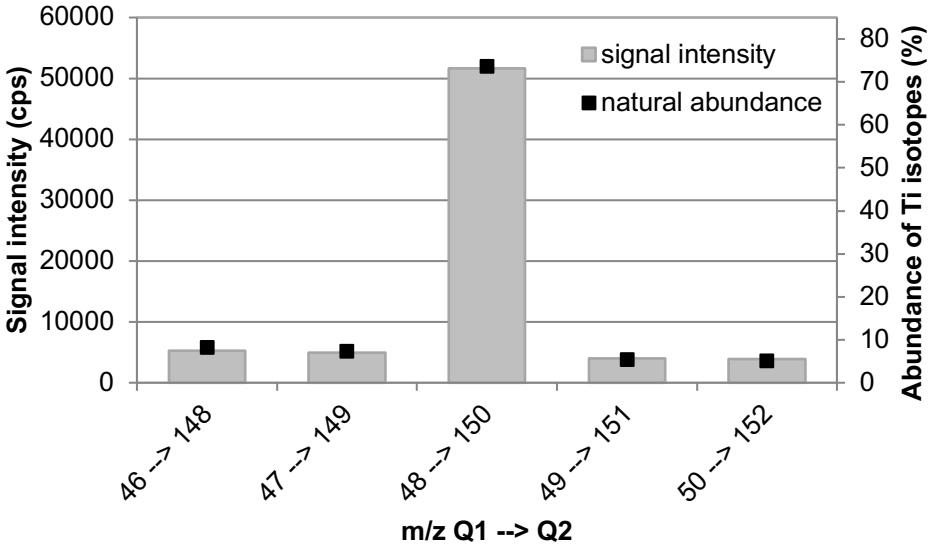

$^{55}Mn(CH_3F)^+$
Intensity (cps)
60000
50000
40000
30000
20000
10000
0
55-->74
55-->89
55-->108
55-->123
55-->142
55-->176
Mass Q1-->Q2 (amu)
0.25
0.50
0.75
1.00
mL min^{-1} CH_3F

Figure 5


60000
50000
40000
30000
20000
10000
0
Signal intensity (cps)
80
70
60
50
40
30
20
10
0
Abundance of Ti isotopes (%)
signal intensity
natural abundance
46 --> 148
47 --> 149
48 --> 150
49 --> 151
50 --> 152
m/z Q1 --> Q2