

To shift, or not to shift: adequate selection of an internal standard in mass-shift approaches using tandem ICP-mass spectrometry (ICP-MS/MS)

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ABSTRACT

The use of an internal standard to correct for potential matrix effects and instrument instability is common practice in ICP-MS. However, with the introduction of a new generation of ICP-MS instrumentation with a tandem mass spectrometry configuration (ICP-MS/MS), the use of chemical resolution in a mass-shift approach has become much more popular, suggesting that the proper selection of an internal standard needs revision. In this particular case, it needs to be decided whether the internal standard should also be subjected to a mass-shift or can simply be monitored on-mass (“to shift, or not to shift”). In this work, 17 elements covering a wide range of masses (24 – 205 amu) and ionization energies (3.89 – 9.39 eV) were measured *via* on-mass and/or mass-shift strategies, and the corresponding atomic ions and reaction product ions were monitored during various systematic experiments. For mass-shifting, an NH₃/He gas mixture was used to obtain NH₃-based reaction product ions (cluster formation). Product ion scanning (PIS) was used for assessing the differences in reactivity between the different analytes and for the identification of the best suited reaction product ions. It was found that the use of chemical resolution can significantly affect the short-term signal stability and that

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3 ion signals measured on-mass are not affected in the same way as those measured mass-shifted.
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5 Variations affecting the signal intensities of both atomic and reaction product ions can be attributed to
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7 the ion-molecule chemistry occurring within the collision/reaction cell and were found to be related with
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9 some degree of initial instability in the cell and differences in reactivity. The use of a sufficiently long
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11 stabilization time, however, avoids or at least mitigates such differences in the behavior between signals
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13 monitored on-mass and after mass-shifting, respectively. Furthermore, the introduction of cell
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15 disturbances, such as those generated after quickly switching between different sets of operating
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17 conditions in a multi-tune method, revealed significant differences in signal behavior between atomic
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19 and reaction product ions, potentially hampering the use of an internal standard monitored on-mass
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21 when the analysis is based on an analyte monitored after mass-shifting. However, the use of a
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23 reasonable waiting time again greatly mitigates such differences, with the duration of this stabilization
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25 time depending on the magnitude of the cell disturbances (*e.g.*, switch between vented and pressurized
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27 mode or only between pressurized modes using different gas flow rates). In addition, also the effect of
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29 varying different instrument settings (plasma power, torch position, and gas and liquid flow rates) was
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31 evaluated, but no remarkable differences were found between signals monitored on-mass and those
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33 mass-shifted. Interestingly, a statistical evaluation of the influence of the different settings on the signal
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35 intensities of all nuclides did not reveal the *a priori* important role of some properties traditionally
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37 suggested for adequate selection of analyte / internal standard pairs, such as mass number or ionization
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39 energy, as also suggested in other recent studies.
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1. Introduction

Inductively coupled plasma-mass spectrometry (ICP-MS) is the most powerful technique for (ultra-)trace elemental and isotopic analysis of a large variety of sample types. However, before accurate and precise ICP-MS analysis results can be obtained, the effects of both spectral and non-spectral interferences need to be adequately addressed.¹ To a large extent, the entire “history of ICP-MS” can be seen as a series of developments aiming at providing the users with novel and increasingly effective tools to overcome spectral interference, most often relying on new mass spectrometer designs. In addition to high-resolution sector field ICP-MS (HR-SF-ICP-MS), the introduction of collision/reaction cell (CRC) technology in quadrupole-based ICP-MS instrumentation (ICP-CRC-QMS) was one of the most important developments in the field.^{2, 3} In ICP-CRC-QMS, a multipole cell is pressurized with a collision and/or reaction gas to overcome spectral overlap by relying on collisions followed by kinetic energy discrimination (KED mode) and/or on selective reactions between the analyte ion(s) or the interfering ion(s) and the molecules of an adequately selected gas (chemical resolution mode).^{4, 5} In contrast to the situation for spectral interferences, the development of new approaches to correct for non-spectral interferences has not been updated that frequently, although some of the latest instrument developments suggest that the traditional strategies need to be revised.^{6, 7} In ICP-MS, the use of an internal standard aiming to correct for instrument instability and/or signal drift and non-spectral interference, *i.e.* signal suppression or enhancement caused by the matrix, is common practice.^{8, 9} The use of an internal standard improves both accuracy and precision on condition that the internal standard is appropriately selected.¹⁰⁻¹² In the late 1980s and 1990s, proper selection of an internal standard in ICP-MS was extensively reported on in the literature and some consensus was reached.¹³⁻¹⁵ It was demonstrated that an ideal analyte / internal standard pair shows a close match in terms of mass number and ionization energy, while the internal standard should be absent in the sample of interest and be measurable under interference-free conditions.^{16, 17} Selection of various internal standards across

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3 the full mass range was recommended for multi-element determination plagued by pronounced matrix
4 effects.
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8 However, recent works have also indicated that ICP-MS instruments of the most recent generations may
9 behave differently compared to older-generation ICP-MS, thus requiring the use of an internal standard
10 to be re-evaluated.¹⁸⁻²⁰ Salazar *et al.* studied the selection of an internal standard when using an ICP-MS
11 instrument with a collision and reaction interface (CRI) and indicated that the use of ⁴⁵Sc as internal
12 standard improved the performance for the determination of 18 out of 28 analyte isotopes evaluated,
13 which was attributed to the closeness in mass number and/or first ionization energy. However, some
14 exceptions were also reported on in this work, such as better results obtained for ⁵⁰V and ⁶³Cu upon
15 internal standard correction using ¹¹⁵In and ¹⁰³Rh (instead of ⁴⁵Sc), respectively.²¹ Also Barros *et al.*²²
16 found significant deviations from the “traditional guidelines” when studying the criteria for selecting the
17 best suited internal standard in ICP-MS. In this case, ⁷Li was found to be the best internal standard for
18 ⁹Be, but surprisingly, e.g., ¹⁹³Ir demonstrated the best performance for ²⁷Al determination. Very recently,
19 Korvela *et al.* reported on the use of internal standards in ICP-MS when using KED and a dynamic
20 reaction cell (DRC).²³ For the DRC mode, it was problematic to find a good internal standard, which was
21 attributed to reactions taking place in the cell with different kinetics and possibly being accompanied by
22 cluster formation, resulting in even more sources of variation that an internal standard is expected to
23 compensate for.
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44 The relatively recent introduction of tandem ICP-mass spectrometry (ICP-MS/MS) and the exponentially
45 growing use of mass-shift approaches to effectively deal with spectral interference require the proper
46 selection of an internal standard to be revised.^{24, 25} ICP-MS/MS provides a better control over the ion-
47 molecule processes occurring within the pressurized multipole cell, thus enabling chemical resolution
48 and mass-shift approaches to be used in a more straightforward way compared to single-quadrupole
49 ICP-CRC-MS instrumentation.^{26, 27} This mass-shift approach is based on the conversion of the analyte ion
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3 into a reaction product ion that can be monitored free from spectral overlap at a different mass-to-
4 charge (m/z) ratio.^{28, 29} While on-mass approaches require the interfering ions to be removed
5 completely, partial conversion may already suffice with such a mass-shift approach. The exponentially
6 growing use of such methodologies adds a new dimension to the selection criteria of an appropriate
7 internal standard in ICP-MS/MS. Amaral *et al.* evaluated the use of an internal standard in ICP-MS/MS for
8 the determination of B in plants.³⁰ In MS/MS mode, B was measured as the $^{11}\text{BO}^+$ reaction product ion to
9 avoid spectral overlap (tailing) in the presence of high concentrations of C, while BeO^+ was found to be
10 the best suited internal standard due to the similar chemical behavior of B and Be in the presence of O_2 .
11 However, to the best of the authors' knowledge, no works to date have systematically addressed the
12 effect of ion-molecule processes, relied on for generating interference-free conditions, on the adequate
13 selection of an internal standard.

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28 In this work, the adequate use of an internal standard in ICP-MS/MS analysis depending on mass-shift
29 approaches has been evaluated in an attempt to elucidate whether the internal standard should be
30 selected based on its closeness in mass to that of the original analyte ion or to that of the reaction
31 product ion. It was also evaluated whether an internal standard should or should not react in a similar
32 way as the analyte ion with the reaction gas.

33 34 35 36 37 38 39 40 **2. Experimental**

41 42 **2.1. Instrumentation**

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45 All measurements were carried out using an Agilent 8800 ICP-MS/MS instrument (ICP-QQQ, Agilent
46 Technologies, Japan). The sample introduction system consisted of a $400 \mu\text{L min}^{-1}$ MicroMist nebulizer
47 (Glass Expansion, Australia) mounted onto a Peltier-cooled (2°C) Scott-type spray chamber. This
48 instrument is equipped with two quadrupole mass units (Q1 and Q2) and a third generation octopole-
49 based collision/reaction cell system (ORS³) located in-between.^{24,25} In this work, the ICP-MS/MS
50 instrument was always operated in MS/MS mode, whereby both Q1 and Q2 were used as 1 amu mass

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3 filters. For mass-shift monitoring of reaction product ions, the cell was pressurized with a mixture of
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5 NH_3/He (10% NH_3 in He) that was introduced through the 3rd gas inlet (mass flow controller adjustable
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7 from 0 to 100%, corresponding to gas flow rates of 0 to 10 mL min⁻¹). In NH_3/He pressurized mode, a
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9 surplus of 1.0 mL min⁻¹ of He was always introduced into the ORS *via* another line, as recommended by
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11 the manufacturer. This supplemental He flow is mandatory for the Agilent 8800 ICP-MS/MS instrument
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13 to minimize the corrosiveness of NH_3 . Furthermore, it needs to be noted that He also plays an important
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15 role in the reactivity between the target analytes and the reaction gas, as it removes excess kinetic
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17 energy resulting in collisional stabilization, which improves reaction efficiency.^{4, 31} The instrument was
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19 always stabilized in no gas or “vented mode” prior to introduction of the mixture NH_3/He , unless
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21 specified differently in the experiments described below (*i.e.* stabilization for a given time while
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23 introducing the reaction gas mixture). To develop mass-shift approaches for the monitoring of the target
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25 elements selected, the best suited reaction product ions were identified using the product ion scanning
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27 (PIS) tool available in ICP-MS/MS instrumentation. In PIS, the m/z ratio of Q1 is fixed at that of the target
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29 nuclide and the entire mass spectrum (2–260 amu) is monitored by scanning Q2, while the CRC is
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31 pressurized with the reaction gas being introduced at a given flow rate. A systematic evaluation of the
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33 PIS results was also used for assessing the differences in reactivity between the different analytes.
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35 Typical ICP-MS/MS instrument settings and data acquisition parameters used throughout the
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37 experiments (unless specified elsewhere) can be found in Table 1. Statistical analysis was performed
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39 using SPSS Statistics 26 software for Windows (IBM Analytics, Brussels, Belgium).
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46 **Table 1.** Instrument settings and data acquisition parameters for the Agilent 8800 ICP-MS/MS
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48 instrument.
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Agilent 8800 ICP-MS/MS	
Reaction gas	NH_3/He
Scan type	MS/MS
Plasma mode	Low matrix

RF power (W)	1550
Pump speed (rpm)	0.1
Sample depth (mm)	4.5
Carrier gas flow rate (L min ⁻¹)	1.12
Reaction gas flow rate (mL min ⁻¹)	3.0*
Extract 1 (V)	-3.0
Q1 bias (V)	0.0
Octopole bias (V)	-5.0
Energy discrimination (V)	-8.4
Extract 2 (V)	-155.0
Wait time offset (ms)	5
Sweeps / replicate	100
Integration time / mass (s)	1
Replicates	5, 10
Total analysis time / sample (s)	434**

*Combined with 1 mL min⁻¹ He gas

**10 replicates

2.2. Reagents and standards

Only high-purity reagents were used throughout this work. Ultra-pure water (resistivity > 18.2 MΩ cm) was obtained from a Milli-Q Element water purification system (Millipore, France). Pro analysis purity level 14 M HNO₃ (ChemLab, Belgium) was further purified by sub-boiling distillation. 1 g L⁻¹ single-element standard solutions of Ag, Cd, Ce, Co, Cs, Cu, Fe, Ga, Ge, In, Mg, Rh, Sc, Ti, Tl, Y and Zn (Instrument Solutions, The Netherlands) were used for method development. To investigate the adequate use of an internal standard in mass-shift approaches, a multi-element standard solution containing all the target elements of interest was prepared from the single-element standard solutions and used throughout the different experiments carried out in this work. All standards were prepared in 0.14 M HNO₃. The ORS was pressurized with the NH₃/He gas mixture (9.93 ± 0.20 Mol - % in He, Mixture CRYSTAL, Air Liquide, Belgium) and pure He (99.9999%, ALPHAGAZ™ 2, Air Liquide, Belgium).

3. Results and discussion

To investigate the adequate use of an internal standard in a mass-shift approach using ICP-MS/MS, 17 elements (Ag, Cd, Ce, Co, Cs, Cu, Fe, Ga, Ge, In, Mg, Rh, Sc, Ti, Tl, Y and Zn) were selected and monitored

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3 in the experiments described in the following sections. An effort was made to cover a wide range of
4 masses (24 – 205 amu) and ionization energies (3.89 – 9.39 eV), as both have earlier been identified as
5 important factors in the appropriate selection of an internal standard in ICP-MS. However, the aim of this
6 work is not to assess the effect of element-specific properties – this has already been extensively
7 reported on in the ICP-MS literature before – but to study the additional effect that using chemical
8 resolution in a mass-shift approach to overcome spectral overlap might have on the selection of a
9 suitable internal standard. For this purpose, NH₃ (a mixture of 10% NH₃ in He) was used as reaction gas
10 to promote the formation of NH₃-based reaction product ions. Previous works based on the use of ICP –
11 selected-ion flow tube (SIFT) – MS demonstrated the high reactivity of NH₃ and the wide variability of
12 product ions formed upon reaction with this gas.³²⁻³⁶ However, some differences between the best
13 suited reaction product ions as identified using ICP-SIFT-MS and those revealed *via* PIS with ICP-MS/MS
14 were found in this work, as were also shown in some of our previous works focusing on the use of
15 methylfluoride as reaction gas.^{28, 31} This indicates that some differences in reactivity can occur when
16 other types of devices and experimental conditions are used. However, both techniques point towards
17 the high reactivity of NH₃ for many of the analytes selected.

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19 In contrast to other widely used reaction gases, such as H₂ and O₂, NH₃ is involved in cluster formation
20 (*i.e.*, the formation of M(NH_x)_z⁺ ions), and thus, the original mass of the atomic analyte ion can differ
21 substantially from that of the best suited reaction product ion selected. For instance, Balcaen *et al.*
22 reported on the interference-free determination of Ti in blood serum using ICP-MS/MS, whereby the
23 nuclides of Ti (m/z = 46 – 50 amu) were monitored as the corresponding Ti(NH₃)₆⁺ reaction product ions
24 (m/z = 148 – 152) after a mass-shift of more than 300%.³⁷ This raises the question of how to select the
25 best internal standard for this type of approach: based on (1) closeness in mass to that of the original
26 atomic ion, (2) closeness in mass to that of the reaction product ion, or (3) similar in-cell chemical
27 conversion, as a result of which the internal standard selected is not only close in mass to that of the
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3 original analyte ion, but also to that of the reaction product ion after mass-shift. *A priori*, the third
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5 approach seems to offer the highest degree of confidence for achieving accurate and precise results, but
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7 it needs to be noted that this condition is also far more restrictive. As a result, selection of an internal
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9 standard under such conditions needs to be appropriately assessed, so that a fit-for-purpose internal
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11 standard can be selected, ensuring sufficiently accurate and precise results without sacrificing user-
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13 friendliness.
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17 As indicated above, the reactivity was assessed *via* a systematic evaluation using PIS. For determination
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19 of the 17 elements selected, 13 on-mass and 12 mass-shift approaches were developed. The elements
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21 showing relatively low reactivity towards NH₃ were monitored on-mass only (Cd, Cs, Ga, In and Tl), while
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23 some elements for which the atomic ions could suffer from spectral overlap were monitored in mass-
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25 shift mode only (Fe, Mg, Sc and Ti). Finally, 8 of the 17 elements (Ag, Ce, Co, Cu, Ge, Rh, Y and Zn) were
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27 monitored both on-mass and mass-shifted. For mass-shift method development, PIS was also used to
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29 identify the best suited reaction product ions. As this work aims at assessing the use of internal
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31 standardization in mass-shift approaches, and thus, analytes and internal standards need to be
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33 measured under the same set of operating conditions, compromise settings were selected. This strategy
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35 is also often required for multi-element determinations, especially when pressurizing the CRC with highly
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37 reactive gases, such as NH₃. Based on the results obtained upon a systematic evaluation using PIS, a
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39 compromise gas flow rate of 3.0 mL min⁻¹ of NH₃/He was selected. Table 2 shows an overview of the
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41 elements studied in this work, including the ionization energy, mass of the original analyte nuclide and
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43 that of the optimum reaction product ion at the compromise gas flow rate. Self-evidently, some analytes
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45 reacted more efficiently at a different gas flow rate, giving rise to different optimum reaction product
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47 ions. Table S1 of the ESI shows the most important findings of the PIS evaluation, such as the comparison
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49 between the signal intensities for the best reaction product ion at an optimized gas flow rate and at the
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51 compromise gas flow rate. The largest differences were found for those elements displaying a better
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3 reactivity at lower NH_3/He flow rates ($\approx 1 \text{ mL min}^{-1} \text{ NH}_3/\text{He}$). Overall, the formation of NH_3 clusters
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5 ($\text{M}(\text{NH}_3)_{2-7}^+$, $\text{M} = \text{Ag, Ce, Co, Cu, Fe, Ge, Mg, Rh, Sc, Ti, Y}$ and Zn) was found to be the preferred reaction
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7 pathway at $3.0 \text{ mL min}^{-1} \text{ NH}_3/\text{He}$, while hydrogen molecule elimination (MNH^+ , $\text{M} = \text{Ce, Ti}$ and Y) and
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9 hydrogen atom elimination (MNH_2^+ , $\text{M} = \text{Ge}$) were sometimes favored at 1.0 mL min^{-1} of NH_3/He . For
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11 some analytes, product ions resulting from all three different reaction pathways, as well as high order
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13 reaction product ions (*e.g.*, $\text{MNH}(\text{NH}_3)_x^+$ and $\text{MNH}_2(\text{NH}_3)_x^+$) were formed in addition to the optimum
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15 ones.
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19 Although some of the elements selected are commonly used as internal standards in ICP-MS (*e.g.*, Ga ,
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21 Ge , Y , Rh , In and/or Ti), all of them were considered as potential analytes and/or internal standards in
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23 this work. It also needs to be noted that all analytes showing a certain reactivity towards NH_3 were
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25 monitored in mass-shift mode for the purpose of this work, although some of them could have been
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27 measured in “vented” mode as well due to the absence of significant spectral overlap.
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31 **Table 2.** Overview of the elements and ICP-MS/MS modes selected in this work to assess proper
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33 selection of an internal standard in mass-shift approaches. The reaction product ions selected are the
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35 optimum ones at the compromise gas flow rate of 3.0 mL min^{-1} of NH_3/He .
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Nuclide	Ionization energy (eV)	Mode	Q1	Q2	Ion monitored
^{24}Mg	7.6	Mass-shift	24	75	$\text{Mg}(\text{NH}_3)_3^+$
^{45}Sc	6.6	Mass-shift	45	130	$\text{Sc}(\text{NH}_3)_5^+$
^{48}Ti	6.8	Mass-shift	48	150	$\text{Ti}(\text{NH}_3)_6^+$
^{56}Fe	7.9	Mass-shift	56	90	$\text{Fe}(\text{NH}_3)_2^+$
^{59}Co	7.9	On-mass	59	59	Co^+
		Mass-shift		93	$\text{Co}(\text{NH}_3)_2^+$
^{65}Cu	7.7	On-mass	65	65	Cu^+
		Mass-shift		99	$\text{Cu}(\text{NH}_3)_2^+$
^{66}Zn	9.4	On-mass	66	66	Zn^+
		Mass-shift		100	$\text{Zn}(\text{NH}_3)_2^+$
^{71}Ga	6.0	On-mass	71	71	Ga^+
^{74}Ge	7.9	On-mass	74	74	Ge^+
		Mass-shift		125	$\text{Ge}(\text{NH}_3)_4^+$

^{89}Y	6.2	On-mass Mass-shift	89	89 191	Y^+ $\text{Y}(\text{NH}_3)_7^+$
^{103}Rh	7.5	On-mass Mass-shift	103	103 171	Rh^+ $\text{Rh}(\text{NH}_3)_4^+$
^{107}Ag	7.6	On-mass Mass-shift	107	107 141	Ag^+ $\text{Ag}(\text{NH}_3)_2^+$
^{111}Cd	9.0	On-mass	111	111	Cd^+
^{115}In	5.8	On-mass	115	115	In^+
^{133}Cs	3.9	On-mass	133	133	Cs^+
^{140}Ce	5.5	On-mass Mass-shift	140	140 225	Ce^+ $\text{Ce}(\text{NH}_3)_5^+$
^{205}Tl	6.1	On-mass	205	205	Tl^+

3.1. Response over time: short- and long-term signal drift

The accuracy of ICP-MS measurement results can be affected by signal drift.^{15, 16} Signal drift occurs as a result of different factors, such as electronics instability and matrix effects,^{38, 39} but the influence of chemical resolution on the short- and long-term signal stability also needs to be accounted for. To evaluate the effect of the ion-molecule chemistry occurring within the CRC on the signal drift, the signal intensities of the nuclides indicated in Table 2 were recorded as a function of time with the cell pressurized with 3.0 mL min^{-1} of the NH_3/He gas mixture (compromise gas flow rate). To assess the sources of signal fluctuation more effectively, short- and long-term experiments were also carried out in vented (no gas) mode.

In a first experiment, the measurement of the target elements as detailed in Table 2 was executed immediately after approximately 30 min of instrumental warm-up with a vented cell, *i.e.*, the signal intensities were registered without additional stabilization time after changing from vented to pressurized (NH_3/He) mode. The results thus obtained for a 2 hour sequence were normalized for comparison purposes by calculating the ratio of the signal intensity to that at 30 min into the measurement session for every nuclide. This normalization criterion was selected because often 30 min stabilization is advised after introduction of a cell gas. Figure 1 shows the average results for the 13 and

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3 12 elements measured on-mass and mass-shifted, respectively, in pressurized mode (3.0 mL min⁻¹ of
4 NH₃/He). In addition, the average results for the 13 elements measured in vented mode were included
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6 for comparison purposes. Interestingly, different signal fluctuations were found for atomic ions
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8 monitored in NH₃/He pressurized mode compared to those monitored in vented mode, which can be
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10 attributed to differences in reactivity between the different analytes (*vide infra*). In the case of the
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12 NH₃/He pressurized mode, significant differences were observed between the behavior of on-mass and
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14 mass-shifted signals, both at the beginning (*t*-test, $t_{\text{experimental}} = 3.33 > t_{\text{critical}} = 2.11$) and at the end of the 2
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16 hours sequence (*t*-test, $t_{\text{experimental}} = 3.47 > t_{\text{critical}} = 2.07$). During the first 15-20 min, the signal intensity
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18 trends for ions monitored on-mass and those monitored mass-shifted differed significantly. A
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20 pronounced decrease in the signal intensity (from 123 ± 28 to 97 ± 2 %) was found in the case of on-mass
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22 monitoring of the atomic ions, while the signal intensities for reaction product ions increased
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24 significantly within the same time range (from 93 ± 13 to 104 ± 3 %). After approximately 30 min, the
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26 signal intensities seem to stabilize for both the atomic and reaction product ions, although a drift to
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28 lower values can still be observed during the two hours duration of this experiment. This signal drift was
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30 found to be slightly more pronounced in the case of on-mass (final value, 91 ± 4 %) monitoring compared
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32 to mass-shifting (final value, 96 ± 3 %). The initial different behavior between on-mass and mass-shift
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34 approaches can be attributed to the stabilization of the in-cell conditions in the ORS of the ICP-MS/MS
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36 instrument.
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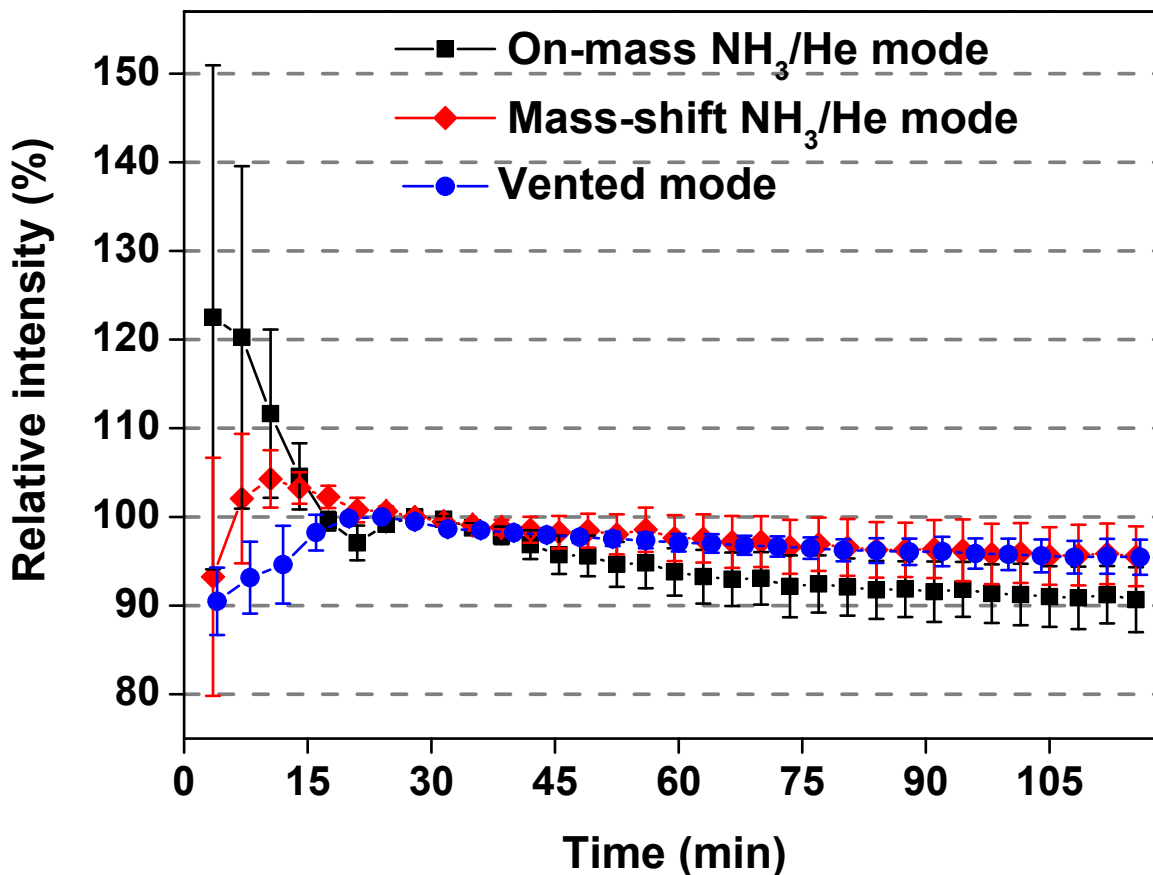


Figure 1. Evaluation of the short-term signal drift for atomic ions monitored on-mass (black squares) and reaction product ions (mass-shift approach – red diamonds) using ICP-MS/MS with the cell pressurized at 3.0 mL min⁻¹ of the NH₃/He gas mixture. For comparison purposes, data obtained for atomic ions monitored in vented mode (blue circles) are included. For the experiments carried out in NH₃/He pressurized mode, the instrument was not previously stabilized with the gas mixture. Uncertainties are expressed as the standard deviation of 13 and 12 relative signal intensities for atomic (both pressurized and vented modes) and reaction product ions, respectively.

On the one hand, this stabilization enhances the efficiency of the gas-phase ion-molecule reactions taking place in the CRC, thus explaining the increase in signal intensity for reaction product ions thus formed. On the other hand, as the higher reactivity leads to a larger fraction of analyte ions converted

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3 into the corresponding reaction product ions, this is necessarily accompanied by a reduction of the signal
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5 intensity for the remaining atomic ions. In fact, significant differences (t -test, $t_{\text{experimental}} = 4.61 > t_{\text{critical}} =$
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7 2.23 when comparing average relative intensities at the end of the 2 hour sequence) were found
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9 between atomic ions monitored on-mass that showed limited or no reactivity towards NH_3/He (Cd, Cs,
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11 Ga, In and Tl) and those that reacted more efficiently with this gas mixture (Ag, Ce, Co, Cu, Ge, Rh, Y and
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13 Zn). Based on these results, atomic ions monitored on-mass that do not react significantly showed a
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15 more similar behavior to the reaction product ions (mass-shift) than to the atomic ions monitored on-
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17 mass that do show reactivity towards NH_3/He (see Figure S1 of the ESI). Similarly, the stability in vented
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19 mode was found to be comparable to that in the pressurized mode for the atomic ions that show limited
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21 reactivity towards the gas mixture and for the reaction product ions. This behavior demonstrates the
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23 largest effect of the ion-molecule chemistry on the short-term signal stability of atomic ions monitored
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25 on-mass that do show high reactivity towards the NH_3/He gas mixture.
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30 To better assess the differences in signal drift between atomic and reaction product ions monitored in
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32 NH_3/He pressurized mode, a direct comparison was performed for the elements studied using both
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34 approaches (Ag, Ce, Co, Cu, Ge, Rh, Y and Zn). The results are shown in Figure 2. As can be seen, the
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36 same trends as those seen in Figure 1 were found in all cases, although some differences between
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38 elements can be noted. Interestingly, the signal drift was much more pronounced for the atomic ions of
39
40 ^{74}Ge , ^{89}Y and ^{140}Ce (on-mass). Once more, this behavior was found to be related with their higher
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42 reactivity towards NH_3 , as demonstrated by the ratios of the signal intensities of the best suited reaction
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44 product ions and the corresponding atomic ions (NH_3/He pressurized mode) and by the ratios of the
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46 signal intensities of the atomic ions measured in vented mode and the same atomic ions measured on-
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48 mass in NH_3/He pressurized mode (see Figure 3).
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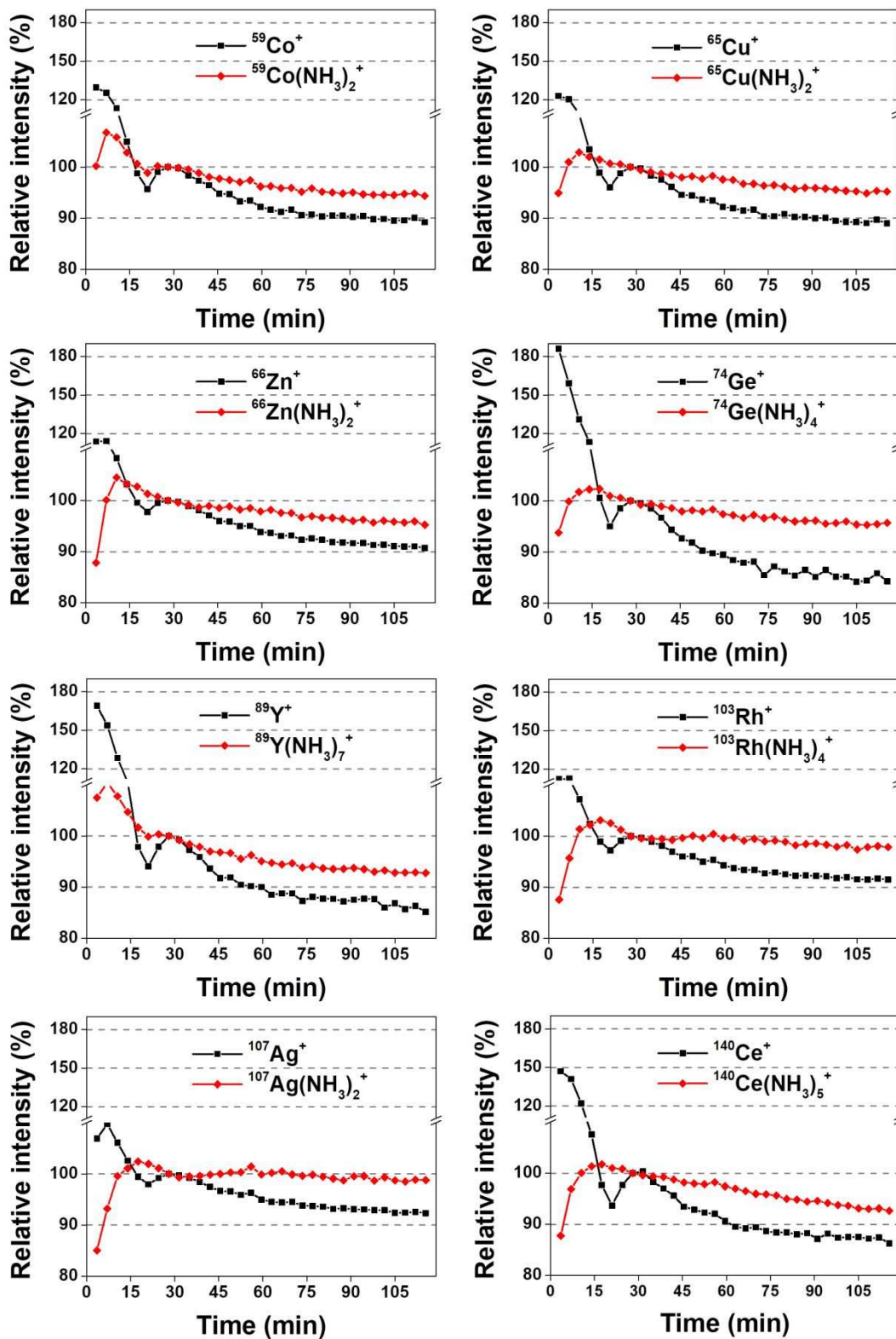
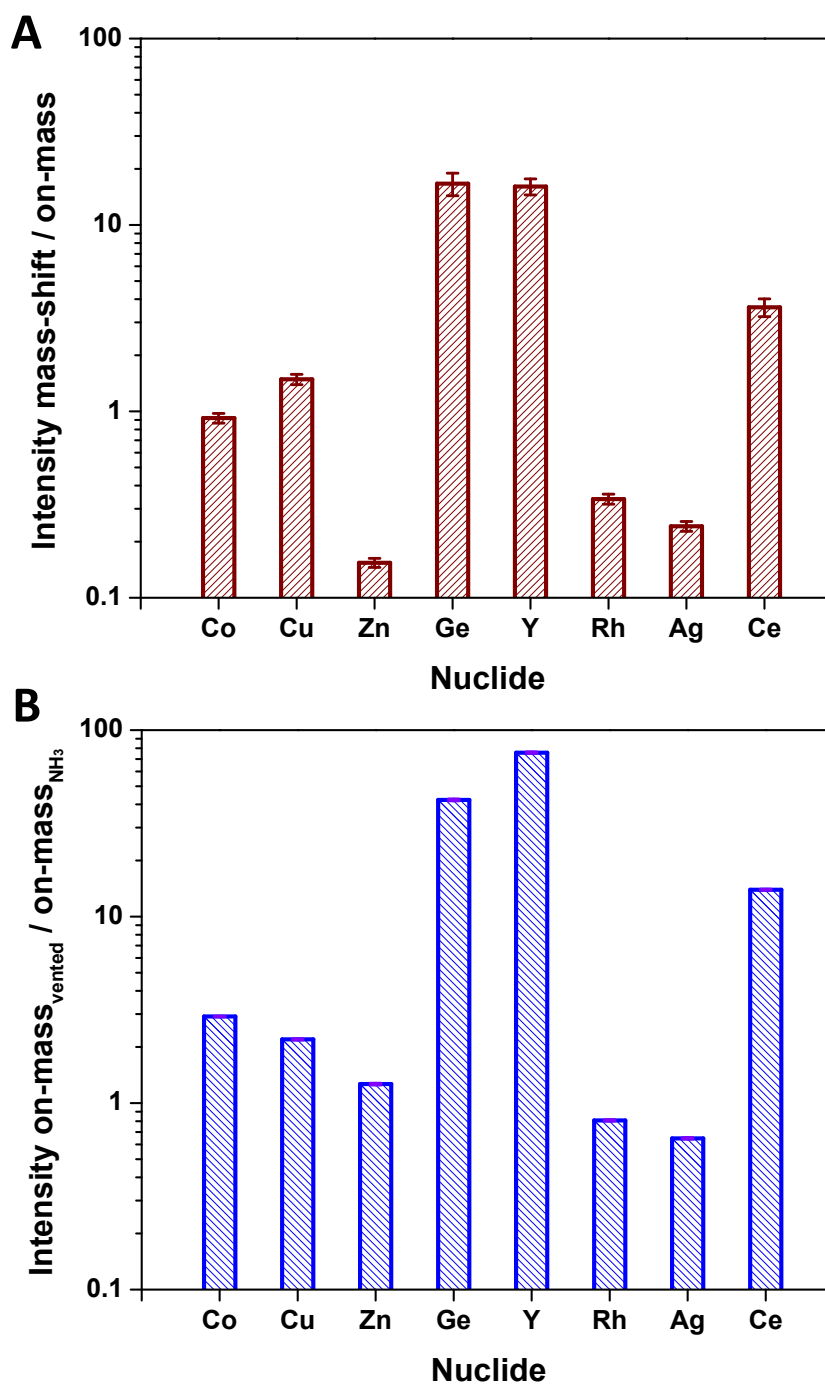


Figure 2. Differences in the short-term signal stability for the same target elements monitored as atomic ion (on-mass, black squares) and reaction product ion (mass-shift, red diamonds). In this experiment, the instrument was not previously stabilized with the NH₃/He gas mixture.



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3 **Figure 3.** (A) Ratios of the signal intensity of the best suited NH₃-based reaction product ion (mass-shift)
4 to that of the corresponding atomic ion (on-mass). Uncertainties are expressed as the standard deviation
5 of the individual signal intensity ratios calculated for the entire data set. (B) Ratios of the signal intensity
6 of the atomic ion measured in vented mode to that of the same atomic ions but measured on-mass in
7 NH₃/He mode.
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10 To further demonstrate the effect of the in-cell chemistry on the short-term signal intensity drift as a
11 result of stabilization of the cell gas pressure and potential reactive losses, additional experiments were
12 carried out with selected analytes (Fe, Ge and Y) for which multiple product ions are formed upon
13 reaction with NH₃. Figures 4A, 4B and 4C show the product ions identified using PIS with the cell
14 pressurized with 3.0 mL min⁻¹ of the NH₃/He gas mixture. It can be seen that these analytes also showed
15 different reaction pathways, such as elimination of a hydrogen atom or a hydrogen molecule, ammonia
16 cluster formation or a combination thereof. Figures 4D, 4E and 4F show the short-term signal intensity
17 behavior observed during multiproduct ion monitoring for Fe, Ge and Y, respectively. After
18 approximately 30 min of signal stabilization, the results demonstrate that the signal intensities for some
19 of the reaction products ions formed (generally those of a higher order – *e.g.*, Fe(NH₃)₃⁺) increase over
20 time, while the signal intensities of the atomic ions decrease significantly, as well as those of the low
21 order reaction product ions (*e.g.*, FeNH₃⁺). The optimum reaction product ions tend to be the most stable
22 ones on a short-term basis. Although the contribution from other system drift components cannot be
23 ruled out, these results clearly demonstrate the effect of stabilization of the cell gas pressure and of the
24 in-cell chemistry on the short-term signal intensity drift for an ORS pressurized with 3.0 mL min⁻¹ of the
25 NH₃/He gas mixture.
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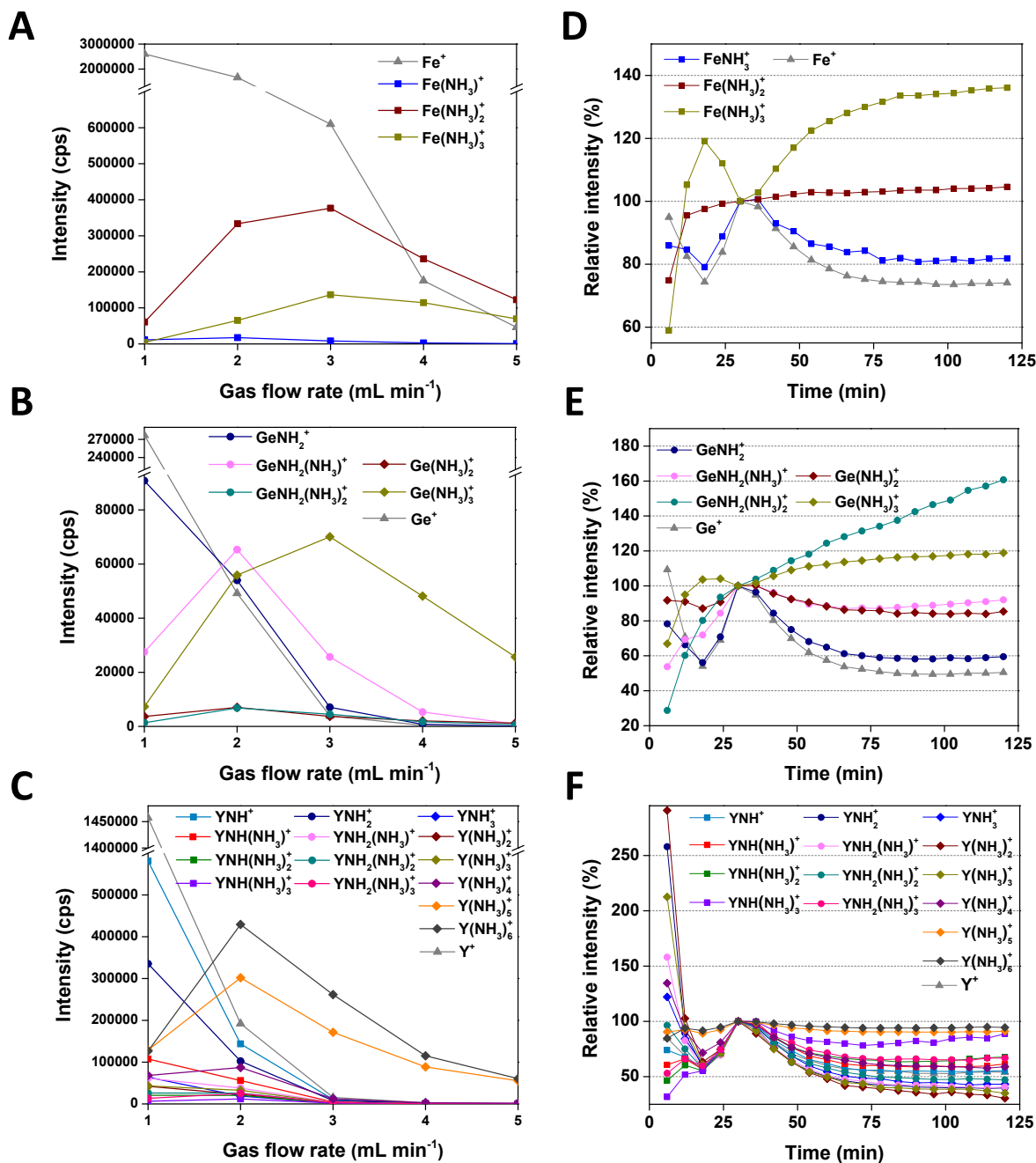


Figure 4. Product ion scans (A-C) and short-term signal drift (A-F) for different Fe-, Ge-, and Y- based reaction product ions (mass-shift) and the corresponding atomic ions (on-mass) with the cell pressurized with 3.0 mL min⁻¹ of the NH₃/He gas mixture.

As indicated above, some analytes (Ce, Ge, Ti, Sc and Y) showed better reactivity at lower NH₃/He gas flow rates, which was often accompanied by a different optimum reaction product ion (see Table S1 of

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3 the ESI). To assess the effect of the gas flow rate on the short-term signal stability, experiments aiming at
4 comparing the signal intensity trends of these atomic ions and their corresponding optimum reaction
5 product ions at each of the gas flow rates (*i.e.*, 1.0 and 3.0 mL min⁻¹ of the NH₃/He gas mixture) were
6 performed. The average results are shown in Figure 5 while those of each analyte are shown in Figure S2
7 of the ESI. As can be seen from these results, the CRC needs more time before “stable conditions” can be
8 achieved when pressurizing at 1.0 mL min⁻¹ of the NH₃/He gas mixture, as actually approximately 3 hours
9 were still not enough to avoid signal perturbations due to in-cell variability (Figure 5A). In contrast, after
10 50 minutes at 3.0 mL min⁻¹ of NH₃/He, the signals of both on-mass and mass-shift ions are stabilized
11 (Figure 5B). These differences can mostly likely be attributed to a longer time of stabilization required
12 when working at lower gas flow rates, as only approximately 0.1 mL min⁻¹ of pure NH₃ (mixture of 10%
13 NH₃ in He) are introduced in this experiment. It also needs to be noted that analytes monitored on-mass
14 behave differently compared to analytes monitored after mass-shift, as when the signal intensity of the
15 analytes monitored on-mass increases, the one measured mass-shifted decreases and *vice versa*. As
16 indicated in the results from the previous experiments (multiproduct ion monitoring), this suggests that
17 cell gas stabilization and potential reactive losses play a major role in the short-term signal stability, thus
18 requiring an appropriate selection of the internal standard to adequately correct for this effect.
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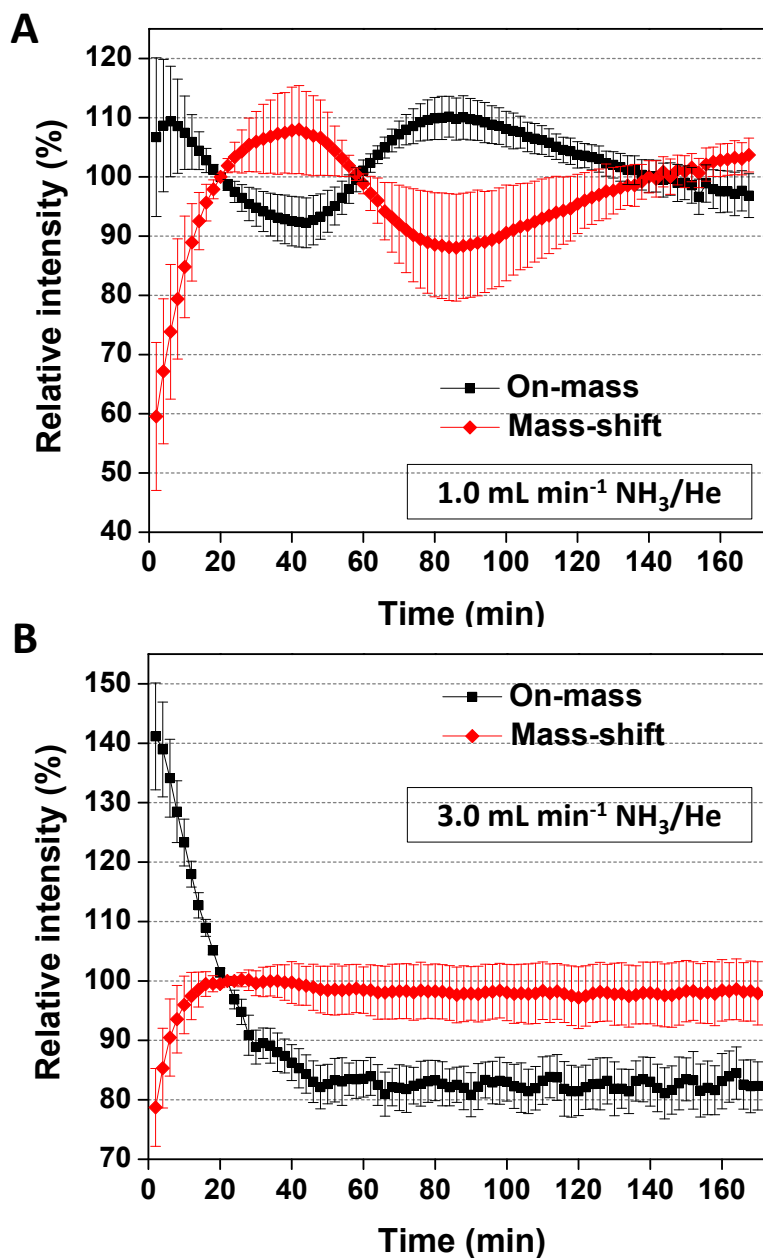


Figure 5. Average short-term signal stability/drift for atomic ions (black squares) and their corresponding optimum reaction product ions (red diamonds) at 1.0 mL min⁻¹ of NH₃/He (A) and at 3.0 mL min⁻¹ of NH₃/He (B) for Sc, Ti, Ge, Y and Ce. In this experiment, the instrument was not previously stabilized with the NH₃/He gas mixture. Uncertainties are expressed as the standard deviation of 5 relative signal intensities for atomic and reaction product ions.

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3 Based on the results of all previous experiments, it seems clear that the appropriate use of an internal
4 standard in a mass-shift approach without sufficient stabilization time is not self-evident. As a result, an
5 in-depth knowledge of the ion-molecule chemistry occurring within the CRC of an ICP-MS/MS instrument
6 is required to appropriately select an analyte / internal standard pair for the short-term signal intensity
7 drift to be adequately corrected for. It also needs to be noted that, in all cases, the signal drift of reaction
8 product ions was found to be lower than that of the atomic ions.
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11 In addition to experiments for assessing the short-term signal stability at different operating conditions,
12 also experiments to evaluate the response over a longer time were carried out. In this case, the
13 instrument conditions were first stabilized by running it for 4 hours with the cell pressurized with the
14 mixture of NH_3/He (3.0 mL min^{-1}) prior to analysis. Subsequently, all nuclides indicated in Table 2 were
15 monitored during approximately 8 hours to assess the long-term signal drift (instrument settings and
16 data acquisition parameters are shown in Table 1). The average relative intensities for the atomic and
17 reaction product ions monitored as a function of time are shown in Figure S3 of the ESI. In contrast to
18 the previous experiments, the average signal drift was within $\pm 5\%$ and no significant differences were
19 found between atomic and reaction product ions (ANOVA, $F_{\text{experimental}} = 0.00014 < F_{\text{critical}} = 3.92$), which
20 can be attributed to the use of sufficiently long stabilization times. For comparison purposes, the long-
21 term signal stability was also evaluated with the cell operated in vented mode (Figure S3 of the ESI). A
22 comparison of both long-term signal intensity drifts tentatively suggests a more pronounced drift in the
23 case of vented mode compared to pressurized mode. Furthermore, a higher variability between analytes
24 (see error bars corresponding to the standard deviation) needs to be pointed out in the case of vented
25 compared to pressurized mode, which can be attributed to the stabilization/thermalization occurring
26 within the CRC of an ICP-QMS instrument after introduction of NH_3/He and He gases.⁴
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52 ***3.2. Response to disturbances in the cell: multi-tune methods***

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3 As indicated in the previous section, the lack of stability within a pressurized multiple cell may induce a
4 different response of atomic and reaction product ions. To avoid bias in the ICP-MS measurement
5 results, this signal intensity variation needs to be adequately corrected for using an appropriate internal
6 standard. The use of a sufficiently long stabilization time of the CRC upon introduction of a reaction gas
7 prior to ICP-MS analysis adequately deals with this problem but cannot always be accomplished. It needs
8 to be noted that this approach is time-consuming, reduces the sample throughput of ICP-MS analysis,
9 and, most importantly, works for methods using a single set of operating conditions only. However, for
10 enabling multi-element analysis under ideal conditions, ICP-MS/MS instrumentation can quickly switch
11 from one set of operating conditions to another within the same measurement sequence (multi-tune
12 method), including adjustment of the CRC gas flow rate and even type of gas. In this way, different
13 operating conditions and gas mixtures can be selected depending on the target analytes of interest, thus
14 improving the potential of this technique for interference-free multi-element analysis, while maintaining
15 the maximum sensitivity for each analyte. This sequential change in the ICP-MS instrument settings may
16 introduce some cell disturbances that can affect the ion-molecule chemistry processes occurring within
17 the CRC. To assess the effect of these cell disturbances on the signal intensities obtained for both atomic
18 and reaction product ions, additional experiments relying on the use of two different multi-tune
19 methods were carried out to shed light onto the selection of a suitable internal standard in mass-shift
20 approaches.

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44 A first experiment consisted of measuring five replicates of the target nuclides indicated in Table 2 using
45 a multi-tune method (see Table S2 of the ESI) that combined measuring with a vented cell and with a cell
46 pressurized with NH_3 as reaction gas ($3.0 \text{ mL min}^{-1} \text{ NH}_3/\text{He}$). This type of method can be routinely used in
47 a multi-element analysis including both analytes that do not suffer from spectral interference
48 (measurement in vented mode) and analytes strongly affected by spectral overlap (measurement in
49 chemical resolution mode). In this case, the instrument settings change rapidly from no gas or vented
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3 mode to a NH₃/He pressurized mode within each measurement replicate. Here, all target nuclides were
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5 monitored in the NH₃/He tune mode, while in no gas mode, ²³⁵U⁺ with an integration time of 30 s was
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7 monitored as a “random” nuclide, as the purpose of this mode is just to test whether switching induces
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9 cell disturbances. In other words, the selection of this analyte is not relevant, as this tune mode only
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11 aims at introducing a change between cell conditions to evaluate the effect for the analytes monitored in
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13 the NH₃/He pressurized mode. In the context of this work, the CRC was previously stabilized with the
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15 reaction gas mixture. To further evaluate the effect of multi-tune methods on signal behavior, a waiting
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17 time before starting to acquire data can be selected to let the signal stabilize when the tune conditions
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19 change. Figures 6A, 6B and 6C show the average relative intensity signals (%) of 5 measurement
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21 replicates obtained for the atomic analyte ions and/or reaction product ions using the multi-tune
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23 method “no gas → 3.0 mL min⁻¹ NH₃”, using 0, 10 and 30 s of stabilization time, respectively. It also
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25 needs to be noted that the design of the experiment (with 5 measurement replicates) enables both
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27 directions to be evaluated (vented-pressurized and pressurized-vented modes). As can be seen in Figure
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29 6A (no additional stabilization time), the average signal intensities obtained for atomic ions drifted
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31 significantly compared to those for the reaction product ions. Like in the experiments discussed in
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33 section 3.1., it was found that the extent of this drift depends on the reactivity, although a common
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35 pattern can be seen for signals monitored on-mass vs those after mass-shifting. Figure 7 shows the full
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37 data set for all atomic ions (A) and reaction product ions (B) monitored (these results were averaged in
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39 Figure 6A). As also indicated above, a different signal drift can be seen for atomic ions monitored on-
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41 mass that showed high reactivity towards NH₃/He compared to those that do not react; the latter
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43 showed a behavior more similar to the reaction product ions (see Figure 7C). It also needs to be noted
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45 that the signal intensities of the product ions formed upon reaction of atomic ions displaying high
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47 reactivity towards the gas mixture did not increase significantly over time despite the drift observed for
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49 the corresponding atomic ions monitored on-mass. As indicated above (section 3.1. - multiproduct ion
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3 monitoring), also other, less suited reaction product ions are formed, while the signal intensities of the
4 optimum reaction product ions seem to be less affected by instabilities in the time window immediately
5 changing the cell conditions, as also shown in Figure 4. Furthermore, the larger mass of the reaction
6 product ions may also have a positive influence on its transmission efficiency (cf. collisional scattering).
7
8 The use of 10 and 30 s of stabilization time (Figure 6B and 6C, respectively), progressively mitigated the
9 signal drift observed for the atomic ions. These results demonstrate that a fast change between cell
10 conditions in a multi-tune method affects the stability of the ion-molecule processes occurring within the
11 CRC. However, the use of a reasonable waiting time reduced (10 s) or even avoided (30 s) such
12 differences in signal behavior between atomic and reaction product ions.
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16 To study this effect under less drastic changes in CRC conditions, a second experiment was carried out
17 using a multi-tune method consisting of 3 different NH_3 gas flow rates ($1.0 \rightarrow 3.0 \rightarrow 5.0 \text{ mL min}^{-1} \text{ NH}_3$);
18 all other instrumental parameters were kept constant (see Table S3 of the ESI). As in the case of the
19 previous experiment, all target nuclides were monitored in the $3.0 \text{ mL min}^{-1} \text{ NH}_3/\text{He}$ tune mode, while
20 the other tune modes (1.0 and $5.0 \text{ mL min}^{-1} \text{ NH}_3/\text{He}$) were only used to induce cell disturbances by
21 modifying the reaction gas flow rate. The results are shown in Figures 6D, 6E and 6F (0, 10 and 30 s of
22 stabilization, respectively). As can be seen from the comparison between these results and those of the
23 previous multi-tune method for each specific stabilization time, the signal drift for the atomic ions was
24 less pronounced in all cases. In fact, the use of 10 s of stabilization already avoided differences in signal
25 drift between atomic and reaction product ions. The smaller effect observed in the case of a multi-tune
26 method based on different NH_3 gas flow rates can be attributed to less pronounced disturbances in the
27 CRC conditions prior to analysis. Based on these results, the signal drifts of atomic and reaction product
28 ions can be significantly different from one another, unless the CRC is given the time to reach stable
29 conditions. This different behavior can be problematic if the internal standard and target analyte are not
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measured using the same approach and this stabilization period is not taken into account. This time of stabilization required depends on the operating conditions and on the extent of cell disturbances.

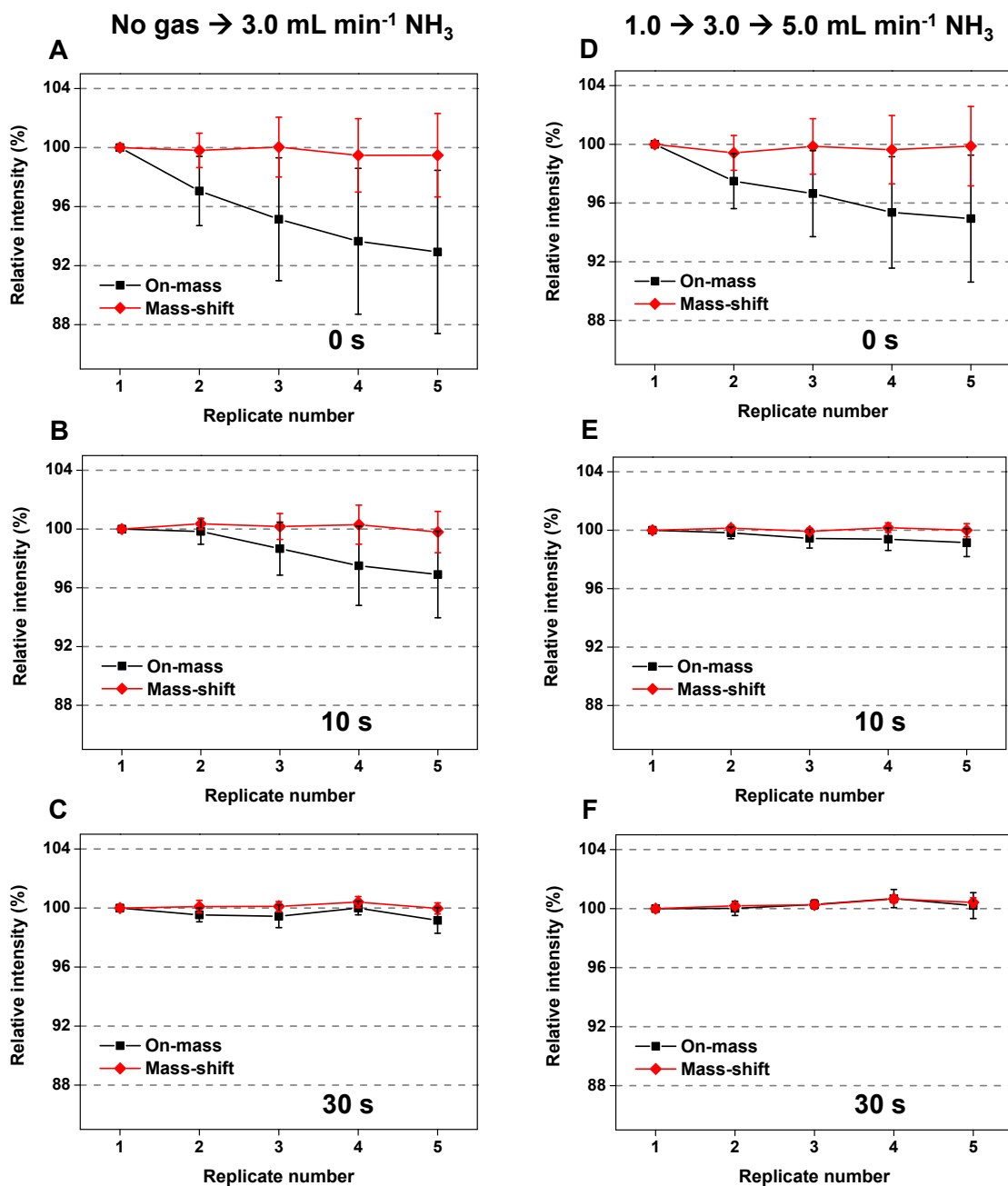


Figure 6. Average relative intensity for atomic ions (black squares) and reaction product ions (red diamonds) monitoring in multi-tune methods (No gas → 3.0 mL min⁻¹ NH₃/He – A, B, C; 1.0 → 3.0 → 5.0 mL min⁻¹ NH₃/He – D, E, F) using different stabilization times (0s – A, D; 10s – B, E; 30s – C, F). The results

show the relative average intensities of all nuclides monitored on-mass and upon mass-shifting (see Table 2) by using the 3.0 mL min⁻¹ NH₃/He tune mode. The no gas and 1.0 and 5.0 mL min⁻¹ NH₃/He tune modes were only used to induce cell disturbances. Uncertainties are expressed as the standard deviation of 13 and 12 relative signal intensities for atomic and reaction product ions, respectively.

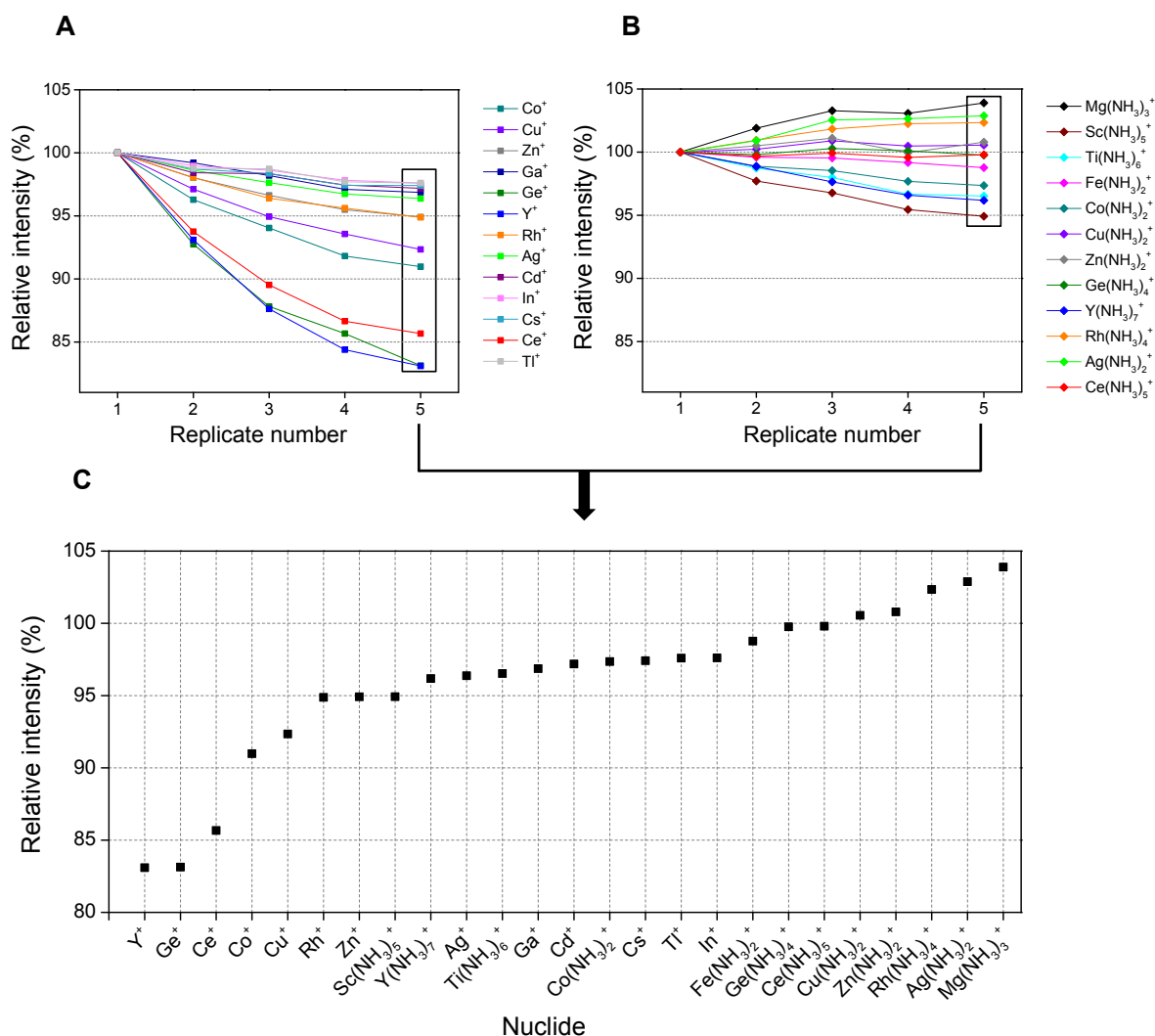


Figure 7. Signal drift expressed as relative intensity for atomic ions (A) and reaction product ions (B) monitored in a multi-tune method (no gas → 3.0 mL min⁻¹ NH₃/He) using 0 s of stabilization time. (A, B) Relative intensities during a sequence consisting of five measurement replicates and (C) comparison of the relative intensities for all atomic and reaction product ions obtained during the fifth replicate.

3.3. Response to changes in instrumental parameters

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3 In addition to differences in behavior between atomic and reaction product ions (signal stability) after
4 cell disturbances, the effect of varying different instrumental parameters on both atomic and reaction
5 product ions was evaluated. Self-evidently, this work aims at assessing the use of internal
6 standardization in the case of mass-shift (pressurized mode) and aims at providing information as to
7 whether the internal standard can be monitored on-mass (but still in pressurized mode) or needs to be
8 mass-shifted as in the case of the target analyte. This means that both analyte and internal standard
9 have to be measured under the same instrumental conditions. However, some parameters affecting the
10 plasma, although constant, can reflect changes similar to those caused by a matrix (matrix effects), and
11 thus also these tests can provide useful information on the suitability of different internal
12 standardization approaches (on-mass vs mass-shift). In this experiment, different "ICP settings",
13 potentially inducing significant ICP-MS system perturbations similarly to those induced as a result of
14 matrix effects, such as plasma power (RF), torch position (sample depth) and liquid (pump speed) and
15 gas (nebulizer gas) flow rates, were sequentially modified (*i.e.*, one parameter was changed while all
16 other settings were kept constant). Figure 8 shows the average relative intensities of the different
17 analytes measured as atomic and as reaction product ions; the intensity of every signal was normalized
18 relative to that under optimum conditions. Based on these results, no significant differences were found
19 between atomic and reaction products of the same analyte, which can be attributed to the low influence
20 of these instrument settings on the ion-molecule chemistry occurring within the CRC of an ICP-MS/MS
21 instrument. The relative intensities of the different analytes are provided separately in Figure S4 of the
22 ESI.

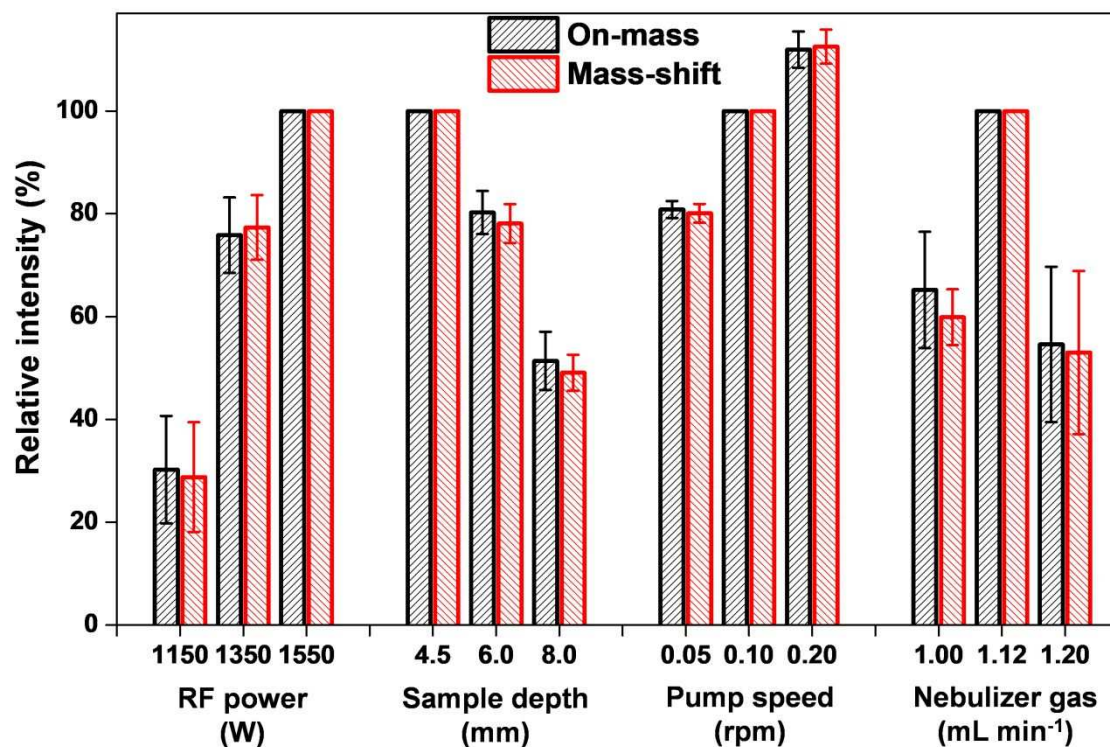


Figure 8. Average relative intensities of all nuclides (see Table 2) measured as atomic or reaction product ion under different instrument settings. The relative intensities were normalized relative to those obtained under optimum conditions (see Table 1). Uncertainties are expressed as the standard deviation of 13 and 12 relative signal intensities for atomic and reaction product ions, respectively.

An additional statistical evaluation was carried out in order to find some ground for adequate selection of analyte / internal standard pairs when using modern ICP-MS instrumentation equipped with CRC technology, such as ICP-MS/MS operated in NH_3/He pressurized mode. A hierarchical cluster analysis (HCA) based on Ward's method and the Squared Euclidean distance was performed with the data from the 25 x 4 matrix (number of atomic and reaction product ions, and instrument settings, respectively). This analysis classifies the nuclides studied in different subgroups (clusters) based on their relative distances, and the results thus obtained are presented in a dendrogram, where the y-axis represents the

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3 distance at which the different clusters merge. The best approach for the selection of the cut-off line to
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5 determine the number of clusters is to combine the information provided by the agglomeration schedule
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7 and the dendrogram. From the agglomeration schedule, the point at which the differences between
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9 coefficients of two consecutive stages start to be larger indicates that the heterogeneity between the
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11 clusters to be merged is increasing, and thus, it suggests the ideal stage to stop the clustering process. In
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13 this case, the best point to stop the cluster analysis was found to be after the 21st stage (red dotted line
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15 in the scree plot of the coefficients – Figure S5 of the ESI), thus eliminating the last three stages. This
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17 selection is reflected in the dendrogram where the last three vertical lines were cut for the cluster
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19 solution leading to the formation of four clusters (the cut-off line crosses four horizontal lines). The four
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21 main clusters were validated *via* one-way ANOVA. The groups can be considered well classified because
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23 there are statistically significant differences between groups at a 95% level of confidence ($p = 0.042$).
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25 Additionally, a dimension reduction was achieved by using principal component analysis (PCA). The
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27 optimum number of PCs was found to be two, as they explained $\approx 95\%$ of the total variance. With the
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29 two factors obtained by PCA and Ward's method data (cluster) obtained by HCA, a cluster graph can be
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31 obtained, as shown in Figure 9. Except in the case of Ag, it needs to be noted that atomic ions (on-mass)
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33 and their corresponding reaction product ions (mass-shift) were always classified in the same cluster,
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35 thus demonstrating the low effect of varying different instrument settings. A more detailed evaluation of
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37 the statistical results showed no evidence for mass number or ionization energies playing a central role
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39 in the classification of the different nuclides according to the variations in ICP instrument settings,
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41 although both have previously been hinted as key factors for the adequate selection of a suitable
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43 internal standard in ICP-MS. However, similar findings have also been reported in recent publications
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45 suggesting that both closeness in mass number and ionization energy could be of less importance in the
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47 case of recent ICP-MS instrumentation equipped with CRC technology compared to ICP-MS
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49 instrumentation of earlier generations.^{6, 7, 18-20} As for almost every element investigated, the atomic ion
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3 and the corresponding reaction product ion are always in the same cluster, it is clear that these signal
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5 intensities are affected similarly by system perturbations mimicked by changes in the ICP instrument
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7 settings and on the condition of absence of any source of variation affecting the in-cell chemistry. This
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9 also entails that an analyte element / internal standard pair that works well in an on-mass monitoring
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11 context is also a good choice in a mass-shift approach.
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15 Overall, when relying on a mass-shift approach to enable interference-free determination using ICP-
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17 MS/MS, adequate selection of an internal standard requires a number of factors to be accounted for
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19 before optimum accuracy and precision can be achieved. The different response over time for atomic
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21 ions (on-mass) and reaction product ions (mass-shift), respectively, points to the important role of the in-
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23 cell chemistry in the selection of an analyte / internal standard pair, while variations in instrument
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25 settings also indicate that the factors that were previously found to be of key importance for IS selection
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27 might no longer be sufficient or even no longer be relevant in the case of mass-shift approaches with
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29 ICP-MS/MS instrumentation. Taking all of the above into account and based on the results obtained in
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31 this work for 17 elements monitored on-mass and/or after mass-shift, Table 3 attempts at
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33 recommending the most suitable analyte / internal standard pairs for atomic and reaction product ions
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35 monitored with an NH₃/He pressurized cell in ICP-MS/MS.
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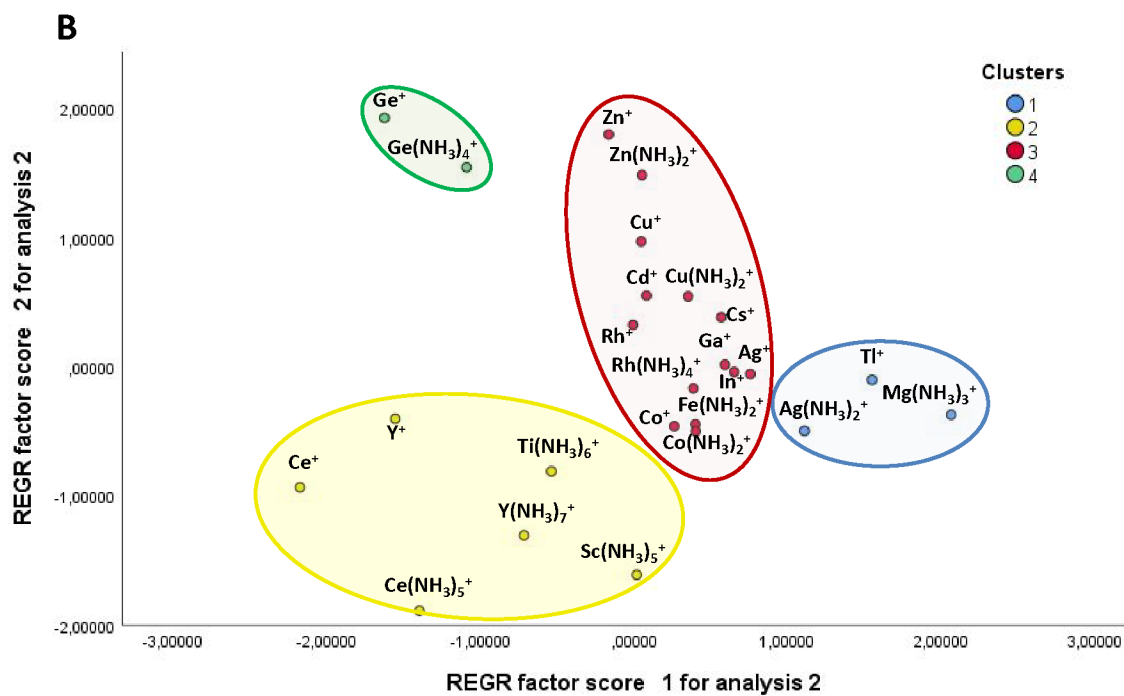
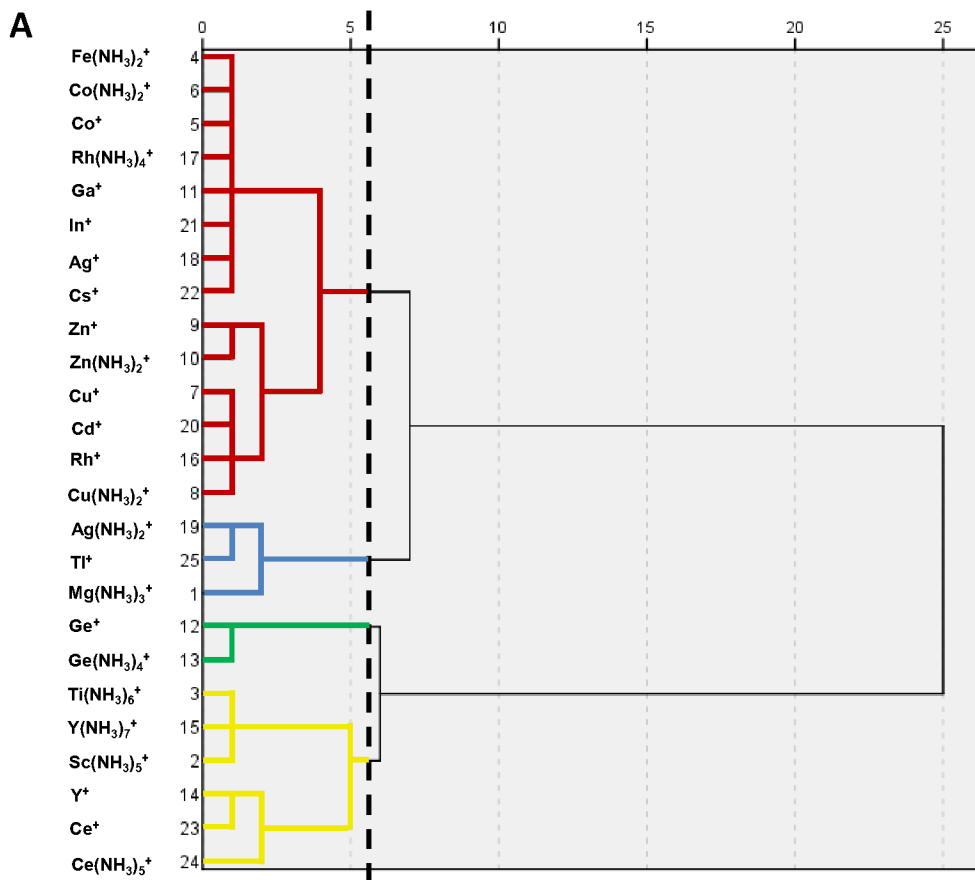


Figure 9. Dendrogram plot obtained from the hierarchical cluster analysis of the instrumental parameters data set (A) and cluster plot of the same data after dendrogram cut (dotted line) corresponding to four clusters (B).

Table 3. Recommended analyte / internal standard pairs for atomic and reaction product ions monitored on-mass and/or after mass-shift using NH_3/He as CRC gas in ICP-MS/MS based on the results for 17 selected elements. For each analyte nuclide, three internal standard species are recommended in order of preference according to the different experiments carried out in this work.

Nuclide	Mode	Analyte	Recommended internal standards
^{24}Mg	Mass-shift	$\text{Mg}(\text{NH}_3)_3^+$	$\text{Ag}(\text{NH}_3)_2^+$, $\text{Rh}(\text{NH}_3)_4^+$, $\text{Zn}(\text{NH}_3)_2^+$
^{45}Sc	Mass-shift	$\text{Sc}(\text{NH}_3)_5^+$	$\text{Y}(\text{NH}_3)_7^+$, $\text{Ti}(\text{NH}_3)_6^+$, Rh^+
^{48}Ti	Mass-shift	$\text{Ti}(\text{NH}_3)_6^+$	$\text{Y}(\text{NH}_3)_7^+$, $\text{Sc}(\text{NH}_3)_5^+$, Ag^+
^{56}Fe	Mass-shift	$\text{Fe}(\text{NH}_3)_2^+$	$\text{Cu}(\text{NH}_3)_2^+$, $\text{Co}(\text{NH}_3)_2^+$, $\text{Ge}(\text{NH}_3)_4^+$
^{59}Co	On-mass	Co^+	Cu^+ , Zn^+ , Rh^+
	Mass-shift	$\text{Co}(\text{NH}_3)_2^+$	Cs^+ , In^+ , $\text{Fe}(\text{NH}_3)_2^+$
^{65}Cu	On-mass	Cu^+	Co^+ , Zn^+ , Rh^+
	Mass-shift	$\text{Cu}(\text{NH}_3)_2^+$	$\text{Zn}(\text{NH}_3)_2^+$, $\text{Ge}(\text{NH}_3)_4^+$, $\text{Fe}(\text{NH}_3)_2^+$
^{66}Zn	On-mass	Zn^+	Rh^+ , $\text{Sc}(\text{NH}_3)_5^+$, Cu^+
	Mass-shift	$\text{Zn}(\text{NH}_3)_2^+$	$\text{Cu}(\text{NH}_3)_2^+$, $\text{Ge}(\text{NH}_3)_4^+$, $\text{Fe}(\text{NH}_3)_2^+$
^{71}Ga	On-mass	Ga^+	Cd^+ , Ag^+ , $\text{Fe}(\text{NH}_3)_2^+$
^{74}Ge	On-mass	Ge^+	Y^+ , Ce^+ , Co^+
	Mass-shift	$\text{Ge}(\text{NH}_3)_4^+$	$\text{Ce}(\text{NH}_3)_5^+$, $\text{Cu}(\text{NH}_3)_2^+$, $\text{Fe}(\text{NH}_3)_2^+$
^{89}Y	On-mass	Y^+	Ge^+ , Ce^+ , Co^+
	Mass-shift	$\text{Y}(\text{NH}_3)_7^+$	$\text{Ti}(\text{NH}_3)_6^+$, Ag^+ , $\text{Sc}(\text{NH}_3)_5^+$
^{103}Rh	On-mass	Rh^+	Zn^+ , $\text{Sc}(\text{NH}_3)_5^+$, Ag^+
	Mass-shift	$\text{Rh}(\text{NH}_3)_4^+$	$\text{Ag}(\text{NH}_3)_2^+$, $\text{Mg}(\text{NH}_3)_3^+$, $\text{Zn}(\text{NH}_3)_2^+$
^{107}Ag	On-mass	Ag^+	$\text{Ti}(\text{NH}_3)_6^+$, Ga^+ , $\text{Y}(\text{NH}_3)_7^+$
	Mass-shift	$\text{Ag}(\text{NH}_3)_2^+$	$\text{Rh}(\text{NH}_3)_4^+$, $\text{Mg}(\text{NH}_3)_3^+$, $\text{Zn}(\text{NH}_3)_2^+$
^{111}Cd	On-mass	Cd^+	Ga^+ , $\text{Co}(\text{NH}_3)_2^+$, Cs^+

^{115}In	On-mass	In^+	$\text{Tl}^+, \text{Cs}^+, \text{Co}(\text{NH}_3)_2^+$
^{133}Cs	On-mass	Cs^+	$\text{In}^+, \text{Co}(\text{NH}_3)_2^+, \text{Tl}^+$
^{140}Ce	On-mass	Ce^+	$\text{Ge}^+, \text{Y}^+, \text{Co}^+$
	Mass-shift	$\text{Ce}(\text{NH}_3)_5^+$	$\text{Ge}(\text{NH}_3)_4^+, \text{Cu}(\text{NH}_3)_2^+, \text{Y}(\text{NH}_3)_7^+$
^{205}Tl	On-mass	Tl^+	$\text{In}^+, \text{Cs}^+, \text{Co}(\text{NH}_3)_2^+$

4. Conclusions

In this work, 17 elements were monitored on-mass (as their atomic ion) and/or after mass-shift (as a reaction product ion) with the aim of answering the question of how to select a suitable internal standard when the analyte ion is mass-shifted to overcome spectral overlap in ICP-MS/MS. The results of the different experiments revealed differences in the behavior of atomic ions compared to reaction product ions, although these differences could always be attributed to an insufficient time of stabilization of the in-cell conditions. Differences in reactivity between the target analytes and the reaction gas and/or in the extent of cell disturbance (*e.g.*, as a result of measurements carried out in multi-tune methods), demonstrated to have an impact on the differences observed between both approaches and on the times of stabilization required. Changes in signal intensities resulting from changes in different instrument settings did not reveal significant differences between both operation modes, while a statistical evaluation of the corresponding results did not provide evidence supporting the selection of a suitable analyte / internal standard pair as a function of some properties that were traditionally considered important, such as closeness in mass number and/or ionization energy. Overall, an adequate selection of an internal standard in a mass-shift approach should ideally also involve the measurement of the selected internal standard in a mass-shift approach whereby both analyte and internal standard display a similar reaction pathway. However, on-mass monitoring of the internal standard can also provide accurate and precise results on condition that there is enough time for stabilization of the in-cell conditions.

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3 **Conflicts of interest**
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6 There are no conflicts to declare.
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Electronic supplementary information (ESI)

To shift, or not to shift: adequate selection of an internal standard in mass-shift approaches using tandem ICP-mass spectrometry (ICP-MS/MS)

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1. Figure S1. Evaluation of the short-term signal drift for atomic ions monitored on-mass that react with NH₃/He (green up-pointing triangles), atomic ions monitored on-mass that do not react (or showed limited reactivity) with NH₃/He (grey down-pointing triangles), reaction product ions (mass-shift – red diamonds), and atomic ions monitored on-mass in vented mode (blue circles). In this experiment, the instrument was not previously stabilized with the NH₃/He gas mixture. Uncertainties are expressed as the standard deviation of 8, 5, 12 and 13 relative signal intensities for atomic ions monitored on-mass that react with NH₃/He, atomic ions monitored on-mass that do not react with NH₃/He, reaction product ions, and atomic ions monitored in vented mode, respectively.
2. Figure S2. Short-term signal stability/drift for atomic ions and their corresponding optimum reaction product ions at 1.0 mL min⁻¹ of NH₃/He (A) and at 3.0 mL min⁻¹ of NH₃/He (B) for Sc, Ti, Ge, Y and Ce. In this experiment, the instrument was not previously stabilized with the NH₃/He gas mixture.

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3 **3.** Figure S3. Evaluation of the long-term signal drift for atomic ions monitored on-mass (black
4 squares) in NH_3/He mode, reaction product ions (mass-shift approach – red diamonds) and atomic
5 ions monitored in vented mode (blue circles) using ICP-MS/MS. In this experiment, the instrument
6 was drift-stabilized by running it for 4 hours with the cell pressurized with NH_3/He (3.0 mL min^{-1})
7 prior to signal monitoring. Uncertainties are expressed as the standard deviation of 13 and 12
8 relative signal intensities for atomic (both pressurized and vented modes) and reaction product
9 ions, respectively.
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- 12 **4.** Figure S4. Relative intensities for all nuclides measured as atomic or reaction product ion under
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- 18 **5.** Figure S5. Scree plot of coefficients obtained after hierarchical cluster analysis by stage (the red
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- 22 **6.** Table S1. Best suited reaction product ion under compromise conditions for multi-element
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- 27 **7.** Table S2. ICP-MS/MS data acquisition parameters for a multi-tune method (no gas, 3.0 mL min^{-1}
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- 31 **8.** Table S3. ICP-MS/MS data acquisition parameters for a multi-tune method (1.0 , 3.0 and 5.0 mL
32 $\text{min}^{-1} \text{ NH}_3/\text{He}$).
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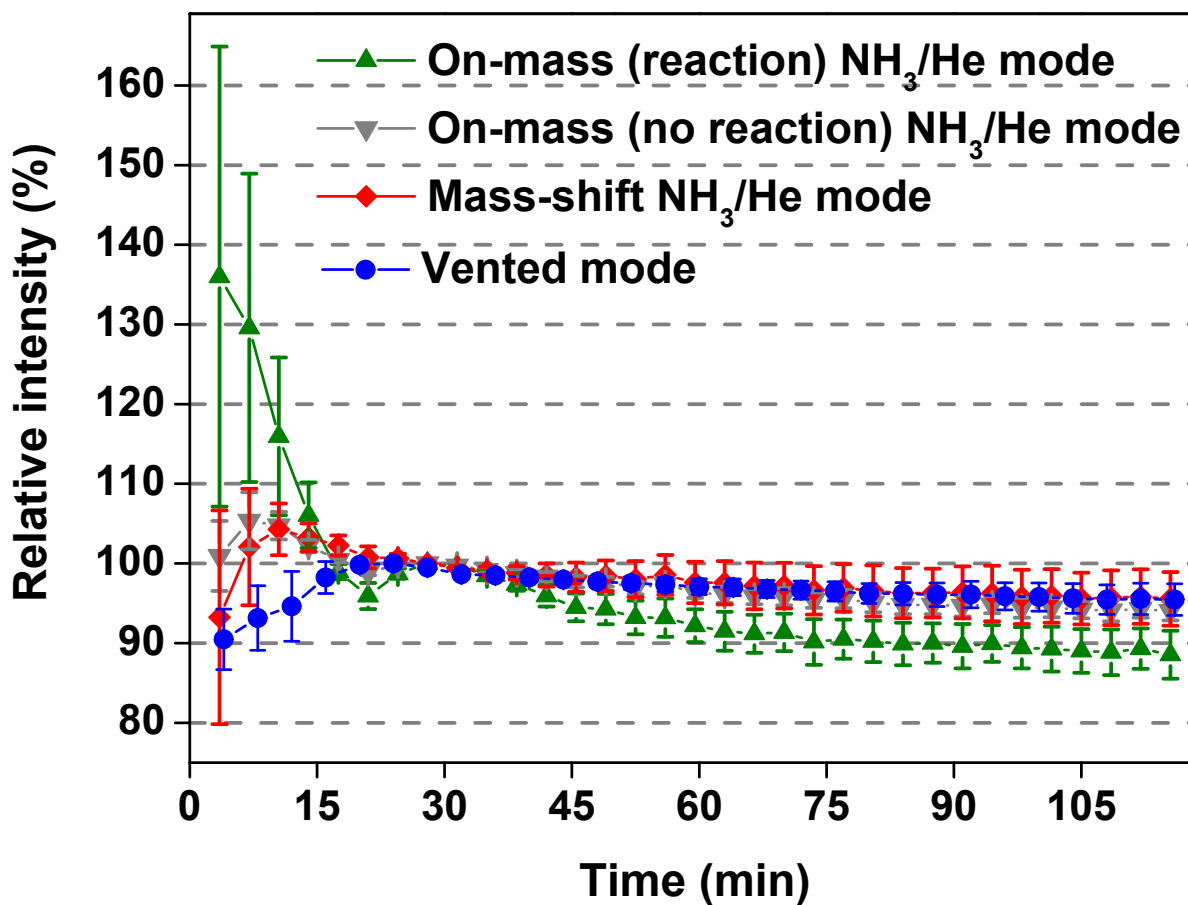


Figure S1. Evaluation of the long-term signal drift for atomic ions monitored on-mass (black squares) in NH₃/He mode, reaction product ions (mass-shift approach – red diamonds) and atomic ions monitored in vented mode (blue circles) using ICP-MS/MS. In this experiment, the instrument was drift-stabilized by running it for 4 hours with the cell pressurized with NH₃/He (3.0 mL min⁻¹) prior to signal monitoring. Uncertainties are expressed as the standard deviation of 13 and 12 relative signal intensities for atomic (both pressurized and vented modes) and reaction product ions, respectively.

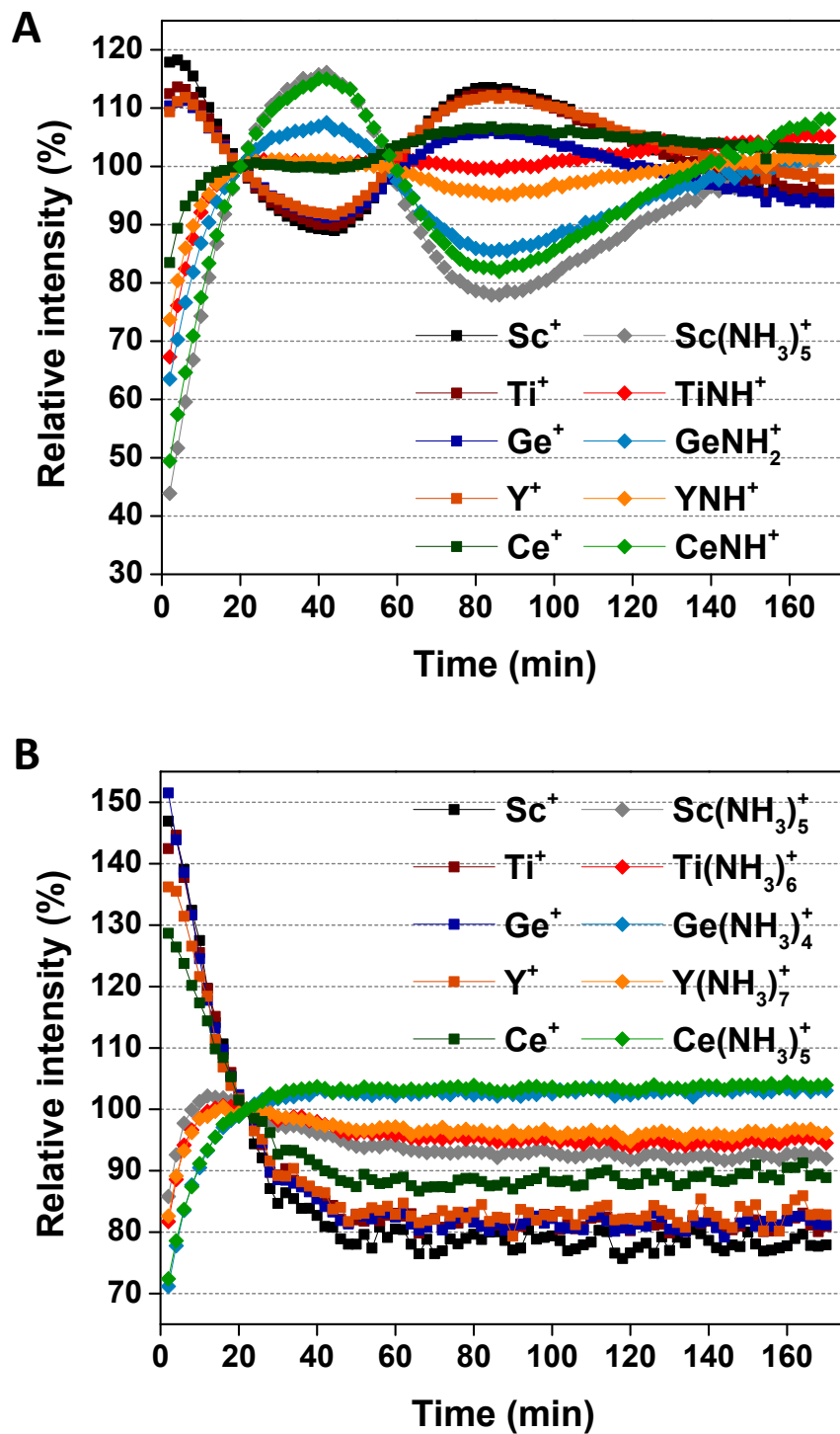


Figure S2. Short-term signal stability/drift for atomic ions and their corresponding optimum reaction product ions at 1.0 mL min⁻¹ of NH₃/He (A) and at 3.0 mL min⁻¹ of NH₃/He (B) for Sc, Ti, Ge, Y and Ce. In this experiment, the instrument was not previously stabilized with the NH₃/He gas mixture.

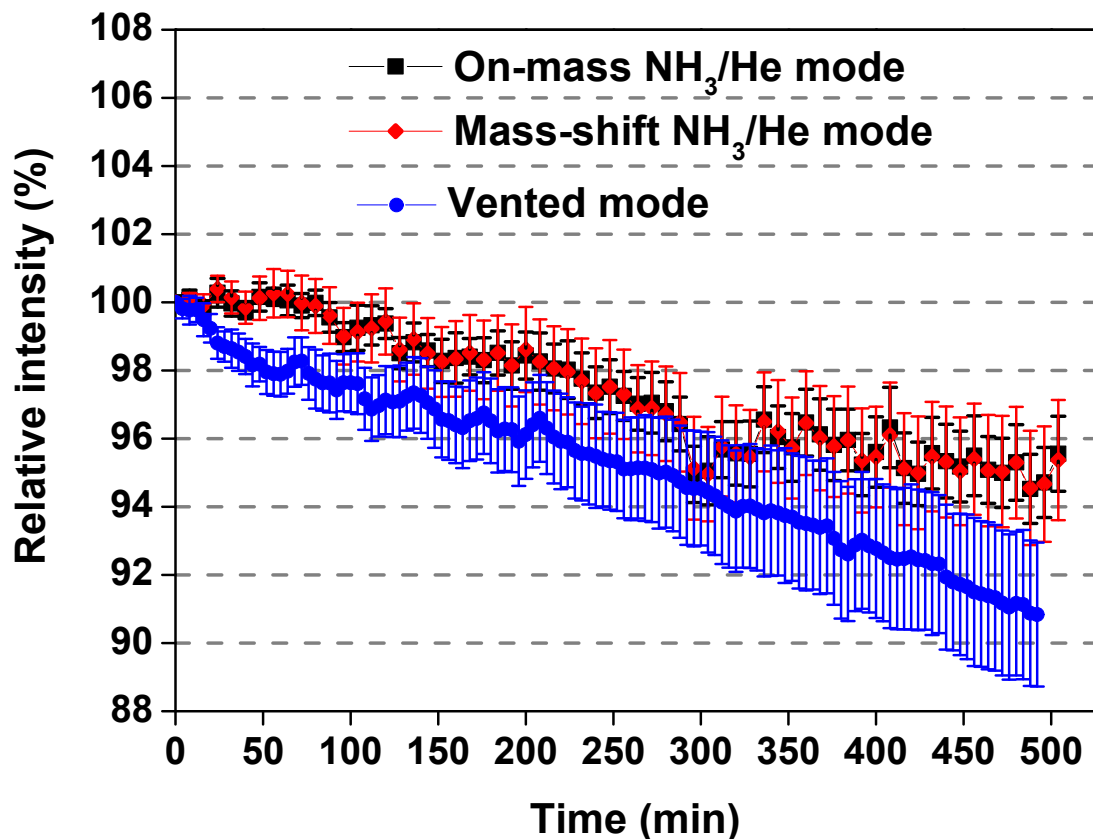
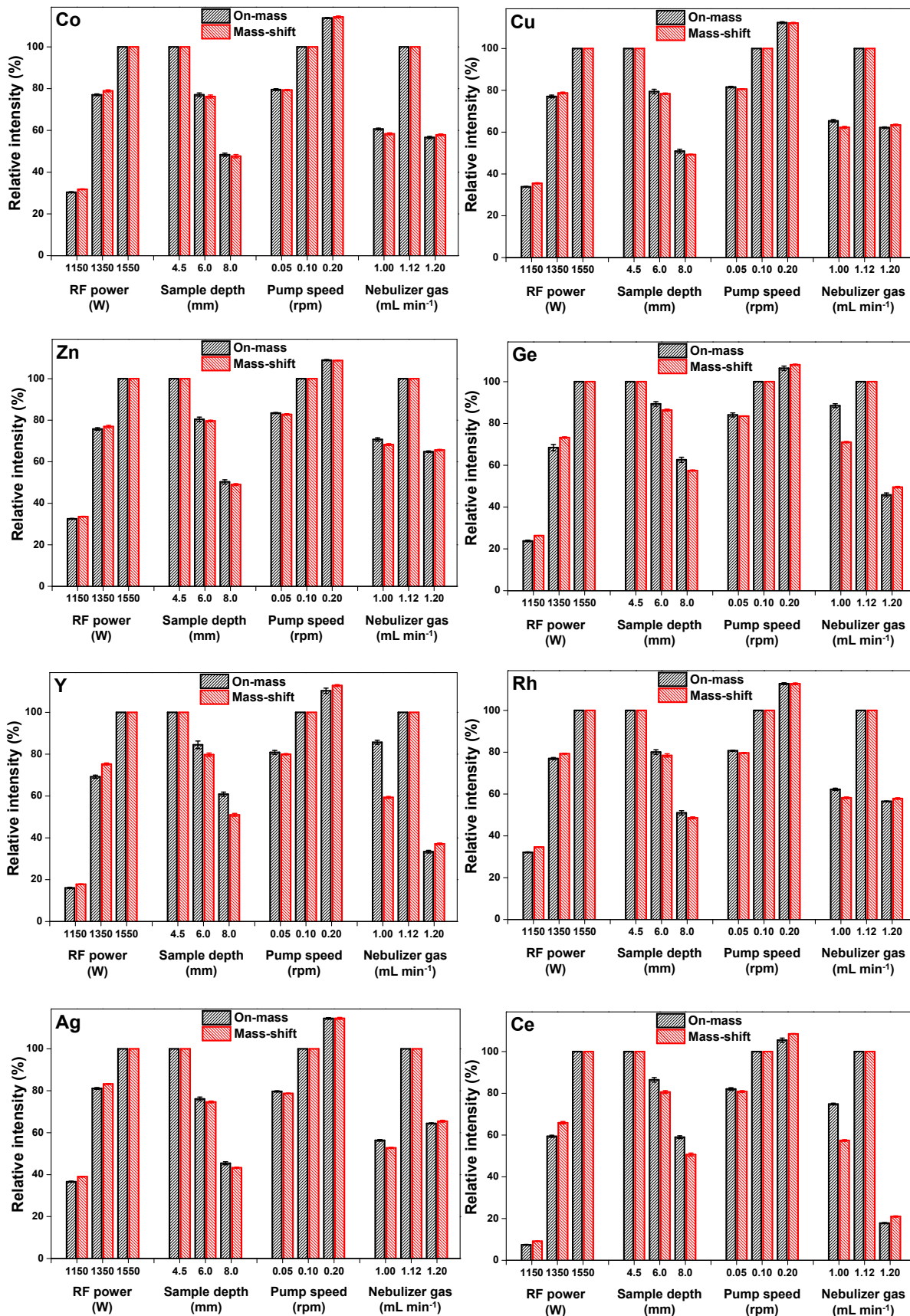
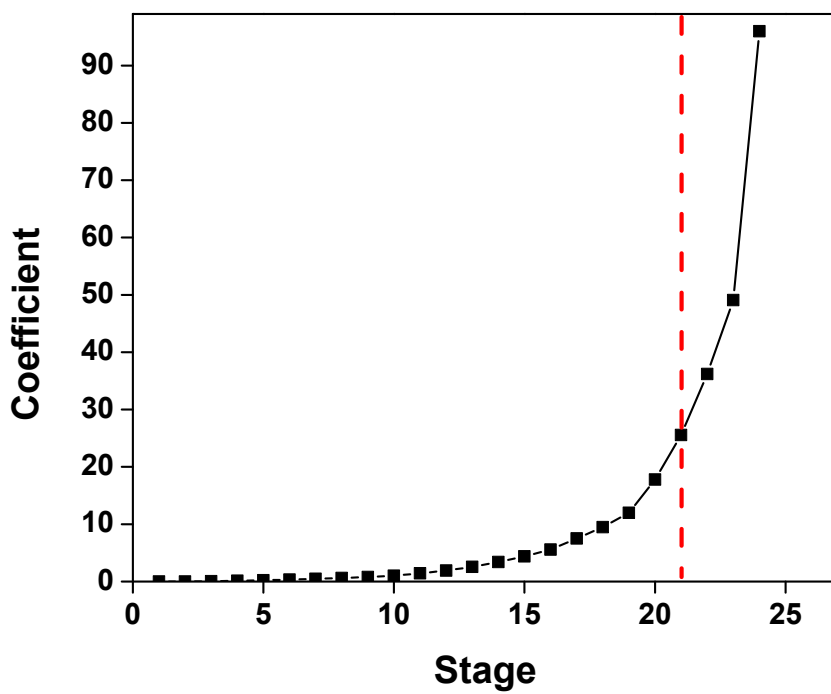


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3 **Figure S4.** Relative intensities for all nuclides measured as atomic or reaction product ion under different
4 instrument settings. The relative intensities were normalized relative to those obtained under optimum
5 conditions (see Table 1). Uncertainties are expressed as the standard deviation of 5 measurement
6 replicates.
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40 **Figure S5.** Scree plot of coefficients obtained after hierarchical cluster analysis by stage (the red dotted
41 line represents the stop of the cluster analysis).
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Table S1. Best suited reaction product ion under compromise conditions for multi-element determination (3.0 mL min⁻¹ of NH₃/He) and the reaction product ion providing the highest signal intensity and the corresponding gas flow rate for all of the target elements.

Nuclide	Gas flow rate (mL min ⁻¹)	Q2	Reaction product ion	Intensity (cps L μg ⁻¹)
²⁴ Mg	3.0	75	Mg(NH ₃) ₃ ⁺	1000
⁴⁵ Sc	1.0	130	Sc(NH ₃) ₅ ⁺	25000
	3.0			12000
⁴⁸ Ti	1.0	63	TiNH ⁺	29000
	3.0			19000
⁵⁶ Fe	3.0	90	Fe(NH ₃) ₂ ⁺	38000
	2.0			47000
⁵⁹ Co	3.0	93	Co(NH ₃) ₂ ⁺	36000
	3.0			38000
⁶⁵ Cu	3.0	99	Cu(NH ₃) ₂ ⁺	38000
⁶⁶ Zn	3.0	100	Zn(NH ₃) ₂ ⁺	1800
	1.0			9100
⁷⁴ Ge	3.0	125	Ge(NH ₃) ₃ ⁺	7000
	1.0			58000
⁸⁹ Y	3.0	191	Y(NH ₃) ₆ ⁺	43000
	4.0			67000
¹⁰³ Rh	3.0	171	Rh(NH ₃) ₄ ⁺	63000
	4.0			9700
¹⁰⁷ Ag	3.0	141	Ag(NH ₃) ₂ ⁺	7500
	1.0			34000
¹⁴⁰ Ce	3.0	225	Ce(NH ₃) ₅ ⁺	17000

Table S2. ICP-MS/MS data acquisition parameters for a multi-tune method (no gas, 3.0 mL min⁻¹ NH₃/He).

Element	No gas		3.0 mL min ⁻¹ NH ₃ /He	
	Q1 → Q2	Int. time/mass (s)	Q1 → Q2	Int. time/mass (s)
Mg	---	---	24 → 75	1
Sc	---	---	45 → 130	1
Ti	---	---	48 → 150	1
Fe	---	---	56 → 90	1
Co	---	---	59 → 59	1
Co	---	---	59 → 93	1
Cu	---	---	65 → 65	1
Cu	---	---	65 → 99	1
Zn	---	---	66 → 66	1
Zn	---	---	66 → 100	1
Ga	---	---	71 → 71	1
Ge	---	---	74 → 74	1
Ge	---	---	74 → 125	1
Y	---	---	89 → 89	1
Y	---	---	89 → 191	1
Rh	---	---	103 → 103	1
Rh	---	---	103 → 171	1
Ag	---	---	107 → 107	1
Ag	---	---	107 → 141	1
Cd	---	---	111 → 111	1
In	---	---	115 → 115	1
Cs	---	---	133 → 133	1
Ce	---	---	140 → 140	1
Ce	---	---	140 → 225	1
Tl	---	---	205 → 205	1
U	235 → 235	30	---	---
Stabilization time (s)	0	10	30	
Replicates	5	5	5	
Total analysis time/sample (s)	378	398	438	

Table S3. ICP-MS/MS data acquisition parameters for a multi-tune method (1.0, 3.0 and 5.0 mL min⁻¹ NH₃/He).

Element	1.0 mL min ⁻¹ NH ₃ /He		3.0 mL min ⁻¹ NH ₃ /He		5.0 mL min ⁻¹ NH ₃ /He	
	Q1 → Q2	Int.time/mass (s)	Q1 → Q2	Int.time/mass (s)	Q1 → Q2	Int.time/mass (s)
Mg	---	---	24→75	1	---	---
Sc	---	---	45→130	1	---	---
Ti	---	---	48→150	1	---	---
Fe	---	---	56→90	1	---	---
Co	---	---	59→59	1	---	---
Co	---	---	59→93	1	---	---
Cu	---	---	65→65	1	---	---
Cu	---	---	65→99	1	---	---
Zn	---	---	66→66	1	---	---
Zn	---	---	66→100	1	---	---
Ga	---	---	71→71	1	---	---
Ge	---	---	74→74	1	---	---
Ge	---	---	74→125	1	---	---
Y	---	---	89→89	1	---	---
Y	---	---	89→191	1	---	---
Rh	---	---	103→103	1	---	---
Rh	---	---	103→171	1	---	---
Ag	---	---	107→107	1	---	---
Ag	---	---	107→141	1	---	---
Cd	---	---	111→111	1	---	---
In	---	---	115→115	1	---	---
Cs	---	---	133→133	1	---	---
Ce	---	---	140→140	1	---	---
Ce	---	---	140→225	1	---	---
Tl	---	---	205→205	1	---	---
U	235→235	30	---	---	235→235	30
Stabilization time (s)		0		10		30
Replicates		5		5		5
Total analysis time/sample (s)		539		569		629