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3 **Characterization of SiO<sub>2</sub> Nanoparticles by Single Particle –**  
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6 **Inductively Coupled Plasma – Tandem Mass Spectrometry (SP-**  
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10 **ICP-MS/MS)**

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**ABSTRACT**

The increase in the use of SiO<sub>2</sub> nanoparticles (NPs) is raising concern about their environmental and health effects, thus necessitating the development of novel methods allowing for their straightforward detection and characterization. Single Particle ICP- mass spectrometry (SP-ICP-MS) is able to provide information on the size of NPs, their particle number density and mass concentration. However, the determination of Si *via* ICP-MS is strongly hampered by the occurrence of spectral overlap from polyatomic species (e.g., CO<sup>+</sup> and N<sub>2</sub><sup>+</sup>).

The use of tandem ICP-MS (ICP-MS/MS) enables interference-free conditions to be obtained, even in the most demanding applications. Upon testing of several gases, the use of CH<sub>3</sub>F (monitoring of SiF<sup>+</sup>, mass-shift approach) and of H<sub>2</sub> (monitoring of Si<sup>+</sup>, on-mass approach) were demonstrated to be the most suitable to overcome the spectral interference affecting ultra-trace Si determination (LoD < 15 ng L<sup>-1</sup>). By using these approaches, SiO<sub>2</sub> NPs (ranging between 80 and 400 nm) can be detected and characterized. For SiO<sub>2</sub> NPs > 100 nm, it was possible to provide accurate results in a straightforward way, as the signals they give rise to are well resolved from that of the background. In the case of 80 and 100 nm NPs, the use of a simple deconvolution approach following a Gaussian model was needed to characterize SiO<sub>2</sub> NPs apparently showing incomplete distributions as a result of the presence of the background signal. Overall, the methods developed using SP-ICP-MS/MS are sensitive and selective enough for interference-free determination of Si at ultra-trace levels, also under the form of SiO<sub>2</sub> NPs.

## 1. INTRODUCTION

Due to their unique physical and chemical properties, the use of nanomaterials is rapidly growing over the last years.<sup>1</sup> As non-metal oxides, SiO<sub>2</sub> nanoparticles (NPs) are used in a large variety of applications, such as in food additives, drugs, coatings, sensors and cosmetics.<sup>2-4</sup> Furthermore, SiO<sub>2</sub> NPs are widely employed for chemical mechanical planarization (CMP), in which their abrasive properties are relied on to polish materials in the semiconductor industry.<sup>5</sup> This massive use of NPs is raising concern about their potential effects on the environment and human health,<sup>6-8</sup> and different international directives exist (*e.g.*, from the European Commission), urging the need to characterize such materials.<sup>9</sup> However, the development of analytical methods that are able to gather information on the main physicochemical properties, such as particle number density and mass concentration, degree of particle aggregation and size distribution of NPs present in different sample matrices, remains a challenging task.<sup>10</sup> Despite the considerable amount of techniques currently available for characterizing nanomaterials, *e.g.*, differential centrifugal sedimentation (DCS), nanoparticle tracking analysis (NTA), dynamic light scattering (DLS), static light scattering (SLS), scanning electron microscopy (SEM) and transmission electronic microscopy (TEM),<sup>4, 10, 11</sup> significant limitations, such as cost, time of analysis, lack of elemental specificity, incompatibility with some sample matrices and relatively high limits of detection (mg L<sup>-1</sup>), still exist.<sup>12, 13</sup>

Single particle – inductively coupled plasma – mass spectrometry (SP-ICP-MS) is a powerful and emerging technique for routine analysis of NPs, which provides a wide range of information, typically elemental composition, particle size, particle number density, mass concentration, and size distribution.<sup>14-17</sup> SP-ICP-MS enables for characterization of NPs in samples with complex matrices, such as those encountered in environmental and clinical applications.<sup>18</sup> In SP mode, ICP-MS is operated in time-resolved analysis (TRA) mode, in which it is capable to detect, count and register NP signals as their corresponding set of pulses collected over a number of subsequent short dwell times. Particle size and particle number density can be calculated based on the intensity of these pulses and

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3 their frequency, respectively, while both are used to provide mass concentration.<sup>19</sup> Although this  
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5 technique has been developed and refined in recent years, many aspects are still susceptible to  
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7 improvement, especially for applications for which pronounced spectral overlap jeopardizes accurate  
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9 ICP-MS analysis.<sup>17, 20, 21</sup> This is the case for SiO<sub>2</sub> NPs, the determination of which is hampered by the  
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11 occurrence of spectral interferences coming from elements ubiquitously present in the plasma itself,  
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13 (e.g., giving rise to signals from <sup>14</sup>N<sup>14</sup>N<sup>+</sup> and <sup>12</sup>C<sup>16</sup>O<sup>+</sup>, overlapping with the signal of the most abundant  
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15 Si isotope at m/z = 28). Thus, the development of novel strategies to tackle the problem of spectral  
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17 overlap in ICP-MS is required when aiming at obtaining reliable SiO<sub>2</sub> NPs characterization *via* SP-ICP-  
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19 MS.

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23 The use of high resolution sector-field ICP-MS (HR-SF-ICP-MS) instrumentation is an elegant approach  
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25 to deal with spectral interferences.<sup>22</sup> With this technique, analyte and interfering ions can be  
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27 separated from each other by increasing the resolution of the double-focusing sector-field mass  
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29 analyzer. However, an increase in mass resolution is typically accompanied by a significant reduction  
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31 in ion transmission efficiency, and thus, in sensitivity (1 – 2 orders of magnitude).<sup>23, 24</sup> In addition, the  
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33 more recent developments in the field of SP-ICP-MS have been made in quadrupole-based ICP-MS  
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35 (ICP-QMS) instruments, especially those related with detection speed and data treatment,<sup>25</sup> which  
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37 probably explains why SP-ICP-MS has been mainly conducted with ICP-QMS instruments so far.  
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39 However, the low mass resolution attainable with a quadrupole mass analyzer (1 amu) is to be  
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41 considered a major limitation in the applicability of SP-ICP-MS for elements affected by spectral  
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43 interference, especially for complex sample matrices.

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47 The relatively recent (2012) introduction of ICP-tandem mass spectrometry (ICP-MS/MS) was a  
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49 significant breakthrough as the MS/MS approach substantially enhances the capabilities of ICP-QMS  
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51 for avoiding spectral interference.<sup>26, 27</sup> ICP-MS/MS instruments are equipped with two quadrupole  
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53 units (Q1 and Q2), and a collision/reaction cell (CRC) located in-between these two quadrupoles, thus  
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55 enabling for a double mass selection. In the MS/MS mode, all ions with a mass-to-charge ratio (m/z)  
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3 different from that of the target nuclide are filtered out by Q1, thus enhancing the control over the  
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5 collisions/reactions taking place in the CRC and permitting a much more efficient resolution of  
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7 interferences.<sup>28, 29</sup>  
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10 Over the last years, selective ion-molecule chemistry in the CRC in ICP-MS/MS instrumentation  
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12 (usually referred to as chemical resolution) has been relied on for the interference-free  
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14 determination of ultra-trace concentrations of several analytes in the most diverse and complex  
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16 sample matrices. In addition to the more common collision/reaction gases (e.g., He, H<sub>2</sub> and/or O<sub>2</sub>),  
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18 the potential of using highly reactive gases, such as NH<sub>3</sub> or CH<sub>3</sub>F, has been demonstrated.<sup>30-32</sup>  
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20 However, the determination of ultra-trace concentrations of Si *via* ICP-MS/MS has been hindered by  
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22 strong spectral overlap affecting all of the Si isotopes, and only a few works to date have reported on  
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24 such determinations.<sup>33, 34</sup> In addition, chemical resolution as a means to avoid spectral interference in  
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26 ICP-MS/MS has been scarcely used in the context of NPs characterization. The applications reporting  
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28 on the use of chemical resolution for NPs studies mostly involved the use of field-flow fractionation  
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30 (FFF).<sup>35-37</sup>  
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35 This work assesses the potential of ICP-MS/MS for creating interference-free conditions for ultra-  
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37 trace Si determination, aiming at the characterization of SiO<sub>2</sub> NPs *via* SP-ICP-MS/MS.  
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## 2. EXPERIMENTAL

### 2.1. Standards, samples and reagents.

Ultra-pure water (resistivity > 18.2 M $\Omega$  cm) was obtained from a Mili-Q Element water purification system (Millipore, France). Appropriate dilutions from a 1 g L<sup>-1</sup> single-elemental standard solution of Si (Instrument Solutions, The Netherlands) were prepared freshly on a daily basis and were used for method development and calibration purposes (concentrations ranging between 0 and 5  $\mu$ g L<sup>-1</sup> under the form of dissolved Si). SiO<sub>2</sub> NPs suspended in water were obtained from nanoComposix (non-functionalized NanoXact<sup>TM</sup> Silica, Czech Republic). Particle size distributions, particle number density and mass concentration for these suspensions (determined by TEM and gravimetric analysis, respectively) were provided by the manufacturer. Table 1 provides a compilation of all relevant information for the stock solutions. For the purpose of counting and sizing SiO<sub>2</sub> NPs, a reference material NIST SRM 8013 – Gold Nanoparticles (AuNPs), of 60 nm nominal diameter (certified diameter: 56.0  $\pm$  0.5 nm) – was used for determining transport efficiency in the ICP-MS instrument used. All NP suspensions were shaken vigorously and sonicated during 10 minutes before their use to avoid particle agglomeration. To minimize the occurrence of double events in SP-ICP-MS mode, appropriate dilutions of the original NP suspensions were prepared. To calculate the dilution factor needed for each of the NP suspensions analyzed, probability calculations based on Poisson statistics were carried out taking into account the exact experimental parameters finally selected for the measurements (*i.e.* dwell time, transport efficiency and sample uptake rate) as to ensure a probability of double events to occur below 5%.<sup>38</sup> For the suspensions of NPs with a diameter below 100 nm, for which the particle distribution signal partially overlapped with that of the background, lower dilution factors leading to increased probabilities of double events were used, as discussed in section 3.2.2. Final dilution factors used for all of the NP suspensions measured are also included in Table 1.

### 2.2. Instrumentation

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3 All measurements were carried out using an Agilent 8800 “triple quadrupole” ICP-MS/MS instrument  
4 (Agilent Technologies, Japan). The sample introduction system comprises a Micromist nebulizer (400  
5  $\mu\text{L min}^{-1}$ ) and a Peltier-cooled Scott-type spray chamber (2 °C). The instrument is equipped with two  
6 quadrupole mass analyzers (Q1 and Q2) and an octopole collision-reaction cell (ORS<sup>3</sup>) mounted in-  
7 between the two quadrupole units (Q1-ORS-Q2). The tandem mass spectrometry configuration  
8 enables this instrument to be operated in two different modes, single quadrupole (SQ) and MS/MS  
9 mode. In SQ mode, Q1 is fully open, while in MS/MS mode, both quadrupoles are used as mass filters  
10 with a single-mass bandpass window. Therefore, the MS/MS mode provides an improved control  
11 over the collisions/reactions occurring within the ORS. This setup also offers precursor and/or  
12 product ion scanning as powerful tools for method development, especially in the context of  
13 interference removal. In this work, the ORS was pressurized with various inert (He) and reactive (H<sub>2</sub>,  
14 O<sub>2</sub>, NH<sub>3</sub>/He (10% NH<sub>3</sub> in He) and CH<sub>3</sub>F/He (10% CH<sub>3</sub>F in He)) gases; also the no gas or “vented” mode  
15 was evaluated for illustrative purposes (the most relevant ICP-MS/MS instrument settings used are  
16 listed in Table 2). All gases were introduced in the instrument *via* their corresponding inlets, except  
17 for the mixture of CH<sub>3</sub>F/He that was introduced *via* the 4<sup>th</sup> line, which is originally intended for the  
18 use of O<sub>2</sub>. Therefore, the CH<sub>3</sub>F/He gas flow rates will be reported as their equivalent O<sub>2</sub> gas flow rates  
19 owing to the calibration of the gas flow controller for the latter. Although NH<sub>3</sub> and CH<sub>3</sub>F were used as  
20 their corresponding mixtures with 90% He, they will be further referred in this text to as NH<sub>3</sub> and/or  
21 CH<sub>3</sub>F reaction gases.  
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### 46 2.3. Data treatment

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48 The raw data obtained using the Agilent ICP-MS MassHunter Software operated in Time Resolved  
49 Analysis (TRA) mode were treated and evaluated externally using a modified spreadsheet previously  
50 described by Peters *et al.*<sup>39</sup> This spreadsheet is composed of two interrelated worksheets used for  
51 calibration and NPs characterization, respectively. For calibration, the transport efficiency (*i.e.*  
52 nebulization efficiency) was determined using NIST SRM 8013 AuNPs. This characteristic was  
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3 determined according to the method described by Pace *et al.*,<sup>40</sup> which takes into account known  
4 mass concentration and particle size and the corresponding pulse frequency observed for calculating  
5 the transport efficiency. In the second worksheet, particle number density, mass concentration and  
6 particle size distribution are calculated for each sample by means of the response factor determined  
7 using the ionic Si standard solutions and the transport efficiency. To decide whether NP pulses differ  
8 significantly from the background signal, the 3s-criterion (3 times the standard deviation of the  
9 background) is relied on.

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11 For SiO<sub>2</sub> NP distributions that are difficult to discern from the background, a simple deconvolution  
12 approach using OriginLab was used for modeling. This approach relies on approximating the raw  
13 distribution by a Gaussian model. The equation thus obtained was used to calculate the particle  
14 diameter, particle number density and mass concentration (see section 3.2.2.).  
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### 28 **3. RESULTS AND DISCUSSION**

#### 29 **3.1. Method development for interference-free determination of Si *via* ICP-MS/MS**

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32 As discussed in the introduction, interference-free determination of ultra-trace concentrations of Si  
33 *via* ICP-QMS remains as a challenging task. The occurrence of strong spectral overlap of the signal of  
34 the major isotope of Si (<sup>28</sup>Si – 92.23 % relative isotopic abundance) and polyatomic species (e.g., CO<sup>+</sup>  
35 and N<sub>2</sub><sup>+</sup>) can jeopardize the ability to distinguish the background signal from the signals generated by  
36 SiO<sub>2</sub> NPs. Therefore, the development of novel methods to overcome spectral interferences is a  
37 prerequisite for enabling determination of very low Si concentrations and/or to characterize SiO<sub>2</sub>  
38 NPs. ICP-MS/MS has demonstrated to be a powerful tool to investigate the reactions occurring within  
39 the collision/reaction cell (CRC) and to develop novel approaches to eliminate or at least mitigate  
40 spectral overlap.<sup>28, 29</sup> In MS/MS mode, *i.e.* in which both quadrupoles are set at a specific m/z ratio,  
41 the cell was operated under different conditions: (i) no gas or “vented mode”, (ii) He “kinetic energy  
42 discrimination (KED) mode” and (iii) H<sub>2</sub>, O<sub>2</sub>, NH<sub>3</sub> and/or CH<sub>3</sub>F “chemical resolution modes”. In  
43 contrast to “vented” or “KED” modes, in which Q1 and Q2 are set at m/z 28, the use of chemical  
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3 resolution, where the interferences are overcome by selective ion-molecule chemistry, the selection  
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5 of the Q2 setting is not always self-evident. *Via* product ion scanning (PIS), with Q1 fixed at  $m/z = 28$   
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7 and the cell pressurized with different reaction gases at different flow rates, the reactivity of Si  
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9 towards these gases was evaluated by means of scanning the entire mass spectrum (2 – 260 amu)  
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11 with Q2. Figure 1 shows an example of the mass spectra obtained in the region 2 – 100 amu (where  
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13 most of the product ions appear) for the different chemical resolution modes, and using the  
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15 optimum gas flow rate for maximizing the sensitivity for the reaction product ions that were finally  
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17 selected. Analysis of the full set of PIS spectra obtained at different gas flow rates allowed for the  
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19 selection of the best-suited reaction product ions. In particular,  $\text{SiH}^+$  (+1,  $m/z=29$ ),  $\text{SiO}^+$  (+16,  $m/z=44$ ),  
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21  $\text{SiNH}_2^+$  (+16,  $m/z=44$ ) and  $\text{SiF}^+$  (+19,  $m/z=47$ ) were the reaction product ions selected for Si  
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23 determination. In addition to mass-shift approaches, the use of  $\text{H}_2$  in an on-mass approach was  
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25 evaluated for its capability to remove  $\text{CO}^+$  and  $\text{N}_2^+$  polyatomic interferences *via* reaction towards  $\text{H}_2$ .  
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27 For fine-tuning, the optimum gas flow rates for every method were selected such as to maximize the  
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29 signal-to-background ratio (intensity for  $5 \mu\text{g L}^{-1}$  Si in MQ  $\text{H}_2\text{O}$ ) using the “ramp cell gas” option  
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31 available in the instrument’s software. Results for this optimization are shown in Figure 2. In this  
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33 figure, the initial improvement in ion sensitivity observed at low flow rates for the  $\text{H}_2$  – on mass  
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35 approach might seem surprising. However, this fact can most likely be attributed to a collisional  
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37 focusing effect typical for instruments equipped with collision/reaction cells.<sup>41, 42</sup> Despite the fact that  
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39 interference-free conditions were achieved, the remnant background signals obtained for every  $m/z$   
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41 monitored and every reaction gas investigated correspond in all cases to a BEC of  $0.29 \pm 0.02 \mu\text{g L}^{-1}$  Si,  
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43 which seems to indicate that there was a slight dissolved Si contamination in the MQ water used, an  
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45 issue well documented for Si determination.<sup>43, 44</sup> Table 3 summarizes the different reaction pathways  
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47 of analyte and interfering ions for the different operation modes evaluated in this work.  
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52 Furthermore, in addition to the MS/MS mode, the different approaches developed were tested for  
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54 their capabilities to avoid spectral overlap when the instrument was operated in single quadrupole  
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56 (SQ) mode *i.e.*, Q1 fully open. SQ was evaluated as a possible approach in the case of “vented” mode  
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3 and of H<sub>2</sub> – on-mass, while for O<sub>2</sub>, NH<sub>3</sub> and CH<sub>3</sub>F, the background signal was found to be very high  
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5 due to the occurrence of spectral interferences at the m/z ratios of the reaction product ions  
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7 selected. This may be related with the formation of unwanted product ions in the CRC, especially for  
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9 highly reactive gases, such as NH<sub>3</sub> and CH<sub>3</sub>F. For H<sub>2</sub> – mass-shift, however, the signal of <sup>28</sup>SiH<sup>+</sup>  
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11 overlapped with that of other Si isotope (<sup>29</sup>Si – 4.69 % abundance), thus only allowing to preserve the  
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13 Si isotopic pattern by using MS/MS mode. For 5 µg L<sup>-1</sup> Si, the signal-to-background ratio for He (KED  
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15 mode) was found to be compromised by a strong reduction in sensitivity; this reduction was even  
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17 more pronounced in SQ, and therefore, this approach was not further considered in the context of  
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19 this work.  
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23 Once the different methods were optimized, calibration data and instrumental limits of detection  
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25 (LoDs) and of quantification (LoQs) were calculated by measuring 5 standard solutions (concentration  
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27 ranging between 0 and 5 µg L<sup>-1</sup> Si). The results obtained for the different operation modes are  
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29 summarized in Table 4. Instrumental LoDs and LoQs were calculated as 3 and 10 times the standard  
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31 deviation on 10 consecutive measurements of a blank solution (MQ H<sub>2</sub>O), divided by the slope of the  
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33 calibration curve, respectively. Even in vented mode, a reduction of the background signal and an  
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35 improvement in the signal-to-background ratio was seen when switching from SQ to MS/MS mode,  
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37 which can be attributed to a better transmission efficiency for atomic ions (Si<sup>+</sup>) throughout the  
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39 tandem mass spectrometer than for polyatomic ions (*e.g.*, CO<sup>+</sup> and N<sub>2</sub><sup>+</sup>). Selection of the best  
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41 approaches was based on the sensitivity of the corresponding method and on the ability to create  
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43 interference-free conditions (best BEC approach<sup>45</sup>). Hence, the use of He (KED mode) and of O<sub>2</sub>  
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45 (mass-shift – SiO<sup>+</sup>) were considered less suitable owing to the poor sensitivity in the first case, and  
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47 the possible occurrence of spectral interferences in the second (see Table 3), which could become  
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49 relevant in cases where the sample matrix contains higher concentrations of C and/or N (*e.g.*, added  
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51 nitric acid or organic solvents). In the case of O<sub>2</sub>, it was also evaluated whether increasing the O<sub>2</sub> gas  
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53 flow rate for monitoring SiO<sub>2</sub><sup>+</sup> as reaction product ion would result in a method suitable for Si  
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55 determination. However, although this approach was successfully applied by Gourgiotis *et al.*<sup>46</sup> in the  
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3 context of isotopic analysis of Si for alteration studies of nuclear waste glasses, the method obtained  
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5 was not sufficiently sensitive for ultra-trace Si determination.

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7 As a conclusion, the use of H<sub>2</sub> (on-mass and mass-shift) and of NH<sub>3</sub> and CH<sub>3</sub>F (mass-shift) seem to be  
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9 the methods of choice for the determination of Si at low concentration levels. As indicated in Table 4,  
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11 instrumental LoDs ranging between 0.01 and 0.05 µg L<sup>-1</sup> were achieved using these approaches (*i.e.*  
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13 chemical resolution in MS/MS mode). With H<sub>2</sub> (on-mass), the highest sensitivity was obtained, but  
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15 with CH<sub>3</sub>F (mass-shift), the lowest LoD was provided. Thus, these two methods were selected for  
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17 further SP-ICP-MS/MS method development, although results of other approaches will be provided  
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19 for comparative purposes.  
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### 22 **3.2. Analysis of SiO<sub>2</sub> NPs via SP-ICP-MS/MS**

#### 23 **3.2.1. Detection of SiO<sub>2</sub> NPs**

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26 Once the different approaches were optimized for interference-free determination of ultra-trace  
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28 concentrations of Si, their suitability for characterizing SiO<sub>2</sub> NPs was evaluated. As described in the  
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30 experimental section, NIST SRM 8013 (AuNPs) was used to determine the transport efficiency, which  
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32 is required in order to convert the particle detection rate obtained for SiO<sub>2</sub> NPs into the particle  
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34 number density. The transport efficiency was found to be 7.2 ± 0.4 %, without significant variations  
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36 between experimental sessions.  
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40 For SP-ICP-MS/MS, the measurement of fast transient signals with a dwell time < 10 ms in Time  
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42 Resolved Analysis (TRA) mode should enable the detection of every single NP. In this context, the  
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44 dwell time is an important parameter that needs to be carefully selected considering the  
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46 characteristics of the ICP-MS instrument used. In this respect, there are two main types of ICP-MS  
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48 instruments: those allowing for dwell times in the µs range and those only allowing for dwell times in  
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50 the ms range, each requiring a different approach for selecting the optimum dwell time. When the  
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52 minimum dwell time allowed by the ICP-MS instrument deployed is significantly shorter than the  
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54 typical duration of an ICP-MS intensity spike caused by a single particle (about 0.5 ms according to  
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56 literature),<sup>38, 47</sup> dwell times in the range of 100 µs are preferred to minimize the background  
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3 contribution to the signal of each NP. However, when the minimum dwell time allowed by the ICP-  
4 MS instrument deployed is longer than the typical signal due to a single particle, the best option  
5 seems to select a dwell time sufficiently low to minimize the background contribution to the signal,  
6 but long enough to minimize the probability of splitting the signal of a single NP in various events.<sup>38</sup>  
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9 Additionally, the particle number density of the NP dispersions measured is also critical in this  
10 methodology as the probability of measuring two or more NPs in a single dwell time needs to be  
11 minimized. In this regard, there tends to be an agreement in the SP-ICP-MS community to use dwell  
12 times of 3-5 ms as the most suitable for instruments allowing dwell times in the ms range only.<sup>14, 39</sup> In  
13 the particular case of SiO<sub>2</sub> NPs, and due to the occurrence of contamination issues affecting ultra-  
14 trace Si determination, a dwell time of 3 ms (the shortest time selectable for the Agilent 8800 ICP-  
15 MS/MS instrument) was finally chosen. Once this selection was made, and as described in detail in  
16 section 2.1, all NP suspensions to be measured with the optimized parameters were adequately  
17 diluted with MQ water to minimize the occurrence of double events. Final dilution factors used for all  
18 of the NP suspensions measured are included in Table 1.  
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33 At this point, it is fair to indicate that the use of dwell times in the order of 100 μs has been reported  
34 on in literature as an additional means to improve the detection capabilities of SP-ICP-MS for smaller  
35 NPs,<sup>20, 25, 48</sup> including SiO<sub>2</sub>.<sup>49</sup> As previously indicated, the use of this approach requires  
36 instrumentation allowing for ultrafast acquisition of data (every 100 μs), as well as additional data  
37 treatment to identify the different events detected for every NP, and an evaluation of this possibility  
38 was beyond the scope of this work.  
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46 As a next step, the different methods developed in the previous section were tested for their  
47 capability to distinguish the signals from a given SiO<sub>2</sub> NP suspension from the background signal.  
48 First, the theoretical size limits of detection ( $LOD_{size}$ ) for every approach were calculated as described  
49 by Laborda *et al.*<sup>14</sup> (see Equation 1).  
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$$LOD_{size} = \left( \frac{18s_B}{\pi\rho X_{NP} K_{ICPMS} K_M} \right)^{1/3} \quad \text{Equation 1}$$

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4  
5 where  $s_B$  is the standard deviation of the continuous background measured in SP-ICP-MS/MS mode,  $\rho$   
6  
7 the density of the NPs,  $X_{NP}$  the mass fraction of the element monitored in the NP,  $K_{ICPMS}$  the detection  
8  
9 efficiency (ratio of the number of ions detected vs the number of atoms introduced into the ICP) and  
10  
11  $K_M (=AN_{AV}/M_M)$  where  $A$  is the atomic abundance of the isotope measured,  $N_{AV}$  the Avogadro  
12  
13 number, and  $M_M$  the atomic mass of the analyte  $M$ . For  $S_B$  calculation in each measurement mode, all  
14  
15 of the  $SiO_2$  NP suspensions and the water blank provided similar results, indicating that the potential  
16  
17 effect of the introduction of larger NPs on the plasma conditions (e.g., plasma cooling)<sup>2, 38</sup> was  
18  
19 negligible for the range of NP sizes evaluated. Theoretical  $LoD_{size}$  determined according to Equation  
20  
21 1 were 50 nm ( $H_2$ ), 70 nm ( $CH_3F$ ), 80 nm ( $O_2$ ), 80 nm ( $NH_3$ ), 90 nm (no gas) and 160 nm (He).

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23  
24 Figure 3 shows the practical  $LoD_{size}$  using the different approaches evaluated in this work obtained  
25  
26 from the frequency distributions for the dispersions of the smallest of the NPs tested that could be  
27  
28 actually differentiated from the background. As seen from this figure, these practical  $LoD_{size}$   
29  
30 corresponded with 75 nm ( $H_2$  – on-mass), 85 nm ( $CH_3F$  – mass-shift), 125 nm (no gas or “vented”  
31  
32 mode and  $NH_3$  – mass shift), 130 nm ( $O_2$ ) and 290 nm (He – on-mass). From these results, it is evident  
33  
34 that practical  $LoD_{size}$  are always higher than theoretical  $LoD_{size}$ ; this is especially noticeable for the  
35  
36 He – on-mass mode. These differences could be related with the relatively high BEC observed in all  
37  
38 measurements due to slight dissolved Si contamination, as indicated before. Thus, the use of higher  
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40 purity water and/or of controlled environments (such as clean room facilities) may allow smaller NPs  
41  
42 to be detected using the same approaches. At this point, it is also interesting to point out that, in the  
43  
44 case of no gas or “vented” mode, the  $LoD_{size}$  will increase with the addition of elements at the origin  
45  
46 of polyatomic interferences (*i.e.* N and/or C). In any case, it seems clear that the use of  $H_2$  ( $Si^+$ , on-  
47  
48 mass) and of  $CH_3F$  ( $SiF^+$ , mass-shift) appear to be the best approaches for  $SiO_2$  NP characterization.  
49  
50  
51 Figure 4 shows the frequency distribution (*i.e.* number of particles detected) of  $SiO_2$  NPs with  
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53 diameters ranging from 80 to 400 nm as a function of signal intensity (cps) when using  $H_2$  – on-mass.  
54  
55 It can be seen that, while the signals for NPs with diameters of 80 and 100 nm are partially obscured  
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3 by the background signal, the signals of NPs > 100 nm are found to be completely resolved by using  
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5 this approach, thus enabling for the determination of their particle size, particle number density and  
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7 mass concentration.  
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### 9 10 **3.2.2. Characterization of SiO<sub>2</sub> NPs**

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12 As indicated before, H<sub>2</sub> – on-mass and CH<sub>3</sub>F – mass-shift were the methods selected in this work for  
13  
14 characterizing SiO<sub>2</sub> NPs. Once detected, the ICP-MS intensity spike generated by a single NP enables  
15  
16 its size (NP diameter) to be determined, while the number of events recorded during the analysis  
17  
18 time (frequency) allows for the concentration (number of particles per volume unit) to be  
19  
20 characterized. As previously indicated, all measurements were performed using a dwell time of 3 ms  
21  
22 and monitoring the transient signals during 60 s. Three measurement replicates were done for every  
23  
24 SiO<sub>2</sub> NP suspension. As explained in detail in section 2.1, the concentrations of these suspensions  
25  
26 were optimized in the range of 0.1 to 5 µg L<sup>-1</sup> of Si in order to reduce the probability of double events  
27  
28 and/or to avoid detector saturation from occurring without compromising counting statistics for NP  
29  
30 distributions. The final dilution factors used for each measurement are included in Table 1. Raw data  
31  
32 were treated using a modified spreadsheet previously described by Peters *et al.*,<sup>39</sup> as indicated in  
33  
34 section 2.3. The SiO<sub>2</sub> particle number density in each suspension (particles L<sup>-1</sup>) was calculated taking  
35  
36 into account the number of NP events detected, the transport efficiency and the sample flow rate  
37  
38 (previously calculated and corresponding to 0.34 mL min<sup>-1</sup>). The mass concentration in each NP  
39  
40 suspension was determined based on (i) the net intensity measured for a single NP event (after  
41  
42 background subtraction), (ii) the corresponding sensitivity for Si under the different conditions  
43  
44 evaluated (which was calculated during every measurement session), (iii) the sample flow rate, (iv)  
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46 the transport efficiency and (v) the molar mass ratio SiO<sub>2</sub>/Si (2.14). Thereafter, the NP diameter was  
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48 calculated as a function of the NP mass and its density, assuming that SiO<sub>2</sub> NPs are spherical.  
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51  
52 This approach was used to calculate particle size, particle number density and mass concentration of  
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54 SiO<sub>2</sub> NP suspensions ranging from 80 to 400 nm using H<sub>2</sub> (on-mass) and CH<sub>3</sub>F (mass-shift). Figure 5  
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56 shows the distributions obtained for different SiO<sub>2</sub> NP sizes as normalized frequency (number of NPs  
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3 of each diameter detected divided by the number of NPs detected with the diameter at the peak  
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5 maximum) vs diameter (nm). As already indicated in section 3.2.1 (see Figures 3 and 4), the  
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7 distributions for NPs with diameters higher than 100 nm were found to be completely resolved from  
8  
9 that of the background signals, therefore allowing for a straightforward characterization of these SiO<sub>2</sub>  
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11 NPs. However, for NPs of 100 nm (CH<sub>3</sub>F – mass-shift approach) and of 80 and 100 nm (H<sub>2</sub> – on-mass  
12  
13 approach), Figure 5 shows a partial overlap of the NP distribution with that of the background  
14  
15 signals. The results of particle diameter (nm), particle number density and mass concentration  
16  
17 (recoveries, %) obtained with this approach are provided in Table 5 in the column *raw distribution*.  
18  
19 From these results, it can be concluded that this approach provides accurate NP sizing (errors below  
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21 5% for the NP diameter, corresponding to errors below 15% in the NP volume) for NPs with a  
22  
23 nominal diameter above 100 nm, with particle number density and mass concentration recoveries  
24  
25 ranging between 87.0 and 99.5%. For 80 and 100 nm, however, the results obtained with the raw  
26  
27 distributions reflect the overlap with the background signal. This was especially noticeable in the low  
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29 recoveries obtained for particle number densities (56.3 – 66.3 %), and the aberrant results for NP  
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31 sizing. In fact, the NP diameter was shown to be significantly higher than the values obtained by TEM,  
32  
33 which is certainly related to an incorrect average size calculation (biased high) due to the  
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35 impossibility to discriminate the signals from the smaller NPs, also present in the NP distribution,  
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37 from the background. The mass concentration derived from the raw distributions was found to be  
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39 less affected by this problem, which needs to be attributed to a significant contribution of the  
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41 background signal to the NP mass concentrations and to the fact that the detectable NPs are the  
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43 larger/heavier ones, thus contributing to a higher extent to the final mass concentration.  
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48 In order to improve the characterization of SiO<sub>2</sub> NPs in those cases in which the distribution partially  
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50 overlaps with the background, a straightforward and user-friendly approach was evaluated. This  
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52 approach was based on a deconvolution of the overlapping distributions of background signals and  
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54 NP signals using the OriginLab data analysis and graphing software. The deconvolution was used to  
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56 resolve or decompose the overlapping peaks into their separate components (deconvolution was  
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also applied by Cornelis and Hassellöv in order to discriminate smaller NPs by SP-ICP-MS).<sup>50</sup> Thus, by applying a simple deconvolution, a corrected distribution for the corresponding NPs was generated by approximating the “raw” distribution by a Gaussian function (see Equation 2).

$$y = y_0 + \frac{A}{w \sqrt{\pi/2}} * e^{-2 \frac{(x-x_0)^2}{w^2}} \quad \text{Equation 2}$$

where  $y_0$  = offset,  $x_0$  = center,  $w$  = width and  $A$  = area.

Application of this deconvolution method becomes more successful as the intensity of the NP distribution peak (number of NPs detected) is maximized relative to the background distribution peak (number of events identified as background). Due to the specific conditions of this work – *i.e.* slight ionic analyte contamination – this could only be done by increasing the concentration of the NP suspension (as extending the measurement time would increase both peaks proportionally). Unfortunately, this comes at the cost of an increased probability for double events to occur. Thus, as can be seen from Table 1, suspensions for the NPs of 80 nm using the H<sub>2</sub> – on-mass approach, and 100 nm for the CH<sub>3</sub>F – mass-shift approach were more concentrated (in terms of particles L<sup>-1</sup>) for this reason. With the dilution factors used, an increased probability of double events up to 10% in the case of H<sub>2</sub> – on-mass, and 28% in the case of CH<sub>3</sub>F – mass-shift was calculated; nevertheless, this option was preferred as it is the only way to obtain accurate results for the sizing of these NPs. An example of the use of this approach is presented in Figure 6, in which it can be seen that both background and NP distributions approximate their corresponding functions well. Therefore, the use of this approach should enable the characterization of SiO<sub>2</sub> NPs that cannot be fully resolved from the background signal.

In order to evaluate the suitability of the deconvolution approach for characterization of NP distributions, the method was applied to SiO<sub>2</sub> NPs with particle sizes higher than 100 nm *i.e.* fully resolved, as well as to SiO<sub>2</sub> NP distributions not fully resolved from the background, *i.e.* 80 and 100 nm (H<sub>2</sub>) and 100 nm (CH<sub>3</sub>F). The results obtained are shown in Table 5, under the designation *deconvolution approach*. It can be seen that accurate results for particle diameter, particle number



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3 density and mass concentration were achieved when applying the corresponding model to complete  
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5 NP distributions, which validates the use of the Gaussian fitting for the NP distributions. For the NP  
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7 distributions partially overlapping the background, accurate sizes were obtained in all cases, while  
8  
9 particle number densities deviated slightly from the expected values (81.6 – 105.8% recoveries). The  
10  
11 latter observation can be explained by the design of the experiment itself. In fact, and as seen from  
12  
13 Figure 6 for H<sub>2</sub> mode, the right part of the NP distribution is not fully coincident with the model,  
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15 which could indicate the existence of a second population of double events, resulting from the  
16  
17 relatively high particle number density used for this experiment. This second distribution does not  
18  
19 seem to significantly affect sizing of the primary distribution, and accurate results are obtained for  
20  
21 this parameter upon application of the deconvolution model. The particle number density values, on  
22  
23 the other hand, cannot be 100% accurate if double events are occurring, although results for this  
24  
25 parameter with the deconvolution model are much closer to the expected values than with the raw  
26  
27 distributions.  
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31 As a final test for method robustness, calibration curves for the different NPs measured were drawn  
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33 and are shown in Figure 7. It has been shown that linearity for these calibration plots can be lost due  
34  
35 to different factors, two of which have been identified as the most serious.<sup>51</sup> On the one hand, the  
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37 linear dynamic range of electron multipliers operated in pulse counting mode is limited, although this  
38  
39 problem can be easily solved working in dual detection mode (pulse counting and analog modes),  
40  
41 provided adequate cross-calibration at the beginning of the measuring session.<sup>38</sup> A more serious  
42  
43 problem can arise due to different degrees of vaporization/ionization for the smaller and the larger  
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45 particles, which may require specific optimization of the measuring conditions for SP-ICP-MS,  
46  
47 especially concerning forward ICP power and sample gas flow rate.<sup>38, 51</sup> As seen from Figure 7,  
48  
49 however, linear calibration curves ( $R^2 = 0.9997$  and  $0.9998$  for H<sub>2</sub> – on mass and CH<sub>3</sub>F – mass shift  
50  
51 approaches, respectively) were obtained in this case covering the entire range of NP sizes studied (80  
52  
53 – 400 nm diameter), which is in good agreement with literature for SiO<sub>2</sub> NPs.<sup>2, 38, 39, 52</sup> It is interesting  
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55 to point out that data shown in the calibration plots were obtained on different days and that no  
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3 specific optimization other than that reported in section 3.1 was performed for measurement of the  
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5 NPs, which indicates that the methods developed are robust for characterizing SiO<sub>2</sub> NPs of different  
6  
7 sizes in the range of 80 to 400 nm.  
8

#### 9 10 **4. CONCLUSION**

11  
12 In this work, the capabilities of ICP-MS/MS using different operation modes *i.e.* no gas or “vented”  
13  
14 mode, He “KED” mode, and H<sub>2</sub>, O<sub>2</sub>, NH<sub>3</sub> and CH<sub>3</sub>F “chemical resolution” modes, were evaluated for  
15  
16 obtaining interference-free conditions for ultra-trace Si determination. After a comprehensive study,  
17  
18 the H<sub>2</sub> – on-mass and of CH<sub>3</sub>F – mass-shift modes were selected to avoid spectral overlap, providing  
19  
20 an instrumental LoD < 15 ng L<sup>-1</sup>. The methods developed were evaluated for characterizing SiO<sub>2</sub> NPs  
21  
22 (ranging between 80 and 400 nm) *via* SP-ICP-MS/MS. The use of a conventional approach was  
23  
24 demonstrated to provide accurate particle size, particle number density and mass concentration for  
25  
26 sizes > 100 nm, while for 80 and 100 nm, the distribution was found to be partially overlap with that  
27  
28 of the background signals. Despite some dissolved Si contamination (BEC = 0.29 ± 0.02 µg L<sup>-1</sup>), the use  
29  
30 of a simple deconvolution approach following a Gaussian model enabled acceptable results to be  
31  
32 obtained for NPs of 80 and 100 nm as well, which are the lowest SiO<sub>2</sub> NP sizes that have been  
33  
34 detected so far *via* SP-ICP-MS with instrumentation only allowing for the use of dwell times in the ms  
35  
36 range, *i.e.* without splitting the signal of a single NP in various events. Although SP-ICP-MS/MS has  
37  
38 been scarcely used to date for NP characterization, it is expected that the results obtained in this  
39  
40 work and the recent development of faster ICP- tandem mass spectrometers (with dwell times as low  
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42 as 0.1 ms) will open new possibilities in this field in the near future.  
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3 **Figure 1.** Full mass spectra in the range of interest (2 – 100 amu) obtained by product ion scanning  
4 for 10  $\mu\text{g L}^{-1}$  Si standard solution with the addition of  $\text{H}_2$  (5  $\text{mL min}^{-1}$  - A),  $\text{O}_2$  (0.2  $\text{mL min}^{-1}$  - B),  $\text{NH}_3$  (1  
5  $\text{mL min}^{-1}$  - C) or  $\text{CH}_3\text{F}$  (0.5  $\text{mL min}^{-1}$  - D) reaction gas. The best-suited reaction product ions finally  
6 selected are indicated in bold.  
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10 **Figure 2.** Selection of the optimum gas flow rate for the product ions selected in the case of (A)  $\text{H}_2$  –  
11 ( $\text{Si}^+$  and  $\text{SiH}^+$ , 1.5 and 4.5  $\text{mL min}^{-1}$ , respectively), (B)  $\text{O}_2$  ( $\text{SiO}^+$ , 0.25  $\text{mL min}^{-1}$ ), (C)  $\text{NH}_3$  ( $\text{SiNH}_2^+$ , 1.0  $\text{mL}$   
12  $\text{min}^{-1}$ ) and (D)  $\text{CH}_3\text{F}$  ( $\text{SiF}^+$ , 0.5  $\text{mL min}^{-1}$ ).  
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17 **Figure 3.** Frequency distribution for the lowest NP sizes detectable using the different approaches  
18 evaluated in this work. Practical  $\text{LOD}_{\text{size}}$  are indicated in red in each figure. Frequency refers to the  
19 number of events of each type (background or NP) detected.  
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24 **Figure 4.** Frequency distributions of  $\text{SiO}_2$  NP suspensions (0.1 – 5  $\mu\text{g L}^{-1}$ ) with different NP diameters  
25 (ranging between 80 and 400 nm) when using  $\text{H}_2$  in an on-mass approach. Frequency refers to the  
26 number of events of each type (background signal or NP) detected.  
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31 **Figure 5.** Particle size distributions calculated for  $\text{SiO}_2$  NP suspensions of different sizes ranging from  
32 80 to 400 nm using  $\text{H}_2$  (on-mass) and  $\text{CH}_3\text{F}$  (mass-shift) approaches in ICP-MS/MS, with  
33 concentrations of the  $\text{SiO}_2$  NP suspensions ranging between 0.1 – 5 and 0.5 – 5  $\mu\text{g L}^{-1}$  for  $\text{H}_2$  and  $\text{CH}_3\text{F}$ ,  
34 respectively. Normalized frequency refers to the number of NPs detected of each size normalized to  
35 the number of NPs counted at the peak maximum.  
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40 **Figure 6.** Deconvolution of the signal distribution of 80 nm  $\text{SiO}_2$  NPs, overlapping with the  
41 background signal distribution for SP-ICP-MS/MS using a  $\text{H}_2$  – on-mass approach and following a  
42 Gaussian model.  
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47 **Figure 7.** Calibration curves for the  $\text{SiO}_2$  NPs with diameters of 80 (only  $\text{H}_2$  – on mass), 100, 200, 300  
48 and 400 nm obtained with the  $\text{H}_2$  – on mass and  $\text{CH}_3\text{F}$  – mass shift methods.  
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**Table 1.** Information on particle size (TEM), particle number density and mass concentration (gravimetric analysis), and dilution factors used for the measurement of the SiO<sub>2</sub> NP dispersions used in this work. Values for the stock solutions are those provided by nanoComposix.

Nominal NP size (nm)	NP reference size (mean) (nm)	Particle number density stock solution (particles mL <sup>-1</sup> )	Mass concentration SiO <sub>2</sub> stock solution (g L <sup>-1</sup> )	Dilution factor H <sub>2</sub> (on-mass) mode	Dilution factor CH <sub>3</sub> F (mass-shift) mode
80	82.6 ± 4.7	1.5 × 10 <sup>13</sup>	10.0	1 × 10 <sup>8</sup>	--
100	99.2 ± 5.8	9.5 × 10 <sup>12</sup>	10.7	1 × 10 <sup>8</sup>	2 × 10 <sup>7</sup>
200	197 ± 14	1.1 × 10 <sup>12</sup>	10.1	1 × 10 <sup>7</sup>	1 × 10 <sup>7</sup>
300	297 ± 12	3.4 × 10 <sup>11</sup>	10.4	1 × 10 <sup>7</sup>	4 × 10 <sup>6</sup>
400	401 ± 26	1.4 × 10 <sup>11</sup>	10.3	2 × 10 <sup>6</sup>	2 × 10 <sup>6</sup>

**Table 2.** Instrument settings for the Agilent 8800 (ICP-MS/MS).

	No gas "Vented" mode		He	H <sub>2</sub> On mass		H <sub>2</sub> Mass-shift	O <sub>2</sub>	NH <sub>3</sub>	CH <sub>3</sub> F
	SQ	MS/MS	MS/MS	SQ	MS/MS	MS/MS	MS/MS	MS/MS	MS/MS
<b>Scan type</b>	SQ	MS/MS	MS/MS	SQ	MS/MS	MS/MS	MS/MS	MS/MS	MS/MS
<b>Plasma mode</b>	Low matrix		Low matrix	Low matrix		Low matrix	Low matrix	Low matrix	Low matrix
<b>Rf power (W)</b>	1550		1550	1550		1550	1550	1550	1550
<b>Carrier gas flow rate (L min<sup>-1</sup>)</b>	1.11		1.11	1.11		1.11	1.11	1.12	1.11
<b>Extract 1 (V)</b>	0.0		0.0	0.0		0.0	0.0	-3.0	-3.0
<b>Q1 bias(V)</b>	-3.0	0.0	0.0	-2.0	0.0	0.0	0.0	-1.0	-1.0
<b>Octopole bias (V)</b>	-8.0		-18.0	-18.0		-21.0	-5.0	-5.0	-5.0
<b>Energy discrimination (V)</b>	5.0		5.0	0.0		-5.0	-8.0	-8.4	-10.0
<b>He flow (mL min<sup>-1</sup>)</b>	---		1.5	---		---	---	1.0	---
<b>H<sub>2</sub> flow (mL min<sup>-1</sup>)</b>	---		---	1.5		4.5	---	---	---
<b>3<sup>rd</sup> gas flow (mL min<sup>-1</sup>)</b>	---		---	---		---	---	1.0	---
<b>4<sup>th</sup> gas flow (mL min<sup>-1</sup>)</b>	---		---	---		---	0.25	---	0.5
<b>Q1 → Q2 masses</b>	28 → 28		28 → 28	28 → 28		28 → 29	28 → 44	28 → 44	28 → 47
<b>Extract 2 (V)</b>	-180.0		-180.0	-170.0		-130.0	-145.0	-190.0	-190.0
<b>Q2 bias (V)</b>	-3.0		-13.0	-18.0		-26.0	-13.0	-13.4	-15.0
<b>Wait time offset (ms)</b>	0		0	0		0	0	0	0
<b>Integration time (TRA) (ms)</b>	3		3	3		3	3	3	3
<b>Total analysis time/sample (s)</b>	60		60	60		60	60	60	60

**Table 3.** Summary of the reaction pathways of Si<sup>+</sup> and interfering ions for different operation modes

<b>(1) No gas – “Vented mode”</b>	<b>(2) Helium – He “KED mode”</b>
$^{28}\text{Si}^+ \rightarrow ^{28}\text{Si}^+$ (on-mass)	$^{28}\text{Si}^+ + \text{He} \rightarrow ^{28}\text{Si}^+$ (on-mass)
$^{28}\text{CO}^+ \rightarrow ^{28}\text{CO}^+$	$^{28}\text{CO}^+ + \text{He} \rightarrow$ Removed by collisions + KED
$^{28}\text{N}_2^+ \rightarrow ^{28}\text{N}_2^+$	$^{28}\text{N}_2^+ + \text{He} \rightarrow$ Removed by collisions + KED
<b>(3) Hydrogen – H<sub>2</sub></b>	<b>(4) Oxygen – O<sub>2</sub></b>
$^{28}\text{Si}^+ + \text{H}_2 \rightarrow ^{28}\text{Si}^+$ (on-mass)	$^{28}\text{Si}^+ + \text{O}_2 \rightarrow ^{44}\text{SiO}^+$ (mass-shift)
$^{28}\text{Si}^+ + \text{H}_2 \rightarrow ^{29}\text{SiH}^+$ (mass-shift)	$^{28}\text{Si}^+ + \text{O}_2 \rightarrow ^{60}\text{SiO}_2^+$ (mass-shift)
$^{28}\text{CO}^+ + \text{H}_2 \rightarrow ^{29}\text{COH}^+ + \text{H}^+$	$^{28}\text{CO}^+ + \text{O}_2 \rightarrow ^{44}\text{CO}_2^+$
$^{28}\text{N}_2^+ + \text{H}_2 \rightarrow ^{29}\text{N}_2\text{H}^+ + \text{H}^+$	$^{28}\text{N}_2^+ + \text{O}_2 \rightarrow ^{44}\text{N}_2\text{O}^+$
<b>(5) Ammonia – NH<sub>3</sub></b>	<b>(6) Methyl fluoride – CH<sub>3</sub>F</b>
$^{28}\text{Si}^+ + \text{NH}_3 \rightarrow ^{44}\text{SiNH}_2^+$ (mass-shift)	$^{28}\text{Si}^+ + \text{CH}_3\text{F} \rightarrow ^{44}\text{SiF}^+ + \text{CH}_3$ (mass-shift)
$^{28}\text{CO}^+ + \text{NH}_3 \rightarrow$ No reaction	$^{28}\text{CO}^+ + \text{CH}_3\text{F} \rightarrow$ No reaction
$^{28}\text{N}_2^+ + \text{NH}_3 \rightarrow$ No reaction	$^{28}\text{N}_2^+ + \text{CH}_3\text{F} \rightarrow$ No reaction

**Table 4.** Calibration data and instrumental limits of detection (LoDs) and of quantification (LoQs) obtained for Si determination using ICP-MS/MS operated in different modes. LoDs and LoQs were calculated as 3 and 10 times the standard deviation on 10 consecutive measurements of a blank solution (MQ H<sub>2</sub>O), divided by the slope of the calibration curve, respectively.

Gas	Mode	Approach	Q1 (amu)	Q2 (amu)	Sensitivity (L counts s <sup>-1</sup> µg <sup>-1</sup> )	Intercept (counts s <sup>-1</sup> )	R <sup>2</sup>	LoD (µg L <sup>-1</sup> )	LoQ (µg L <sup>-1</sup> )
<b>No gas</b>	SQ	On-mass	--	28	34800	830000	0.9996	0.9	3
	MS/MS	On-mass	28	28	21800	76100	0.9996	0.05	0.2
<b>He</b>	MS/MS	On-mass	28	28	287	471	0.9992	0.2	0.6
<b>H<sub>2</sub></b>	SQ	On-mass	--	28	43700	24300	0.9991	0.05	0.2
	MS/MS	On-mass	28	28	26900	7430	0.99998	0.02	0.05
	MS/MS	Mass-shift	28	29	4980	4240	0.9998	0.05	0.2
<b>O<sub>2</sub></b>	MS/MS	Mass-shift	28	44	8700	2470	0.9998	0.02	0.05
<b>NH<sub>3</sub></b>	MS/MS	Mass-shift	28	44	3160	948	0.99998	0.03	0.1
<b>CH<sub>3</sub>F</b>	MS/MS	Mass-shift	28	47	13100	4070	0.9997	0.01	0.03

**Table 5.** Characterization of SiO<sub>2</sub> NPs using CH<sub>3</sub>F (mass-shift) and H<sub>2</sub> (on-mass) as reaction gases in ICP-MS/MS

Methyl fluoride (CH <sub>3</sub> F) – MS/MS – Mass-shift approach						
Particle diameter (TEM) (nm) <sup>a</sup>	Particle diameter (nm) <sup>b</sup>		Particle number density Recovery (%) <sup>c</sup>		Mass concentration Recovery (%) <sup>c</sup>	
	Raw distribution	Deconvolution approach	Raw distribution	Deconvolution approach	Raw distribution	Deconvolution approach
99.2 ± 5.8	106 ± 20	94 ± 13	57 ± 2	82 ± 2	90 ± 3	94 ± 4
197.1 ± 13.5	191 ± 19	188 ± 16	94 ± 8	100 ± 8	100 ± 4	105 ± 3
297.2 ± 11.5	282 ± 24	283 ± 14	94 ± 1	100 ± 1	95 ± 1	101 ± 2
401.0 ± 25.5	378 ± 34	368 ± 12	92 ± 2	105 ± 2	95 ± 2	101 ± 2

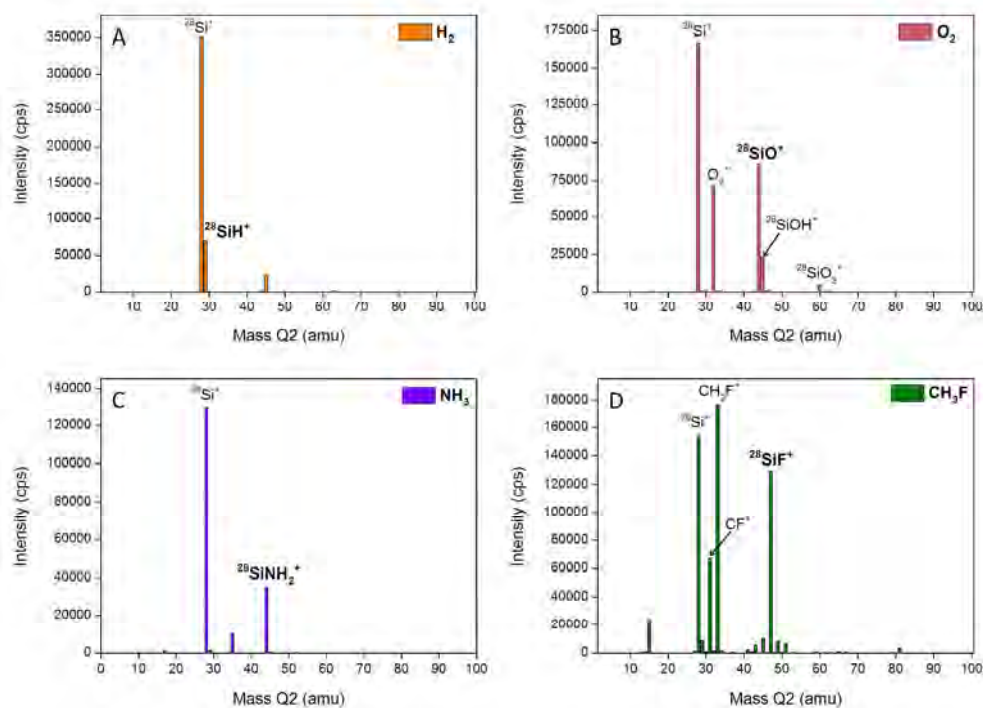
  

Hydrogen (H <sub>2</sub> ) – MS/MS – On-mass approach						
Particle diameter (TEM) (nm) <sup>a</sup>	Particle diameter (nm) <sup>b</sup>		Particle number density Recovery (%) <sup>c</sup>		Mass concentration Recovery (%) <sup>c</sup>	
	Raw distribution	Deconvolution approach	Raw distribution	Deconvolution approach	Raw distribution	Deconvolution approach
82.6 ± 4.7	90 ± 9	80 ± 10	64 ± 3	106 ± 4	100 ± 3	111 ± 2
99.2 ± 5.8	104 ± 15	93 ± 12	66 ± 2	84 ± 6	98 ± 2	94 ± 6
197.1 ± 13.5	191 ± 18	190 ± 14	87 ± 3	101 ± 2	92 ± 3	107 ± 2
297.2 ± 11.5	285 ± 15	286 ± 12	93 ± 2	97 ± 5	96 ± 2	102 ± 7
401.0 ± 25.5	381 ± 37	373 ± 16	90 ± 2	95 ± 4	96 ± 3	108 ± 8

<sup>a</sup> Uncertainty values for the particle diameter determined by TEM are those provided by the manufacturer and correspond to the standard deviation of the size distribution for the NPs.

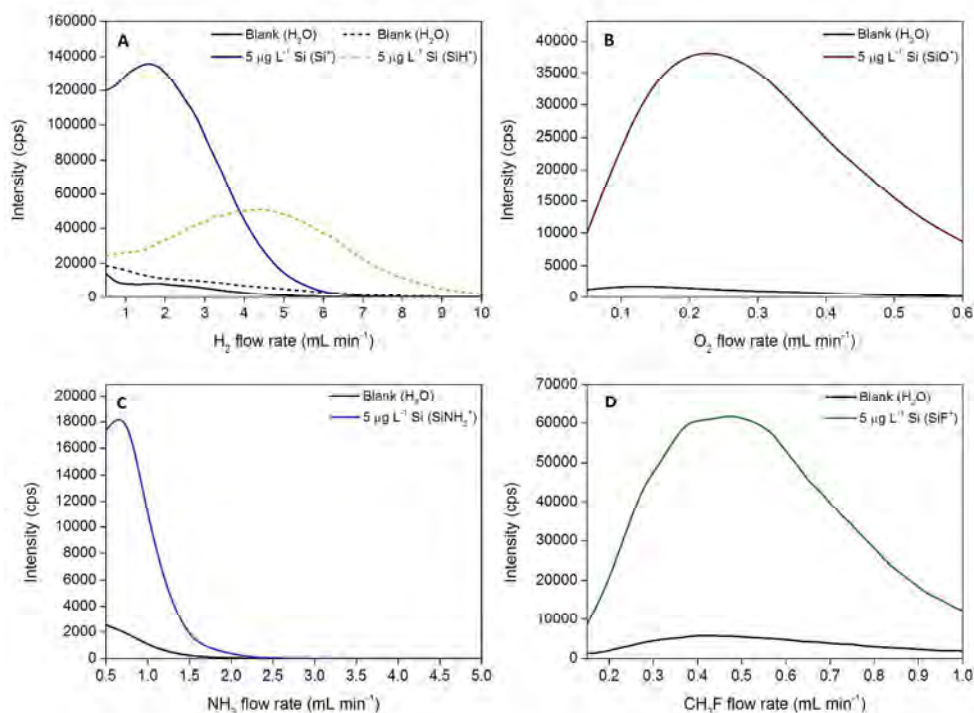
<sup>b</sup> Uncertainty values for the particle diameter determined by SP-ICP-MS/MS correspond to the standard deviation of the size distribution for the NPs.

<sup>c</sup> Uncertainty values for the particle number density and mass concentration recoveries correspond to the standard deviation of three replicate measurements of 60 s each.



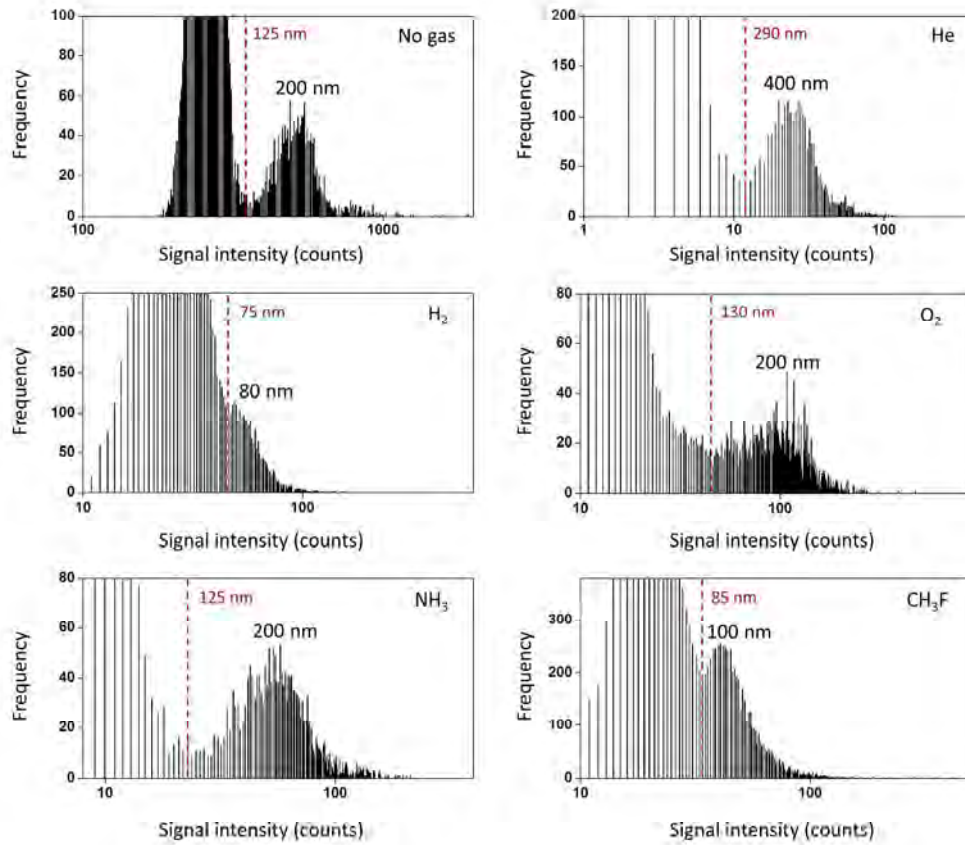
**Figure 1.** Full mass spectra in the range of interest (2 – 100 amu) obtained by product ion scanning for  $10 \mu\text{g L}^{-1}$  Si standard solution with the addition of  $\text{H}_2$  ( $5 \text{ mL min}^{-1}$  - A),  $\text{O}_2$  ( $0.2 \text{ mL min}^{-1}$  - B),  $\text{NH}_3$  ( $1 \text{ mL min}^{-1}$  - C) or  $\text{CH}_3\text{F}$  ( $0.5 \text{ mL min}^{-1}$  - D) reaction gas. The best-suited reaction product ions finally selected are indicated in bold.

254x190mm (300 x 300 DPI)



**Figure 2.** Selection of the optimum gas flow rate for the product ions selected in the case of (A) H<sub>2</sub><sup>+</sup> (Si<sup>+</sup> and SiH<sup>+</sup>, 1.5 and 4.5 mL min<sup>-1</sup>, respectively), (B) O<sub>2</sub> (SiO<sup>+</sup>, 0.25 mL min<sup>-1</sup>), (C) NH<sub>3</sub> (SiNH<sub>2</sub><sup>+</sup>, 1.0 mL min<sup>-1</sup>) and (D) CH<sub>3</sub>F (SiF<sup>+</sup>, 0.5 mL min<sup>-1</sup>).

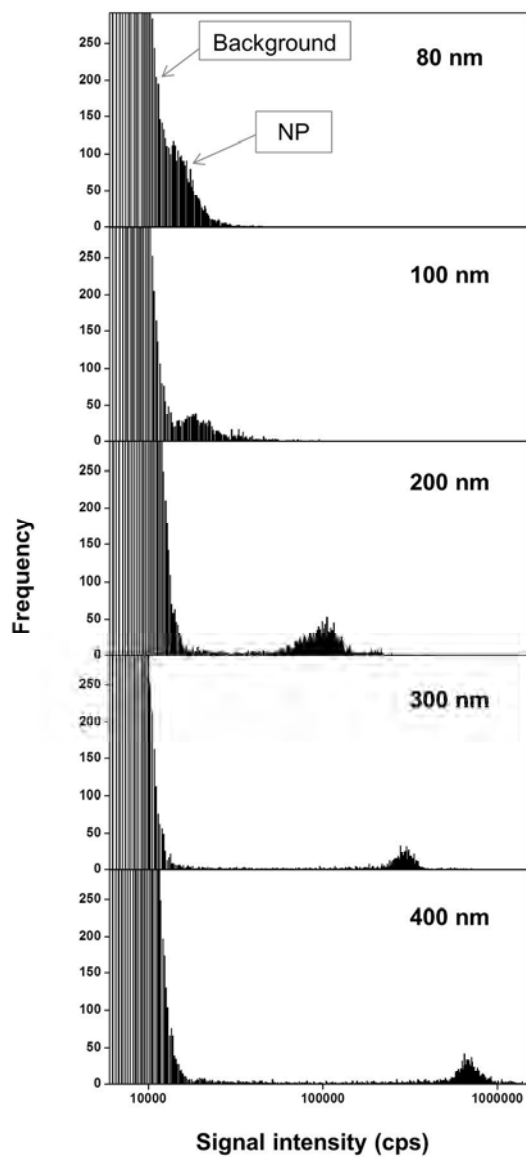
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**Figure 3.** Frequency distribution for the lowest NP sizes detectable using the different approaches evaluated in this work. Practical LOD<sub>size</sub> are indicated in red in each figure. Frequency refers to the number of events of each type (background or NP) detected.

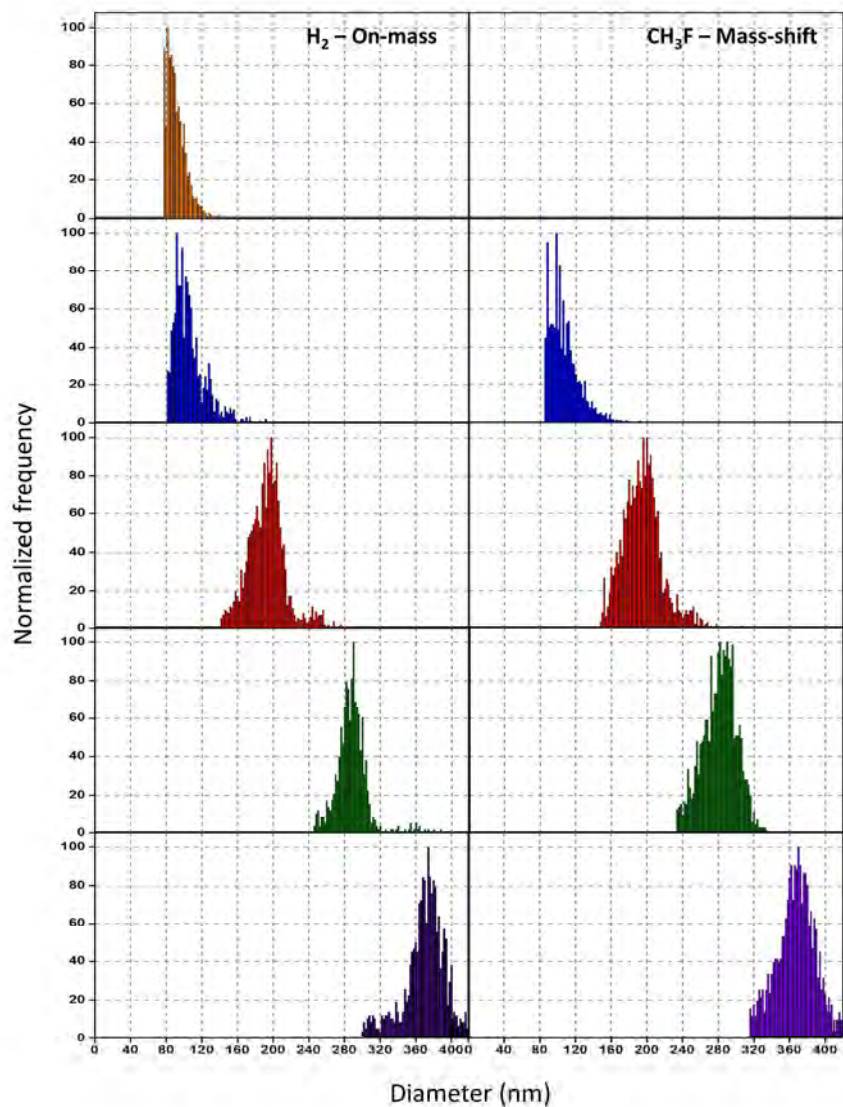
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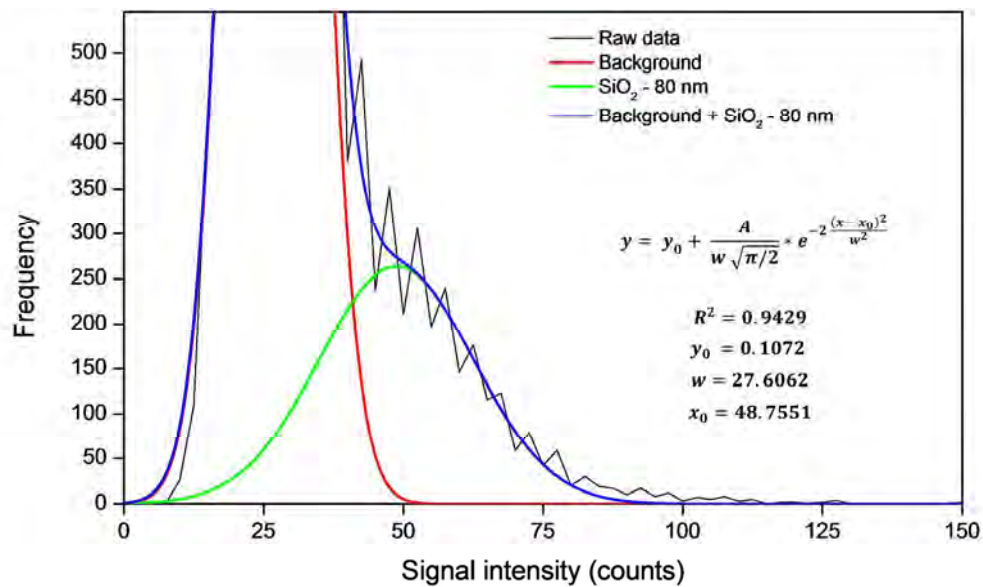
**Figure 4.** Frequency distributions of SiO<sub>2</sub> NP suspensions (0.1 – 5 µg L<sup>-1</sup>) with different NP diameters (ranging between 80 and 400 nm) when using H<sub>2</sub> in an on-mass approach. Frequency refers to the number of events of each type (background signal or NP) detected.

190x254mm (300 x 300 DPI)



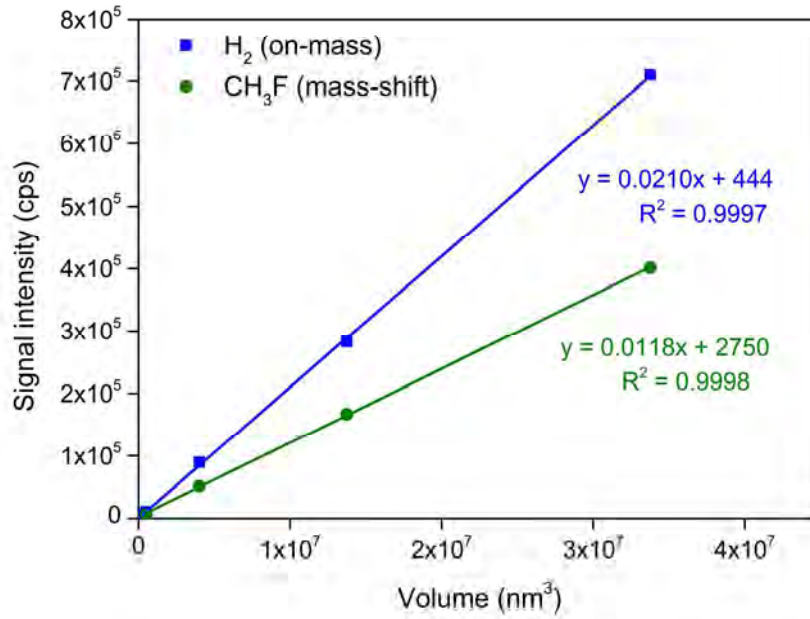
**Figure 5.** Particle size distributions calculated for SiO<sub>2</sub> NP suspensions of different sizes ranging from 80 to 400 nm using H<sub>2</sub> (on-mass) and CH<sub>3</sub>F (mass-shift) approaches in ICP-MS/MS, with concentrations of the SiO<sub>2</sub> NP suspensions ranging between 0.1 – 5 and 0.5 – 5 µg L<sup>-1</sup> for H<sub>2</sub> and CH<sub>3</sub>F, respectively. Normalized frequency refers to the number of NPs detected of each size normalized to the number of NPs counted at the peak maximum.

190x250mm (300 x 300 DPI)



**Figure 6.** Deconvolution of the signal distribution of 80 nm SiO<sub>2</sub> NPs, overlapping with the background signal distribution for SP-ICP-MS/MS using a H<sub>2</sub> - on-mass approach and following a Gaussian model.

254x190mm (300 x 300 DPI)



**Figure 7.** Calibration curves for the SiO<sub>2</sub> NPs with diameters of 80 (only H<sub>2</sub> – on mass), 100, 200, 300 and 400 nm obtained with the H<sub>2</sub> – on mass and CH<sub>3</sub>F – mass shift methods.

199x139mm (300 x 300 DPI)