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## Isotopically Labeled Nanoparticles at Relevant Concentrations: How Low Can We Go? The Case of CdSe/ZnS QDs in Surface Waters

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► **To cite this version:**

Nurul Supiandi, G. Charron, M. Tharaud, L. Cordier, J.-M. Guigner, et al.. Isotopically Labeled Nanoparticles at Relevant Concentrations: How Low Can We Go? The Case of CdSe/ZnS QDs in Surface Waters. *Environmental Science and Technology*, 2019, 53 (5), pp.2586-2594. 10.1021/acs.est.8b04096 . hal-02308552

**HAL Id: hal-02308552**

<https://hal.sorbonne-universite.fr/hal-02308552v1>

Submitted on 8 Oct 2019

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1 Isotopically labelled nanoparticles at relevant  
2 concentrations: how low can we go? - The case of  
3 CdSe/ZnS QDs in surface waters

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12 **KEYWORDS:** detection limits, nanoparticles, isotopic labelling, quantum dots, aquatic matrices,

13 HR-ICP-MS

14

15 ABSTRACT. Analytical barriers impose to work at nanoparticles (NPs) concentration orders of  
16 magnitude higher than the expected NPs concentrations in the environment. To overcome these  
17 limitations, the use of non-traditional stable isotope tracers incorporated in NPs (spiked-NPs)  
18 coupled with HR-ICP-MS has been proposed. The performance and efficiency of this analytical  
19 method was assessed in the case of quantum dots (QDs). Multi-isotopically labelled  
20  $^{111}\text{Cd}^{77}\text{Se}/^{68}\text{ZnS}$  QDs were synthesized and their dissemination in natural aquatic matrices (river,  
21 estuarine and sea waters) was modelled at very low concentrations (from 0.1 to 5000 ppt). The QD  
22 limits of quantification (QD-LOQ) in each matrix were calculated according to the isotopic tracer.  
23 In ultrapure and simple medium ( $\text{HNO}_3$  2%), Zn, Cd and Se originated from the QDs were  
24 quantifiable at concentrations of 10, 0.3 and 6 ppt, respectively, which is lower than the  
25 conventional HR-ICP-MS LOQs. In aquatic matrices, the QD-LOQs increase 10-, 130-, and 250-  
26 fold for Zn, Cd, and Se, respectively, but remain relevant of environmental concentrations (3.4 ppt  
27  $\leq \text{QD-LOQs} \leq 2.5$  ppb). These results validate the use of isotopically-labelled ENPs at relevant  
28 concentrations in experimental studies related to either their fate, behavior or toxicity in most  
29 aquatic matrices.

30

## 31 INTRODUCTION

32 Engineered nanoparticles (ENPs) are widely used in various consumer products due to their  
33 exceptional chemical, optical, magnetic or mechanical properties.<sup>1</sup> To name a few, TiO<sub>2</sub> NPs are  
34 used as photocatalyst in water and air treatment,<sup>2</sup> or as whitening agent in paints and in food and  
35 food packaging products,<sup>3-5</sup> Ag NPs are added to fabrics for anti-bacterial purpose,<sup>6-12</sup> ZnO NPs  
36 act as UV absorbers in sunscreens,<sup>13-15</sup> and CeO<sub>2</sub> NPs are incorporated in catalytic converters in  
37 the automotive industry.<sup>16</sup> Quantum dots (QDs), namely fluorescent nanocrystals made of semi-  
38 conducting materials, are used in lightning and light display devices for color and brightness  
39 enhancement, in solar panels and bio-sensors.<sup>17-22</sup> The use and disposal of these products leads to  
40 the release of nanomaterials in wastewater or in the environment (*e.g.* surface waters, soils).  
41 Surface waters which are known as one of the major vectors of ENPs dispersion in environment,<sup>23</sup>  
42 have inspired numerous publications aiming at determining ENPs fate and behavior in surface  
43 waters, in particular through assessing their colloidal and chemical stabilities.<sup>24-30</sup> However, these  
44 physico-chemical studies were often conducted at ENPs concentrations that are orders of  
45 magnitude higher than the levels expected from their dissemination in aquatic environments. The  
46 concentration of ENPs has been shown to affect their dissolution and their aggregation state,  
47 thereby potentially impacting their behavior. For instance, the increase in ZnO NPs concentrations  
48 decreased their dissolution,<sup>31</sup> whereas their homoaggregation increased with increasing  
49 concentrations.<sup>32</sup> Therefore, working at environmentally relevant concentrations is critical when  
50 studying the fate and behavior of ENPs in natural systems.

51 Nevertheless, working at realistic concentrations also means overcoming two common analytical  
52 barriers: i) unsuitable instrumental detection limits and ii) the geochemical environmental

53 background, *i.e.* the natural occurrence of some constitutive elements of the ENPs in the  
54 environment. Recent development of methods such as single counting ICP-MS (sp-ICP-MS) allow  
55 the detection of NPs with limit of detections achieving ppt levels. However, when studying the  
56 behavior (e.g. dissolution) of a type of NPs in an environmental medium e.g. river/seawater  
57 containing already the same constitutive elements as the NPs, sp-ICP-MS will not be able  
58 distinguishing between natural and anthropogenic nanomaterial. Hence, recent studies have  
59 proposed the use of non-traditional stable isotopes to overcome these analytical barriers, *i.e.* the  
60 use of isotopically modified or “spiked” ENPs which can be quantified by Inductively Coupled  
61 Plasma Mass Spectrometry (ICP-MS).<sup>33-37</sup> For instance, this strategy was employed to determine  
62 the bio-uptake of TiO<sub>2</sub>, Ag, and ZnO NPs in aquatic organisms, using <sup>47</sup>Ti, <sup>109</sup>Ag, <sup>67</sup>Zn tracers,  
63 respectively.<sup>33,38,39</sup> Quantitative detection of the ENPs was achieved at concentrations as low as  
64 5 ppb, 6 ppt, and 1 ppm for <sup>47</sup>TiO<sub>2</sub>, <sup>109</sup>Ag, and <sup>67</sup>ZnO NPs, respectively, showing the advantages  
65 of ENPs isotopic labelling. Although the necessity to work at realistic concentrations has been  
66 recently discussed,<sup>37-39</sup> the exposure concentrations generally used in many ENPs fate and behavior  
67 studies remain higher than the estimated ones in natural media and, so far, none has tried to  
68 accurately determine to which extent the labelling of ENPs with stable isotopes would allow to  
69 work at the cutting edge of analytical barriers in ENPs fate and behavior studies.

70 In the present study, we aimed to determine for the first time the analytical limits of the ENP  
71 isotopic labelling technique in aquatic matrices (river, estuarine, and seawaters). Quantum dots  
72 with a CdSe/ZnS core/shell structure enriched in <sup>111</sup>Cd, <sup>77</sup>Se, and <sup>68</sup>Zn (hereafter called multispiked  
73 QDs) were synthesized for the first time in this study. Even though the estimated QDs concentration  
74 in aquatic environment is less than 1 ppt,<sup>40,41</sup> their increasing environmental release will

75 unavoidably follow due to the increasing presence of QDs in consumer products, especially  
76 electronic devices (*e.g.* TV set or light bulbs) – therefore, CdSe/ZnS QDs make for a worthy  
77 analytical case. As a representative example of core/shell-structured nanomaterials, their reactivity  
78 is expected to be more complex than that of homogeneous NPs. These ENPs make for a challenging  
79 system on which to gauge the analytical limits of the isotopic labelling strategy. These multispiked  
80 QDs were then dispersed at very low and environmentally relevant concentrations (ppt-ppb) into  
81 the chosen aquatic matrices. Measurements by HR-ICP-MS and subsequent chemometric  
82 processing allowed to accurately determine the limits of quantifications according to the element  
83 labelled and to the matrix composition (QD-LOQ). Chemometrics was proven to be an efficient  
84 analytical approach *e.g.* during method optimization.<sup>42</sup> This work is expected to provide valuable  
85 basis to any future study aiming at using isotopically labelled ENPs to determine their fate,  
86 behavior, or toxicity in natural media while working at relevant concentrations.

87

## 88 **MATERIALS AND METHODS**

### 89 *Composition of aquatic matrices*

90 The Seine river water was chosen first, as it is highly representative of both a natural carbonate-  
91 rich system and a highly anthropized watershed, which is relevant next to the possibility of an  
92 accidental release of ENPs. The Seine river water sample was collected behind the University  
93 Pierre et Marie Curie (Quai Saint-Bernard, Jardin Tino Rossi, Paris, France, 48.8475° N, 2.3614°  
94 E), and filtered through a 0.2 µm cellulose acetate membrane, stored in pre-cleaned, acid-washed  
95 polyethylene bottles and divided in three subsamples for: i) major and trace elemental analyses,  
96 where the aliquot was acidified with 15 N distilled nitric acid to obtain 2% of nitric acid in the

97 samples, ii) analysis of anions ( $\text{Cl}^-$ ,  $\text{SO}_4^{2-}$ ,  $\text{NO}_3^-$ ), and iii) the determination of isotopic labelling  
98 limits experiments. Sampling and analytical procedures were described by Benedetti et al.<sup>43</sup> The  
99 chemical composition of the Seine water sample is displayed in [Table S1](#).

100 The second surface water chosen was a synthetic seawater (SW), prepared following the  
101 American Society for Testing and Materials (ASTM) International guidelines ([Table S2](#)).  
102 Dissolved Zn, Cd and Se with natural isotopic abundances were also added to this SW at  
103 concentrations provided by Seine Normandie Water Agency.<sup>44</sup>

104 Afterwards, from the precedent Seine river water and SW, three different solutions of estuarine  
105 waters were prepared by mixing the Seine river water sample and the SW solution (V/V) by the  
106 ratios 75:25 (estuarine water 1), 50:50 (estuarine water 2), and 25:75 (estuarine water 3). All waters  
107 were stored at 4°C in pre-cleaned, acid-washed polyethylene bottles.

108

### 109 ***Synthesis of multi-isotopically labelled CdSe/ZnS quantum dots***

110 All chemical products with natural isotopic composition were purchased from Sigma Aldrich:  
111 sulfur (S, 99.9%, powder), oleic acid (OA, technical, 90%), trioctylphosphine (TOP, 90%), 1-  
112 octadecene (ODE, 90%), chloroform ( $\text{CHCl}_3$ , 99%), and thioglycolic acid (TGA, 99%). Chemicals  
113 with modified isotopic composition were purchased from ISOFLEX USA: cadmium oxide (CdO  
114 powder) enriched at 96.00% in  $^{111}\text{Cd}$ , zinc oxide (ZnO powder) enriched at 99.16% in  $^{68}\text{Zn}$ , and  
115 selenium (Se powder) enriched at 99.20% in  $^{77}\text{Se}$ .

116 A common route towards CdSe/ZnS nanocrystals consists in nucleating CdSe cores by quickly  
117 injecting a chalcogenide mixture into a hot organic solution of the metal salts in a process known  
118 as the hot injection method. The growth of the ZnS shell is either achieved in a subsequent step or

119 one-pot in the same step as nucleation, as described by Bae *et al.*<sup>45</sup> In this protocol, cadmium oxide,  
120 zinc acetate, elemental selenium and elemental sulfur were used as the metal and chalcogen  
121 precursors, respectively. Transposing this route to multi-spiked CdSe/ZnS QDs raised difficulties  
122 regarding the availability of isotopically-modified precursors of suitable isotopic enrichments.  
123 <sup>111</sup>CdO and <sup>77</sup>Se powders were commercially available with <sup>111</sup>Cd and <sup>77</sup>Se abundances markedly  
124 different from the natural ones (96.00% and 99.20%, respectively) that could impart a high isotopic  
125 contrast to the QDs compared to the natural background. However, zinc acetate was commercially  
126 available with a 48% <sup>68</sup>Zn abundance only, which did not contrast enough with the 18% natural  
127 abundance to support detection of the spiked QDs in the ppt range in natural matrices. Therefore,  
128 Bae's protocol was adapted to start from ZnO as the zinc precursor, as it was commercially  
129 available with 99.16% enrichment in <sup>68</sup>Zn.

130 Multi-spiked CdSe/ZnS QDs were synthesized by the hot injection method in octadecene  
131 following an adaptation of the protocol from Bae *et al.*<sup>45</sup> The modification consisted in substituting  
132 <sup>68</sup>Zn-enriched ZnO for the initial zinc acetate precursor which was not available with a suitable  
133 modified isotopic composition.<sup>45</sup> Briefly, 51.364 g (0.4 mmol) of <sup>111</sup>Cd-enriched CdO, 325.56 g  
134 (4 mmol) of <sup>68</sup>Zn-enriched ZnO, 6.746 g (23.88 mmol) of oleic acid, 20 mg (0.2 mmol) of succinic  
135 anhydride and 23 mL octadecene were placed in a 100 mL three-necked round bottom flask  
136 equipped with a temperature probe, a coil condenser and connected to an inert line. The flask was  
137 nested into a heating mantle whose power was controlled by a temperature controller connected to  
138 the temperature probe. The mixture was degassed under 10 mbar, heated to 150°C and maintained  
139 under these conditions for 20 min. Next, the montage was filled with N<sub>2</sub> and further heated to  
140 180°C for 10 min and then 250°C for 10 more minutes to fully dissolve the ZnO powder. The



141 temperature was then increased to 310°C. At this temperature, a mixture of 31.584 mg (0.4 mmol)  
142 of <sup>77</sup>Se-enriched selenium and 128.28 mg (4 mmol) sulfur dissolved in 3 mL of trioctylphosphine  
143 under N<sub>2</sub> atmosphere was quickly injected into the reaction flask under vigorous stirring.  
144 Immediately after injection, the temperature was lowered to 300°C and the flask was kept at this  
145 temperature for 15 min to promote the growth of the nanocrystals. The flask was then cooled down  
146 to room temperature. The QDs were precipitated with 100 mL of acetone by centrifugation at 6000  
147 rpm and then purified to remove excess reactants by redispersion-precipitation cycles twice with  
148 90 mL acetone and once with 40 mL methanol.

149 Then, water-soluble QDs were prepared by replacing the oleic acid ligands attached to the surface  
150 of the QDs with thioglycolic acid (TGA). In a 100-mL round bottom flask, a solution of 10 mL of  
151 chloroform and 1.6 mL of thioglycolic acid (TGA) was prepared. Next, the flask was nested into  
152 an ultrasonic bath and 460 μL of the multi-spiked QDs stock solution were added under sonication  
153 and maintained under sonication for 1 min. The flask was then equipped with a condenser and  
154 transferred into a water bath. The reaction mixture was stirred using a stir bar and heated under  
155 reflux for 2 hours. After cooling to room temperature, the TGA-coated QDs were precipitated by  
156 centrifugation at 6000 rpm and then purified by redispersion-precipitation cycles twice with 10 mL  
157 chloroform and once with 10 mL acetone. Finally, the TGA-coated QDs were dispersed in pH 8  
158 borate buffer and purified using Centricon® Centrifugal Filter Units (30kD MWCO) by  
159 exchanging the solvent once with a fresh portion of pH 8 borate buffer and 4 times with ultrapure  
160 water adjusted at pH 10. The final solution had a volume of 10 mL.

161

162 ***Quantum dots characterization***

163 Optical characterization of QDs was carried out by measuring the UV–vis absorption spectra of  
164 the TGA-coated QDs stock solution with Thermo Scientific Evolution™ 600 UV–vis spectrometer.  
165 The fluorescence signal was collected using the Horiba Scientific FluoroMax®-4  
166 spectrofluorometer.

167 Diluted suspensions QDs were deposited on copper grid to observe their sizes and shapes by  
168 Transmission Electron Microscopy (TEM), using a JEOL 2100F electron microscope operating at  
169 200 kV and equipped with a field emission gun, a high-resolution UHR pole piece and a Gatan GIF  
170 2001 imaging filter. To perform chemical analysis, this microscope was coupled with electron-  
171 dispersive X-ray spectroscopy (EDXS) using a JEOL detector with an ultrathin window allowing  
172 detection of low atomic mass elements. TEM pictures were analysed with the software ImageJ  
173 1.51n.

174 The total concentrations of Cd, Se, and Zn in the TGA-coated QDs stock solution were measured  
175 by ICP-OES (Thermo Scientific iCAP 6000 Series) after a complete acid digestion with HF/HNO<sub>3</sub>  
176 (see protocol in SI) and then after simple acidification (2% of nitric acid) to evaluate the necessity  
177 of using complete acid digestion for all experimental samples.

178

179 ***Model dissemination of QDs in aquatic matrices***

180 All materials used in these experiments (PP tubes, bottles and pipette tips) were washed with  
181 HCl 1 N to eliminate possible contaminations in trace metals, especially Zn, Cd and Se.

182 TGA-coated CdSe/ZnS quantum dots were added separately in all 5 selected natural surface  
183 waters, at target concentrations varying from 0.1 to 5000 ppt of Zn issued from the QDs, resulting

184 in 0.03 to 1500 ppt in Cd and 0.02 to 1000 ppt in Se. These choices are in the lowest relevant range  
185 of the ENPs estimated concentrations in surface waters (ppt to ppb levels).<sup>40</sup> The QDs were also  
186 added, with the same target concentrations, in both HNO<sub>3</sub> 2% and NaNO<sub>3</sub> 0.01M, used as control  
187 media, since there is no occurrence of natural Zn, Cd and Se in both solutions, and the  
188 NaNO<sub>3</sub> 0.01 M solution is representative of the highest typical ionic strength found in river and  
189 estuarine waters.<sup>46</sup> All samples were triplicated to assess the experimental reproducibility.

190 After QDs addition to these media, all samples were agitated then acidified to obtain 2% of nitric  
191 acid in the samples, then left overnight prior to dilution and analysis. Simple acidification was  
192 sufficient to completely dissolve the QDs, thus the complete acid digestion with HF/HNO<sub>3</sub> was not  
193 further performed. The acidification step is representative of the final step used in many studies  
194 prior to ENPs analysis.<sup>26,27</sup> For HNO<sub>3</sub> 2%, NaNO<sub>3</sub> 0.01M matrices and Seine river water sample,  
195 no further dilution was needed prior the HR-ICP-MS analysis. For synthetic seawater and estuarine  
196 water samples, 50-fold dilutions were performed for best instrument performance and stability.<sup>47</sup>

197

### 198 *Quantitative analysis by ICP-MS*

199 External standard solutions containing 1, 5, 10, 100, 500, 1000 and 5000 ppt of total Cd, Se and  
200 Zn were prepared in HNO<sub>3</sub> 2 %. During the whole analysis, a solution containing 5 ppb of rhodium  
201 (<sup>103</sup>Rh) prepared in HNO<sub>3</sub> 2% was used as internal standard solution to correct from instrumental  
202 drift and mass bias, and connected online to the sample tubing using a T-adaptor. The isotopes of  
203 Cd (<sup>106</sup>Cd, <sup>108</sup>Cd, <sup>110</sup>Cd, <sup>111</sup>Cd, <sup>112</sup>Cd, <sup>113</sup>Cd, <sup>114</sup>Cd and <sup>116</sup>Cd), Zn (<sup>64</sup>Zn, <sup>66</sup>Zn, <sup>67</sup>Zn, <sup>68</sup>Zn and <sup>70</sup>Zn),  
204 and Se (<sup>74</sup>Se, <sup>76</sup>Se, <sup>77</sup>Se, <sup>78</sup>Se, <sup>80</sup>Se, <sup>82</sup>Se) were analyzed with HR-ICP-MS (ThermoScientific  
205 Element II). The isotopes <sup>105</sup>Pd, <sup>115</sup>In, <sup>118</sup>Sn, <sup>60</sup>Ni and <sup>72</sup>Ge were also analyzed to correct possible

206 isobaric interferences.<sup>48</sup> Each intensity used for data treatment corresponds to the average of 15  
207 blocks of 3 replicate measurements, allowing an internal reproducibility with standard error better  
208 than 5%. Within each session, reproducibility of the multi-element reference material (TM-23.4  
209 Lake Ontario water from National Research Council Canada) was checked at the beginning and  
210 the end of each analysis sequence and yielded on average 6.6% shift from the certified values. Most  
211 of the sub-procedural variation was found to be within the methods stated overall external  
212 reproducibility<sup>49</sup> determined on the three experimental replicates.

213

#### 214 *Calculation of spiked QDs concentrations*

215 The contrast in isotopic compositions between the multi-spiked QDs and the natural background  
216 forms the basis of the quantification of the QDs from HR-ICP-MS measurements. The calculation  
217 is an adaptation from Dybowska *et al.*<sup>33</sup> and is detailed in SI.

218

## 219 **RESULTS AND DISCUSSION**

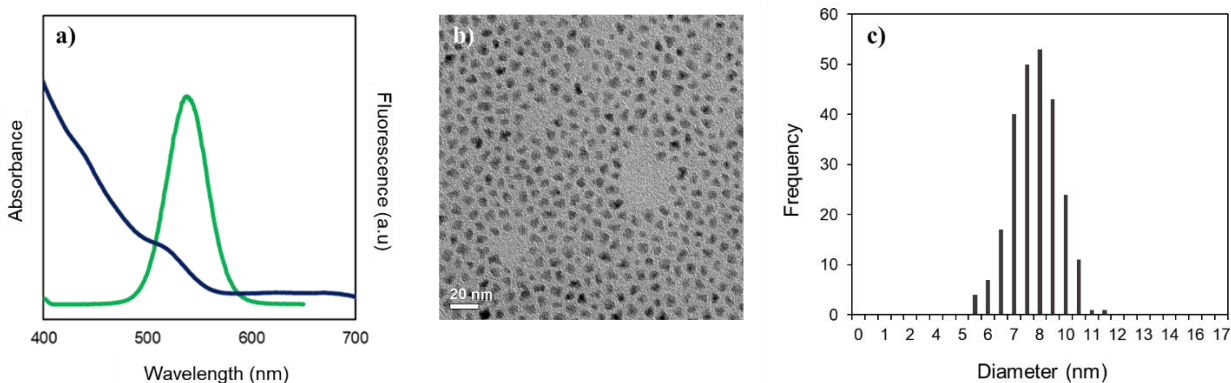
### 220 *QDs synthesis and characterization*

221 Prior to the synthesis of multi-spiked QDs, the synthesis protocol was first conducted as a test  
222 run using non-isotopically enriched precursors. Green QDs with an emission centered at 540 nm  
223 were obtained. Their absorption spectrum features well resolved excitonic peaks and their emission  
224 peak has a full width at half maximum (FWHM) of 35 nm, which is in good agreement with the  
225 observations of Bae *et al.* (see SI, Figure S1). When the synthesis was conducted with the  
226 isotopically enriched precursors, difficulties were encountered regarding the dissolution of the ZnO  
227 precursor. To fully dissolve the powder, it was necessary to heat the metal precursor solution up to

228 250°C and to maintain it at this temperature for 10 minutes. The resulting multi-spiked QDs also  
229 have a green emission centered at 540 nm, however the excitonic peaks are damped and the  
230 emission linewidth increases to 40 nm (Figure 1a), indicating that the quality of the nanocrystals  
231 has degraded slightly compared to that of the test run QDs. Nevertheless, those properties are still  
232 comparable to the QDs described in the original report. The QDs size distribution estimated from  
233 a TEM image was  $7.9 \pm 1.1$  nm for  $n = 250$  (Figure 1b and c). An EDXS spectrum is provided in  
234 SI (Figure S2) confirming the presence of Zn, Cd, and Se in the QDs.

235 To allow QDs dissemination in aqueous matrices, the QDs were functionalized by substituting  
236 thioglycolic acid (TGA) with the oleic acid ligands stemming from the initial synthesis. TEM  
237 images are provided in SI (Figure S2). The final TGA-coated QDs stock solution in pH 10 water  
238 contains  $101.1 \pm 1.0$  ppm of Zn,  $31.8 \pm 0.3$  ppm of Cd,  $19.2 \pm 0.3$  ppm of Se, and  $404 \pm 41$  ppm of  
239 S by ICP-OES.

240



241  
242 **Figure 1.** a) UV-vis absorption spectrum (blue line) of the multi-spiked quantum dots and  
243 corresponding fluorescence emission spectrum (green line) under 400 nm excitation; b) TEM

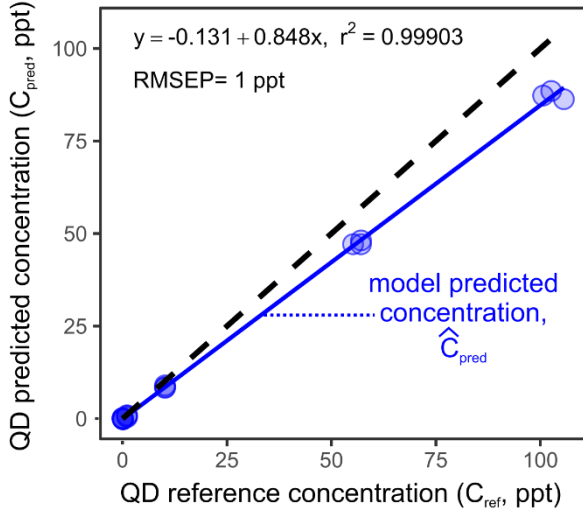
244 image of CdSe/ZnS QDs dispersed in chloroform; c) Size distribution of the QDs estimated from  
245 the TEM image.

246  
247 The isotopic compositions of the multi-spiked QDs regarding Zn, Cd and Se were assessed by  
248 HR-ICP-MS and compared to the natural ones (Figure S3). The multi-spiked QDs feature 95.89,  
249 99.11 and 98.95% enrichments in  $^{111}\text{Cd}$ ,  $^{68}\text{Zn}$  and  $^{77}\text{Se}$  respectively. These abundances are slightly  
250 lower than those certified by ISO FLEX for the starting materials, most probably because of minor  
251 contamination by chemicals during the synthesis steps. Nevertheless, the QD modified isotopic  
252 composition is in sharp contrast with that of the natural background (12.80%, 18.80%, and 7.64%  
253 for  $^{111}\text{Cd}$ ,  $^{68}\text{Zn}$  and  $^{77}\text{Se}$  respectively).

254  
255 *Assessment of analytical performances*

256 Recovery plots were built by representing the QDs concentration estimated using Eq. S8  
257 (hereafter referred to as predicted concentration) as a function of the theoretically known  
258 concentrations of QDs added in different matrices (reference concentration in the following), as  
259 exemplified in the case of the Seine matrix and on the basis of the  $^{68}\text{Zn}$  tracer in Figure 2.

260



261  
 262 **Figure 2.**  $C_{pred}$  vs.  $C_{ref}$  recovery plots for estimations of QDs concentration based on the  $^{68}\text{Zn}$   
 263 tracer. The plain blue line indicates the best linear fit and the dashed black line the ideal  $C_{pred} =$   
 264  $C_{ref}$  recovery plot.

265  
 266 The slope of the best linear regression model leads to the recovery rate of the analytical method,  
 267 namely the fraction of detected QDs amongst the QDs actually present in the sample (which is  
 268 related to the bias by  $Bias = (1 - Recovery) \times 100$ ). The precision on the predicted QD  
 269 concentration was estimated from the Root Mean Square Error of Prediction (RMSEP, defined in  
 270 Eq. 1) of the regression model. The limit of quantification was chosen as the concentration for  
 271 which the risk of reporting a false positive or a false negative falls below 0.1%. Briefly, for a set  
 272 of samples with reference concentration  $C_0, C_1, C_2, \dots, C_n$  where  $C_0$  corresponds to the “blank”  
 273 samples, *i.e.* to pure matrix samples, the QD-LOQ was practically determined as follows. A t-test  
 274 was performed to compare the mean value of the predicted concentrations for the blank samples  
 275 with that of the predicted concentrations for the samples having the reference concentration  $C_1$ . If

276 the t-test concluded that the two means were significantly different at the 99.9% confidence level,  
277 then  $C_1$  was designated as the QD-LOQ. If not, then the t-test was conducted using the samples  
278 having  $C_2$  concentration. The process was repeated with increasing  $C_i$  concentrations until the  
279 calculated t value exceeded the critical t-value at the 99.9% confidence level (Figure 3). Since our  
280 set of QD spiked samples covers several decades, there are only few experimental points in the  
281 vicinity of the QD-LOQ. The QD-LOQ determined from the series of t-test conducted on the  
282 experimental data then corresponds to an overestimation of the true QD-LOQ. Therefore, a second  
283 series of t-tests were conducted using the experimental blank samples and the model predicted  
284 values at intermediate concentrations (with  $\widehat{C}_{i,pred}$  as the mean and RMSEP as the standard  
285 deviation). This estimation is also conservative since it assigns overestimated standard deviations  
286 to points at low reference concentrations as the RMSEP is calculated from data covering several  
287 decades. The lowest of the two estimates of QD-LOQ was therefore retained.

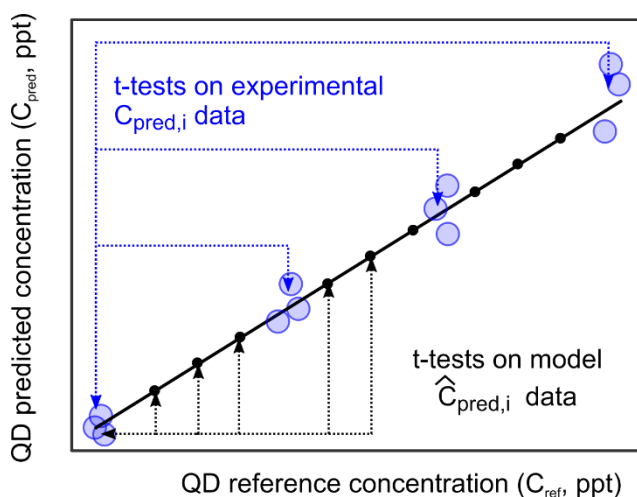
288

289 
$$RMSEP = \sqrt{\frac{\sum(C_{pred,i} - \hat{C}_{pred,i})^2}{n}}$$
 where n is the number of samples. Eq. 1

290

291





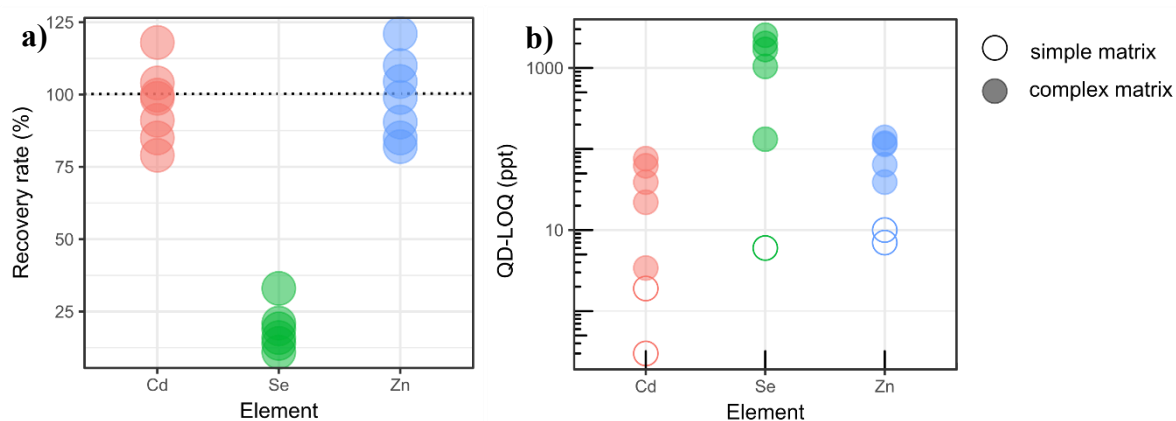
292  
 293 **Figure 3.** Overview of methodology applied to estimate the QD-LOQ from the recovery plot or its  
 294 model.

295  
 296 The recovery plots for the  $^{68}\text{Zn}$ ,  $^{111}\text{Cd}$  and  $^{77}\text{Se}$  in all investigated matrices are presented in SI  
 297 (Figures S5 to S24), along with the intensity vs. isotope concentration calibration plots that were  
 298 used to build them. The biases of all recovery plots are also summarized in SI (Table S3). The  $t$   
 299 values for different QDs concentrations in Cd, Zn and Se calculated in all five matrices are also  
 300 provided in SI (Table S5 to S7).

301  
 302 ***Analytical performances: QD-LOQ and precision***

303 **Figure 4a** displays the observed recovery rates by element. The recovery rates for Cd and Zn are  
 304 excellent at  $99 \pm 14 \%$  and  $97 \pm 13 \%$  on average for all investigated matrices. However, the  
 305 recovery rate for Se is poor at  $19 \pm 8 \%$ , indicating that the method lacks sensitivity when the  $^{77}\text{Se}$   
 306 tracer is used. This is related to the instrumental resolutions at which the three different elements  
 307 were measured. Briefly, Cd isotopes were measured in low resolution (LR) since this element is

308 not strongly impacted by polyatomic or isobaric interferences. Zn isotopes had to be measured in  
309 middle resolution (MR) to solve polyatomic interference issues (e.g.  $^{48}\text{Ca}^{16}\text{O}^+$ ,  $^{32}\text{S}^{16}\text{O}^{18}\text{O}^+$ ,  
310  $^{40}\text{Ar}^{14}\text{N}_2^+$ ), resulting in counts numbers about 10% of those typically measured in LR. In the case  
311 of Se, it was necessary to perform the measurements in high resolution (HR) to overcome  
312 polyatomic interferences mostly caused by argon (Ar), e.g.  $^{36}\text{Ar}^{40}\text{Ar}^1\text{H}^+$ ,  $^{40}\text{Ar}_2^+$ , due to the use of  
313 Ar as the plasma gas. The intensity signal measured is then around 3% of the total signal measured  
314 in LR, which is related to the resolution slit width defining the mass resolution, R ( $R_{\text{LR}} = 300$ ,  $R_{\text{MR}}$   
315  $= 4000$ , and  $R_{\text{HR}} = 10000$ ). An ANOVA calculation on a model describing the recovery rate as a  
316 linear function of the ICP resolution confirmed that the resolution had a significant impact at the  
317 99.9 % confidence level (Tables S9 and S10, model M1). Count numbers were further lowered  
318 by the fact that the QD concentrations in term of Se were about 2 and 6 times lower on average  
319 than that of Cd and Zn respectively. The unsatisfactory results obtained in the case of Se highlight  
320 the limits of the spiking method for tracking NPs: for elements subjected to strong polyatomic  
321 interferences, it will not be possible to access spike concentrations below the ppb level. However,  
322 some specific technical solutions such as hydride generation<sup>50</sup> could allow overcoming this  
323 limitation.  
324



325

326 **Figure 4.** Recovery rates grouped by tracer element, for all matrices confounded (a) and QD-LOQs  
 327 grouped by tracer element, for simple matrices (empty symbols) and complex matrices (filled  
 328 symbols) (b).

329

330 [Figure 4b](#) and [Table 1](#) display the QD-LOQs of the multi-spiked QDs grouped by tracer element.  
 331 In oversimplified media ( $\text{HNO}_3$  2% and  $\text{NaNO}_3$  0.01N) where the background levels in Zn, Cd,  
 332 and Se are below the HR-ICP-MS LOQ (30, 3, and 62 ppt for Zn, Cd and Se, respectively), the  
 333 QD-LOQ of Zn, Cd, and Se were 10, 0.3, and 6 ppt, respectively, and in  $\text{NaNO}_3$  0.01N were 7 and  
 334 2 ppt for Zn and Cd, respectively. In contrast, in complex matrices such as Seine river water, the  
 335 QD-LOQ<sub>Zn</sub> increases to 39 ppt. In estuarine water 1 (Seine/SW 75:25), estuarine water 2  
 336 (Seine/SW 50:50), estuarine water 3 (Seine/SW 25:75), and SW, the QD-LOQ<sub>Zn</sub> increases to 139,  
 337 118, 64, and 112 ppt, respectively. The QD-LOQ in Seine, estuarine water 1, 2, 3, and SW, were  
 338 3.4, 22, 39, 76, and 62 ppt, respectively for Cd and 132, 1044, 2534, 2003, and 1689 ppt,  
 339 respectively for Se.

341 **Table 1.** GBC, QD-LOQ, precision (RMSEP), and RLOQ in different matrices. The conventional  
 342 HR-ICP-MS LOQ are: Zn 30 ppt, Cd 3 ppt, Se 60 ppt. n.a.: not available.

	HNO <sub>3</sub> 2%	NaNO <sub>3</sub> 10 <sup>-2</sup> M	Seine	Seine/SW 75:25	Seine/SW 50:50	Seine/SW 25:75	SW	
Zn	GBC (ppt)	< LOQ <sub>Zn</sub>	< LOQ <sub>Zn</sub>	3718 ± 186	3416 ± 171	2169 ± 108	1493 ± 75	1345 ± 67
	QD-LOQ (ppt)	10	7	39	139	118	64	112
	Precision (ppt)	0.8	1	8	27	42	38	23
	QD-RLOQ	-	-	1.0%	3.9%	5.2%	4.1%	7.7%
Cd	GBC (ppt)	< LOQ <sub>Cd</sub>	< LOQ <sub>Cd</sub>	8.4 ± 0.4	23 ± 1.2	42 ± 2.1	81 ± 4.0	75 ± 3.8
	QD-LOQ (ppt)	0.31	1.9	3.4	22	39	76	62
	Precision (ppt)	0.11	0.30	0.78	7.5	8.9	14	10
	QD-RLOQ	-	-	29%	49%	48%	48%	45%
Se	GBC (ppt)	< LOQ <sub>Se</sub>	n.a.	1069 ± 53	933 ± 47	649 ± 33	617 ± 31	683 ± 34
	QD-LOQ (ppt)	6	n.a.	132	1044	2534	2003	1689
	Precision (ppt)	0.4	n.a.	5	25	64	36	36
	QD-RLOQ	-	-	11%	53%	80%	77%	71%

343  
 344 Unsurprisingly in light of the poor recovery rates observed for Se, QD-LOQ<sub>Se</sub> are one order of  
 345 magnitude higher on average than QD-LOQ<sub>Zn</sub> and QD-LOQ<sub>Cd</sub>. An ANOVA calculation confirmed  
 346 that the ICP resolution significantly affects the QD-LOQ at the 99% confidence level ([Tables S9](#)  
 347 [and S11, model M2](#)). In the following, the QD-LOQs according to Se will not be further discussed.

348 For Cd and Zn tracers, QD-LOQs have mean values of 29 and 70 ppt. However, the QD-LOQs in  
349 complex matrices (Seine, sea and estuarine waters) are 37 and 11 times those observed in simple  
350 matrices (HNO<sub>3</sub> and NaNO<sub>3</sub>) for Cd and Zn respectively. Despite this one-order-of-magnitude  
351 increase, the multispiked QDs can be detected in realistic surface water samples in concentrations  
352 as low as 41 ppt in Cd and 95 ppt in Zn on average, which are about 3 to 6 order of magnitudes  
353 lower than the typical concentrations used in ENPs dissemination and toxicity studies (ppb-ppm  
354 level).<sup>36,51-53</sup> These results demonstrate the significant added value of the isotopic labelling  
355 technique in order to model the environmental fate of ENPs in conditions mimicking as best as  
356 possible the natural media.

357 The increase of the QD-LOQs in complex matrices compared to the ones in simplified media  
358 could be explained by three possible arguments. First, simplified media contain virtually zero  
359 geochemical background contribution of the spike elements. Indeed, the concentrations in Cd and  
360 Zn in the blank samples in the case of HNO<sub>3</sub> and NaNO<sub>3</sub> were below the LOQs for their respective  
361 isotopes. When moving from these simple media to complex matrices, geochemical background  
362 Cd and Zn concentrations increase up to 75 ppt (in sea water) and 3.7 ppb (in Seine water), that is  
363 11 and 3.5 times more than the upper limit of the QD concentration ranges that were investigated  
364 in this study. Therefore, the characteristic isotopic fingerprint of the multispiked QDs gets diluted  
365 into a large geochemical contribution having the natural isotopic pattern of abundances. This effect  
366 will be looked into using the geochemical background concentrations (GBC) of the tracer element  
367 in each sample.

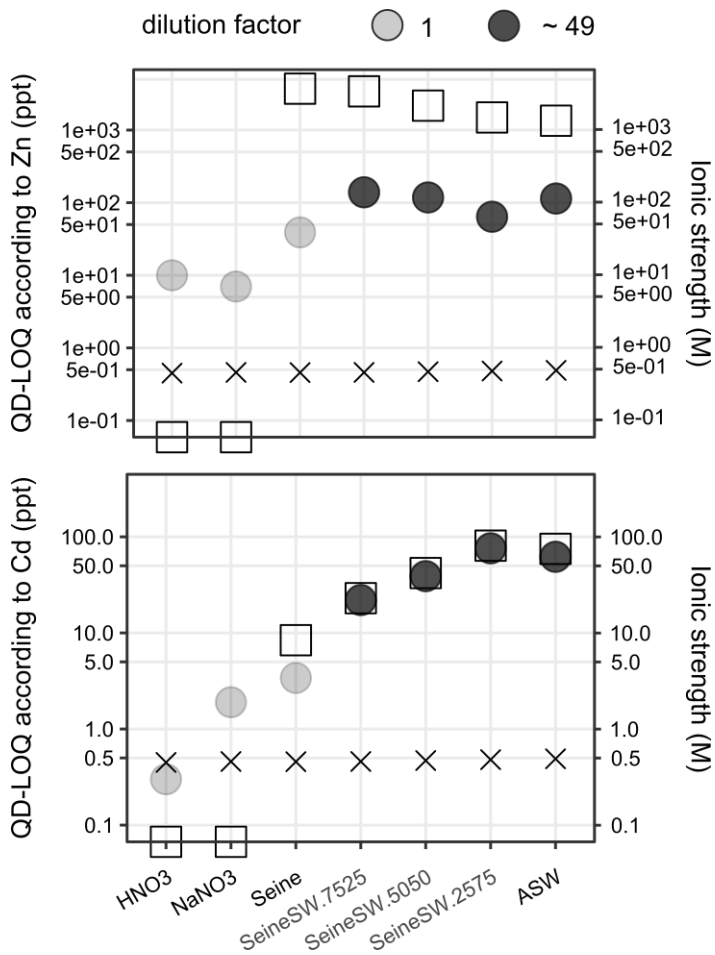
368 Second, complex matrices contain a high concentration of dissolved salts. These can affect  
369 intensity readings compared to readings that would have been observed at equal tracer

370 concentration in HNO<sub>3</sub>, which is the matrix in which the  $I(^A X)$  vs.  $C_A$  calibration plots were  
371 acquired, in a phenomenon known as matrix effect<sup>46</sup> which will be investigated using the ionic  
372 strength in the solutions analyzed in the instrument as metric.

373 Finally, the sea water and estuarine water samples contain high dissolved salt concentrations  
374 (Table S2, total dissolved solids TDS<sub>sw</sub> = 40.8 g/L, I = 0.69M) that may damage the instrument  
375 and drastically decrease its sensitivity. These samples had to be diluted prior to ICP-MS analysis,  
376 to reach at most the maximum recommended TDS values for ICP-MS analysis (2 g/L)<sup>47,54</sup> resulting  
377 in lower tracer concentrations and therefore to lower count numbers. This last effect will be  
378 examined using the dilution factor applied to each sample.

379 On Figure 5, the QD-LOQs according to Cd and Zn tracers were plotted along with the  
380 geochemical background concentrations for each matrix and the ionic strength (after dilution if any  
381 was required), with an indication of the dilution factor that was applied before ICP-MS analysis.  
382 First, the ionic strength of the solutions analyzed in ICP-MS appears constant throughout the  
383 various matrices because the acidification at 2% HNO<sub>3</sub> prior to analysis levels it in all analyzed  
384 samples. Therefore, matrix effects cannot account for the increase in QD-LOQs observed when  
385 moving from simple media to complex aquatic matrices. Second, for both Cd and Zn, the lowest  
386 QD-LOQs are the one determined in matrices that did not necessitate dilution prior analysis, so the  
387 dilution factor seems to have a significant impact on the QD-LOQ. Last, when Cd is used as a  
388 tracer, the QD-LOQs seem to strongly correlate with the GBC. To confirm these graphical findings,  
389 ANOVA calculations were conducted. When attempting to model the whole set of QD-LOQs for  
390 Cd and Zn, it was found that only the dilution factor and GBC were significant at the 99%  
391 confidence level (model M3, Table S12). The QD-LOQs based on Zn were found to depend only

392 on the dilution factor (model M4, Table S13, Figure S25), while those based on Cd had a strong  
393 and exclusive correlation with the GBC (model M5, Table S14, Figure S26). These results are in  
394 line with the instrumental constraints pertaining to the Zn and Cd detection. As Zn is analyzed in  
395 MR for which signal intensity is on the order of 10% of that of LR measurements, it is expected to  
396 be more strongly impacted by further shrinking of the count numbers upon dilution than Cd. On  
397 the other hand, the LR measurements in the case of Cd have a smaller discrimination power  
398 between isotopes:  $^{110}\text{Cd}$  and  $^{111}\text{Cd}$  are less distinct in LR than  $^{66}\text{Zn}$  and  $^{68}\text{Zn}$  in MR, all the more  
399 since the latter are separated by two units of mass number. In the presence of increasing GBC of  
400 Cd with natural abundance, the  $^{111}\text{Cd}/^{110}\text{Cd}$  ratio is damped, which may result in impaired  
401 estimation of the  $^{111}\text{Cd}$  contribution.  
402



403  
 404 **Figure 5.** Limits of quantification of multi-spiked QDs (QD-LOQs, dots, in ppt), geochemical  
 405 background concentration (GBC, squares, also in ppt), ionic strength of the solutions as analyzed  
 406 in ICP-MS (crosses, in moles.L<sup>-1</sup>) and dilution factor applied prior to ICP analysis (mapped to the  
 407 transparency of the dot symbols) in the various aquatic matrices, according to the Zn tracer (top)  
 408 and to the Cd tracer (bottom).

409



410 Therefore, the QD-LOQs can be affected by the GBC in the matrices, dilution factor, and analysis  
411 resolution. Hence, the relevance of the isotopic spiking method will depend on the element and the  
412 matrix targeted in the study. These factors should be considered, for example when choosing the  
413 concentration of spiked QDs (or spiked Zn/Cd/Se-containing ENPs) to be used in studies related  
414 to ENPs fate and behavior.

415 To summarize, the limits of quantifications of isotopically labelled CdSe/ZnS quantum dots (QD-  
416 LOQs) in natural aquatic matrices were accurately determined by combining HR-ICP-MS and  
417 chemometric analysis. QD-LOQs were found varying between 3.4 and 2500 ppt according to the  
418 element and the aquatic matrix, which is within the range of ENPs concentrations that are expected  
419 in natural surface waters (*e.g.* 2000, 170, and 100, and <10 ppt for TiO<sub>2</sub>, ZnO, Ag, and QDs NPs  
420 respectively).<sup>23,40,41,55-58</sup> Furthermore, our results indicate that the use of isotopic labelling of ENPs  
421 coupled with HR-ICP-MS allows to work at ENPs concentrations about 3 to 6 orders of magnitude  
422 lower than the typical concentrations used in numerous ENPs fate and toxicity studies (*e.g.* ZnO at  
423 100 ppb-163 ppm, QDs at 60-3600 ppb).<sup>26,27,29,51-53</sup> Finally, this method does not require the  
424 commonly employed feature (*e.g.* optical emission) for fluorescent ENPs such as QDs, which  
425 photoluminescent properties can easily be quenched. The QD-LOQs calculated in the present study  
426 are up to 2 orders of magnitude more sensitive than methods based on QDs photoluminescence  
427 measurement.<sup>59</sup>

428

### 429 ***Perspective: Relative QD-LOQ***

430 Remarkably, the order of magnitude of relative QD-LOQ (or QD-RLOQ), expressed as the ratio  
431 of the QD-LOQ to the sum of QD-LOQ and the total natural element concentration already present

432 in the matrix (Eq. 2) seems to be characteristic of a given element (Table 1). This variability could  
433 then be used to draw estimations of the QD-LOQs in matrices not investigated in the present study,  
434 provided that the GBC of that new matrix is known. The knowledge of an expected order of  
435 magnitude for the QD-LOQ enables to choose the lowest, and therefore closest to the natural media,  
436 concentration of QDs to work with in model dissemination experiments, so as to be able to harvest  
437 quantitative data by HR-ICP-MS from said experiments. We recommend though to choose such  
438 working QD concentration bearing in mind that due to aggregation phenomena, not all  
439 disseminated QDs will actually dissolve.

$$440 \quad QD \ RLOQ = \frac{QD \ LOQ}{QD \ LOQ + GBC} * 100 \quad \text{Eq. 2}$$

441 This percentage allows to accurately assess the efficiency of the spiking method by considering  
442 the GBC in the matrix. Globally, we propose that the RLOQ values defined in the present study  
443 can be further used to determine the concentration of Zn/Cd/Se-containing ENPs to be used in any  
444 experiment related to their fate/behavior/toxicity by using isotopic labelling technique. However,  
445 one should consider a slightly higher ENPs concentration when studying their dissolution since the  
446 dissolved ENPs concentration is initially unknown. For instance, if Zn from Zn-containing ENPs  
447 is expected to dissolve at most 50%, the ENPs concentration used should be at least 2 times the  
448 QD-LOQ. Future studies related to ENPs fate, behavior, and toxicity in aquatic environments  
449 should be, as much as possible, carried out at environmentally relevant concentrations through the  
450 use of isotopically labelled ENPs, on the basis of the QD-LOQs estimated in the present study. The  
451 use of relevant concentrations in future experimental work should result in a better and accurate  
452 understanding on the ENPs fate, behavior, and toxicity.

453

454 ASSOCIATED CONTENT

455 **Supporting Information**

456 Compositions of aquatic matrices (Tables S1 and S2), Acid digestion protocol, Calculations of  
457 spiked QDs concentrations for Zn, Cd, and Se, Absorption and emission spectra of the test run QDs  
458 (Figure S1), QDs characterization images (Figure S2), Isotopic composition of multispiked QDs  
459 (Figure S3), Daily determination of the conventional HR-ICP-MS limit of quantification (LOQ)  
460 and its standard error (Figure S4), HR-ICP-MS calibration and spiked QDs concentration recovery  
461 plots (Figures S5 to S24), bias of the recovery plots (Table S3), *t* table (Table S4), calculated  
462 statistic *t* values (Table S5 to S7), ANOVA test tables (Table S8 to S14) and correlation figures  
463 (Figures S25 and S26).

464 This material is available free of charge via the Internet at <http://pubs.acs.org>

465

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470 The manuscript was written through contributions of all authors. All authors have given approval  
471 to the final version of the manuscript. <sup>† ‡ Δ</sup> These authors contributed equally.

472 **Funding Sources**

473 This research project (nanospike.fr) was fully supported by the French Agency for Food,  
474 Environmental and Occupational Health & Safety (ANSES) under the convention N° EST-  
475 2013/1/264. Part of this work was supported by the IPGP multidisciplinary program PARI and by  
476 Paris-IdF region SESAME Grant n°12015908.

477 **Notes**

478 The authors declare no competing financial interest.

479

480 **ABBREVIATIONS**

481 ENPs, engineered nanoparticles; FWHM, full width at half maximum; GBC, geochemical  
482 background concentrations; QDs, quantum dots, QD-LOQ, limit of quantification of spiked QDs  
483 according to the element labelled and to the matrix composition; QD-RLOQ, relative QD-LOQ.

484

485 **ACKNOWLEDGEMENT**

486 Our thanks go out to the team technical staff, especially to Mr. Mickaël Tharaud and Ms. Laure  
487 Cordier, for the assistance during various multi-elemental analyses. Parts of this work were  
488 supported by IPGP multidisciplinary program PARI, and by Paris–IdF region SESAME Grant no.  
489 12015908.



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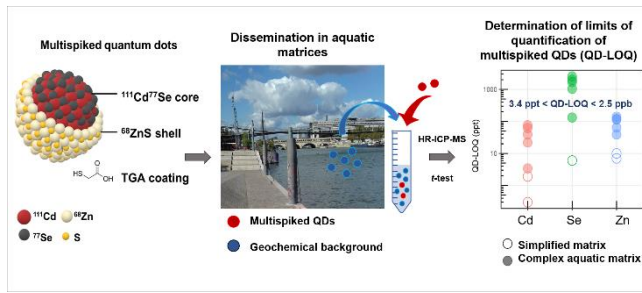


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