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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 (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.¹ To name a few, TiO₂ NPs are
34 used as photocatalyst in water and air treatment,² or as whitening agent in paints and in food and
35 food packaging products,³⁻⁵ Ag NPs are added to fabrics for anti-bacterial purpose,⁶⁻¹² ZnO NPs
36 act as UV absorbers in sunscreens,¹³⁻¹⁵ and CeO₂ NPs are incorporated in catalytic converters in
37 the automotive industry.¹⁶ 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.¹⁷⁻²² 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,²³
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.²⁴⁻³⁰ 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,³¹ whereas their homoaggregation increased with increasing
49 concentrations.³² 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).³³⁻³⁷ For instance, this strategy was employed to determine
62 the bio-uptake of TiO₂, Ag, and ZnO NPs in aquatic organisms, using ⁴⁷Ti, ¹⁰⁹Ag, ⁶⁷Zn tracers,
63 respectively.^{33,38,39} Quantitative detection of the ENPs was achieved at concentrations as low as
64 5 ppb, 6 ppt, and 1 ppm for ⁴⁷TiO₂, ¹⁰⁹Ag, and ⁶⁷ZnO NPs, respectively, showing the advantages
65 of ENPs isotopic labelling. Although the necessity to work at realistic concentrations has been
66 recently discussed,³⁷⁻³⁹ 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 ¹¹¹Cd, ⁷⁷Se, and ⁶⁸Zn (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,^{40,41} 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.⁴² 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 (Cl^- , SO_4^{2-} , NO_3^-), and iii) the determination of isotopic labelling
98 limits experiments. Sampling and analytical procedures were described by Benedetti et al.⁴³ 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.⁴⁴

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 (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}Cd , zinc oxide (ZnO powder) enriched at 99.16% in ^{68}Zn , and
115 selenium (Se powder) enriched at 99.20% in ^{77}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.*⁴⁵ 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 ¹¹¹CdO and ⁷⁷Se powders were commercially available with ¹¹¹Cd and ⁷⁷Se 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% ⁶⁸Zn 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 ⁶⁸Zn.

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.*⁴⁵ The modification consisted in substituting
132 ⁶⁸Zn-enriched ZnO for the initial zinc acetate precursor which was not available with a suitable
133 modified isotopic composition.⁴⁵ Briefly, 51.364 g (0.4 mmol) of ¹¹¹Cd-enriched CdO, 325.56 g
134 (4 mmol) of ⁶⁸Zn-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 N₂ 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 ⁷⁷Se-enriched selenium and 128.28 mg (4 mmol) sulfur dissolved in 3 mL of trioctylphosphine
143 under N₂ 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/HNO₃
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).⁴⁰ The QDs were also
186 added, with the same target concentrations, in both HNO₃ 2% and NaNO₃ 0.01M, used as control
187 media, since there is no occurrence of natural Zn, Cd and Se in both solutions, and the
188 NaNO₃ 0.01 M solution is representative of the highest typical ionic strength found in river and
189 estuarine waters.⁴⁶ 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/HNO₃ was not
193 further performed. The acidification step is representative of the final step used in many studies
194 prior to ENPs analysis.^{26,27} For HNO₃ 2%, NaNO₃ 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.⁴⁷

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 HNO₃ 2 %. During the whole analysis, a solution containing 5 ppb of rhodium
201 (¹⁰³Rh) prepared in HNO₃ 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 (¹⁰⁶Cd, ¹⁰⁸Cd, ¹¹⁰Cd, ¹¹¹Cd, ¹¹²Cd, ¹¹³Cd, ¹¹⁴Cd and ¹¹⁶Cd), Zn (⁶⁴Zn, ⁶⁶Zn, ⁶⁷Zn, ⁶⁸Zn and ⁷⁰Zn),
204 and Se (⁷⁴Se, ⁷⁶Se, ⁷⁷Se, ⁷⁸Se, ⁸⁰Se, ⁸²Se) were analyzed with HR-ICP-MS (ThermoScientific
205 Element II). The isotopes ¹⁰⁵Pd, ¹¹⁵In, ¹¹⁸Sn, ⁶⁰Ni and ⁷²Ge were also analyzed to correct possible

206 isobaric interferences.⁴⁸ 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 reproducibility⁴⁹ 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.*³³ and is detailed in SI.

218

219 **RESULTS AND DISCUSSION**

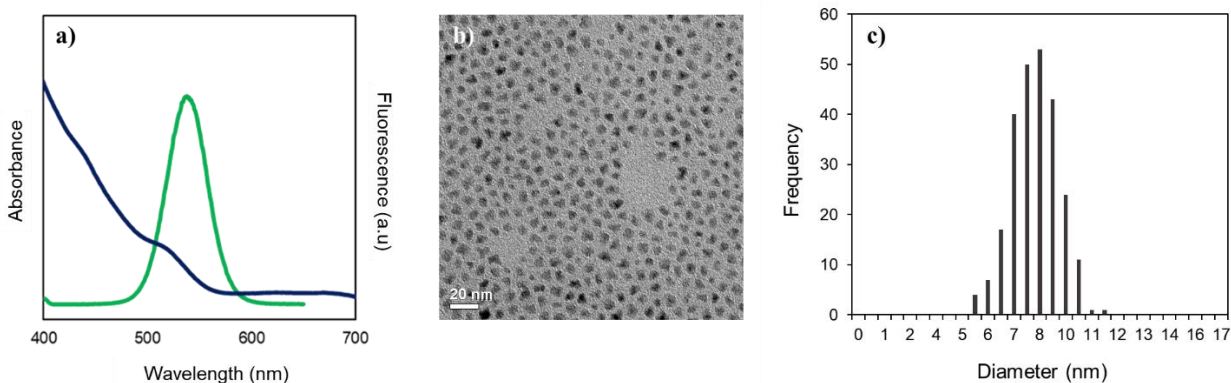
220 *QDs synthesis and characterization*

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 ± 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 ± 1.0 ppm of Zn, 31.8 ± 0.3 ppm of Cd, 19.2 ± 0.3 ppm of Se, and 404 ± 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

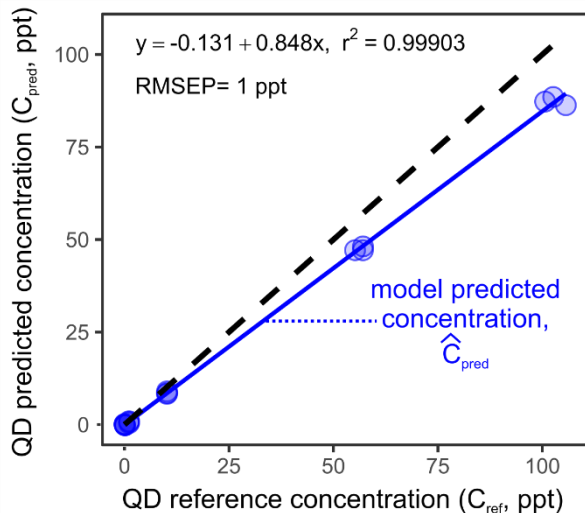
244 image of CdSe/ZnS QDs dispersed in chloroform; c) Size distribution of the QDs estimated from
245 the TEM image.

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}Cd , ^{68}Zn and ^{77}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}Cd , ^{68}Zn and ^{77}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}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}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

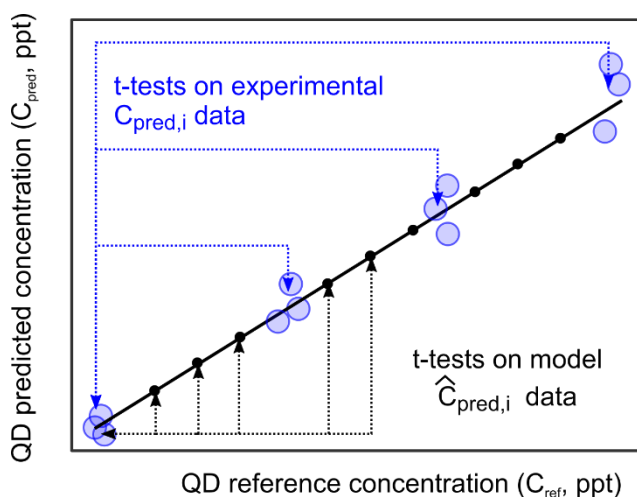
276 the t-test concluded that the two means were significantly different at the 99.9% confidence level,
277 then C_1 was designated as the QD-LOQ. If not, then the t-test was conducted using the samples
278 having C_2 concentration. The process was repeated with increasing C_i concentrations until the
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



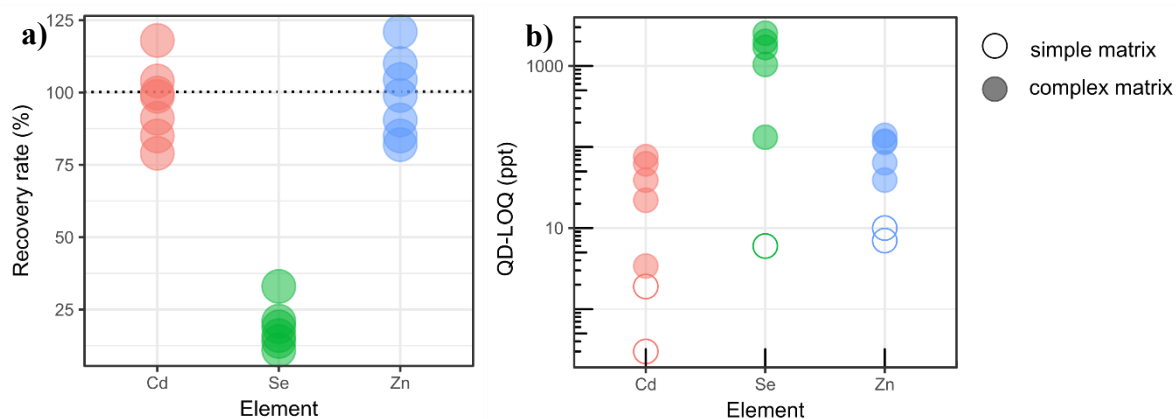
292
 293 **Figure 3.** Overview of methodology applied to estimate the QD-LOQ from the recovery plot or its
 294 model.

295
 296 The recovery plots for the ^{68}Zn , ^{111}Cd and ^{77}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}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_{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 generation⁵⁰ 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 (HNO_3 2% and 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 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_{Zn} 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_{Zn} 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 ₃ 2%	NaNO ₃ 10 ⁻² M	Seine	Seine/SW 75:25	Seine/SW 50:50	Seine/SW 25:75	SW	
Zn	GBC (ppt)	< LOQ _{Zn}	< LOQ _{Zn}	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 _{Cd}	< LOQ _{Cd}	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 _{Se}	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_{Se} are one order of
 345 magnitude higher on average than QD-LOQ_{Zn} and QD-LOQ_{Cd}. 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 (HNO₃ and NaNO₃) 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).^{36,51-53} 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 HNO₃ and NaNO₃ 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

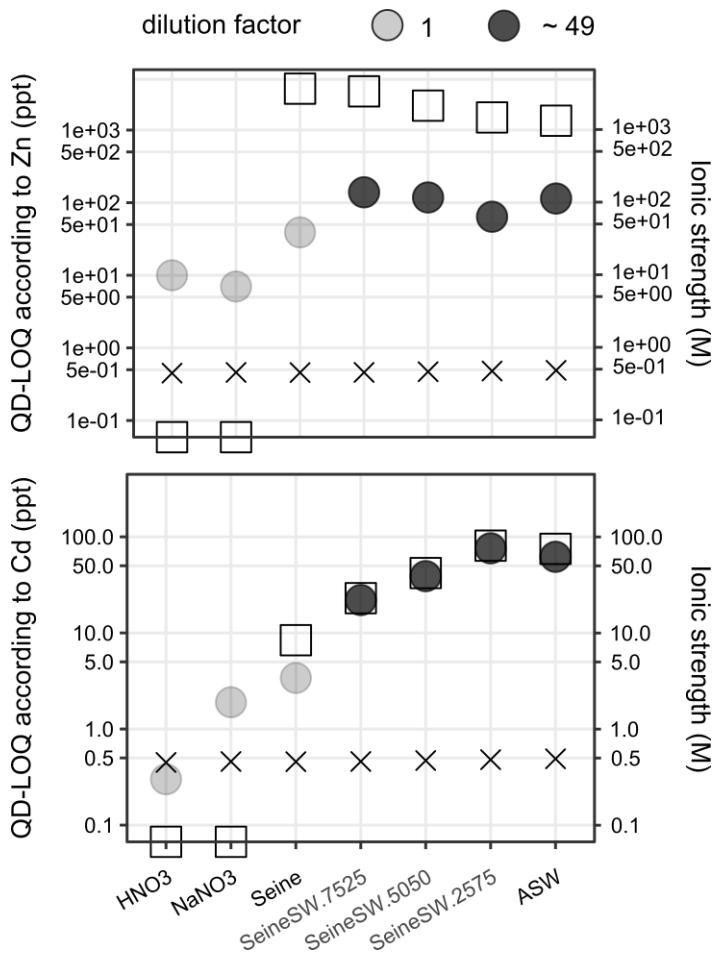
370 concentration in HNO₃, which is the matrix in which the $I(^AX)$ vs. C_A calibration plots were
371 acquired, in a phenomenon known as matrix effect⁴⁶ which will be investigated using the ionic
372 strength in the solutions analyzed in the instrument as metric.

373 Finally, the sea water and estuarine water samples contain high dissolved salt concentrations
374 (Table S2, total dissolved solids TDS_{sw} = 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)^{47,54} 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% HNO₃ 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}Cd and ^{111}Cd are less distinct in LR than ^{66}Zn and ^{68}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}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⁻¹) 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).

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 TiO₂, ZnO, Ag, and QDs NPs
420 respectively).^{23,40,41,55-58} 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).^{26,27,29,51-53} 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.⁵⁹

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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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

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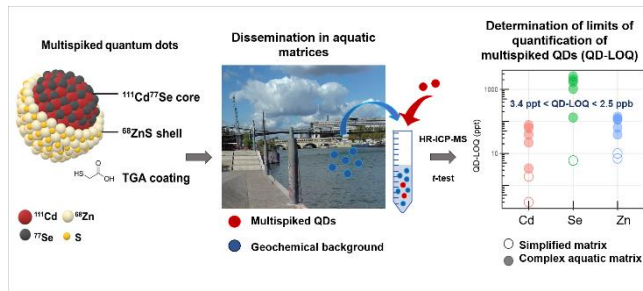
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