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Interlaboratory comparison of centrifugal ultrafiltration with ICP-MS detection in a first-step towards methods to screen for nanomaterial release during certification of drinking water contact materials

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HIGHLIGHTS

- Third-party certification for nano- enabled water devices requires proven analytical techniques.
- Centrifugal ultrafiltration followed by ICP-MS was evaluated in a round robin.
- Method accurately discriminated between nanoparticles and ions of the same composition.
- Method can be easily implemented in most laboratories without specialized equipment.

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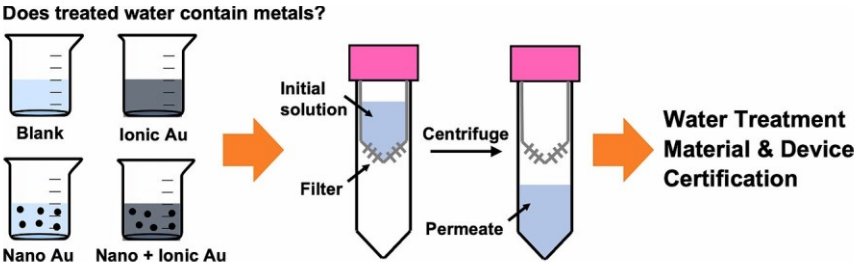
GRAPHICAL ABSTRACT



ABSTRACT

A key requirement for evaluating the safety of nano-enabled water treatment devices is measuring concentrations of insoluble nanomaterials released from devices into water that may be ingested by consumers. Therefore, there is a need for simple technique that uses commonly available commercial laboratory techniques to discriminate between nanoparticles and dissolved by-products of the nanomaterial (e.g., ionic metals). Such capabilities would enable screening for particulate or dissolved metals released into water from nanomaterial-containing drinking water contact materials (e.g., paint coatings) or devices (e.g., filters). This multi-laboratory study sought to investigate the use of relatively inexpensive centrifugal ultrafilters to separate nanoparticulate from ionic metal in combination with inductively-coupled plasma mass spectrometry (ICP-MS) detection. The accuracy, precision, and reproducibility for the proposed method were assessed using mixtures of nanoparticulate and ionic gold (Au) in a standard and widely utilized model water matrix (NSF International Standard 53/61). Concentrations for both ionic and nanoparticulate gold based upon measurements of Au mass in the initial solutions and Au permeating the centrifugal ultrafilters. Results across different solution compositions and different participating labs showed that ionic and nanoparticulate Au could be consistently discriminated with ppb concentrations typically resulting in <10 % error. A mass balance was not achieved because nanoparticles were

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retained on membranes embedded in plastic holders inside the centrifuge tubes, and the entire apparatus could not be acid and/or microwave digested. This was a minor limitation considering the ultrafiltration method is a screening tool, and gold concentration in the permeate indicates the presence of ionic metal rather than nanoforms. With further development, this approach could prove to be an effective tool in screening for nanomaterial release from water-system or device materials as part of third-party certification processes of drinking water compatible products.

1. Introduction

Nanomaterials are increasingly used in water treatment applications (Adeleye et al., 2016). The intrinsically high specific surface area and unique chemical properties of engineered nanoparticles may be used as adsorbents (Gai and Deng, 2021; Powell et al., 2020) to remove or (photo)catalysts (Li et al., 2008) to decompose contaminants. Nano- scale silver (Ehdaie et al., 2014; Heidarpour et al., 2011) and copper (Gilbertson et al., 2016) are used in membranes, cartridge filters and carbon block filters to control microbial growth. These uses are associated with health and safety concerns from exposure to insoluble, inorganic nanoparticles in treated drinking water, which is a current barrier to implementing nano-enabled technologies (Westerhoff et al., 2016). Industry (Kidd et al., 2021) and the public (Kidd et al., 2020) have expressed desire for third-party validation of the safety of specifically nano-enabled water treatment devices. In the water sector, NSF® (formerly the National Sanitation Foundation International) is a third- party public health and safety organization that offers certification, training, testing, and standard practices for processes or products involved in preparing food or drinking water. NSF® certification allows organizations or businesses to comply with government regulations and assure consumers of product quality. However, while NSF® testing and certification currently addresses migration of chemicals into drinking water, it currently does not specifically address materials (e.g., pipes, coatings, etc.) or treatment devices (e.g., filters) that use nanotechnology that may release insoluble nanoparticles into drinking water. There is a need to expand NSF® standards to account for nanomaterial enabled technologies.

A key requirement in the effort of evaluating the safety of nano- enabled water treatment devices is measuring concentrations of insoluble nanomaterials released into water during product use, potentially in a solution also containing an ionic fraction of the same element. In contrast to chemical leaching of soluble species alone, the size and morphology of released nanoparticles in water samples directly informs safety, sustainability, and performance troubleshooting and validation of nano-enabled materials. Therefore, an NSF® Nanomaterials Task Group, including stakeholders from regulatory agencies, academia, and industry, has been actively searching for and developing both analytical and risk assessment procedures to address nanomaterial safety in drinking water treatment systems and components. To this end, there is a need for robust, sensitive, and selective techniques to discriminate and quantify nanoparticulate vs. dissolved (ionic) metals in water distribution products and water treatment methods or devices. Electron microscopy techniques (e.g., scanning electron microscopy) are well known for characterizing nanomaterials at high spatial resolution, but they are time-consuming, require expensive equipment, and are challenging to quantify concentrations of nanoforms in water routinely. Optical scattering techniques, such as dynamic light scattering (DLS) or nanoparticle tracking analysis (NTA) are useful for characterizing nanomaterials, but they lack the specificity needed for inorganic nanomaterials and are vulnerable to matrix interferences from other particulates (e.g., organics) in water (Giorgi et al., 2021; Marucco et al., 2019). In particular, DLS has limited capability to quantify mass concentrations, especially at low concentrations, and is biased towards larger particles (Filipe et al., 2010). NTA can detect particle size with improved size resolution and particle number concentrations (Filipe et al., 2010; Hole et al., 2013), but it is still limited in that particles of different composition are practically indistinguishable. Inductively-coupled plasma with either mass spectrometry (ICP-MS) or optical emission spectroscopy (ICP-OES) detection is appealing for measuring inorganic nanomaterials because these instruments are highly specific and sensitive to most metals and widely available in commercial laboratories. While robust, standalone ICP methods typically measure only total dissolved concentrations of metals in water, following acid digestion. Special operational modes or pretreatment can be used to differentiate nanomaterials from ionic forms of metals. Single particle ICP-MS (Laborda et al., 2014; Mansor et al., 2021; Mozhayeva and Engelhard, 2020) or time-of-flight mass spectrometry (Montano et al., 2022˜ ; Naasz et al., 2018) are emerging analytical methods to differentiate between ionic and nanoparticulate forms of metals, but are not currently available in most commercial labs.

Another strategy to separate nanomaterials from their ionic metal counterparts is to use centrifugal ultrafiltration separation, followed by ICP-MS/OES detection. Centrifugal ultrafilters are commonly used in biochemical applications to isolate proteins, viruses, etc., but are also useful in selectively excluding nanoparticles from sample solutions. Several reviews have discussed the benefits and applications of centrifugal ultrafiltration in characterizing nanoparticle suspensions (Liu et al., 2012; Misra et al., 2012; Odzak et al., 2014), such as its ability to provide size fractionation in complex colloids. In addition, Ladner et al. effectively explored the mechanisms by which nanomaterials are excluded in these finely porous filters (Ladner et al., 2012). A review of recent papers using centrifugal ultrafiltration to separate nanomaterials (Table 1) reveals the popularity of this method across disciplines. Many of these experiments are performed at relatively high nanoparticle concentrations, well above what is expected to be present in drinking water. In addition, many experiments utilize materials of varying solubility, for which dissolution over time complicates quantification of the nanoparticles. Moreover, it is difficult to compare results across studies due to different experimental conditions (e.g., ultrafilter cut-off, water composition). Thus, the goal of this interlaboratory study was to assess the accuracy, precision, robustness, and reproducibility of centrifugal ultrafiltration separation with ICP-MS detection as a simple and high- throughput method to quantify and discriminate between known insoluble nanoparticles and ions of the same element. In doing so, the authors intend to propose a first-step in the process of screening for nanomaterials in extractant fluids of drinking water contact materials. In this investigation, gold (Au) was chosen as the test material due to its chemical stability, availability in reliable standards of both ionic and nanoparticle forms, and prior use in studies involving centrifugal ultrafiltration (Alele et al., 2016; Kokubo et al., 2020; Ladner et al., 2012; Nishida et al., 2009). Centrifugal ultrafiltration experiments were performed at three institutions over several months on solutions containing Au nanoparticles, ionic Au, or mixtures. Showing acceptable accuracy and precision for centrifugal ultrafiltration with ICP-MS detection across multiple laboratories would provide the opportunity for an NSF® workflow to determine leaching of engineered nanomaterials from drinking water contact materials or devices beginning with techniques accessible to most commercial labs.

2. Materials and methods

2.1. Interlaboratory organization

To test the robustness and repeatability of the centrifugal ultrafiltration method, the same experiments were performed at three institutions: Arizona State University (ASU, Lab 1), University of Texas at El Paso (UTEP, Lab 2), and Colorado School of Mines (CSM, Lab 3). Lab 1 acted as the primary laboratory to distribute materials and to compile results. Each laboratory performed centrifugal ultrafiltration and ICP- MS measurements in triplicate, and Lab 1 repeated the entire experiment three separate times (weeks apart) to further test the robustness of the method and stock solutions over this extended study. Stock solutions were prepared on 12/12/22, shipped on 12/14/22, and used on 12/21/ 22 for Lab 1 experiment 1, 01/12/23 for Lab 1 experiment 2, 01/13/23 for Lab 2, 01/31/23 for Lab 3, and 03/08/23 for Lab 1 experiment 3.

2.2. Materials

NSF® prepared 30 L of NSF International Standard 61 (N-1.9) pH 8 exposure water (NSF/ANSI, 2016) in batch tanks by dissolving the following into nanopure water: 122 mg·L^{-1} dissolved inorganic carbon as $NaHCO_3$ and 2 mg·L^{-1} free chlorine. Solution pH was then adjusted using 0.1 M HCl. This water matrix was shipped to ASU and used to prepare all stock solutions. Due to free chlorine loss in shipping and storage, upon use the test water contained no detectable dissolved chlorine by colorimetric assay, and therefore it is not considered as part of the matrix in these experiments. So, to summarize, the NSF International Standard water matrix consists of 10.2 mM $NaHCO_3$ and 0.15 mM HCl in nanopure water. Centrifugal ultrafilter units (Amicon, 30 kDa, 4 mL) were obtained and used as received. These ultrafilters consist of a polypropylene centrifuge tube, high-density polyethylene (HDPE) cap and liner, and regenerated cellulose membrane. A 4-mL sample volume was sufficient for both weighing the mass of the filtered liquid and measuring Au concentration via ICP-MS. The 30 kDa molecular weight cut-off (MWCO) was chosen because it represents a particle size of approximately a few nanometers and is within the range of filters used by studies in Table 1. An ionic $AuCl_4$ ICP-MS standard (1 mg Au·mL^{-1} in HCl) was obtained from Millipore Sigma and used to prepare ICP-MS standards and ionic Au fractions. Au nanospheres (50 nm, 99.99 %, citrate capped) were purchased as an aqueous suspension at 1 mg Au·mL^{-1} from Nanocomposix and used as received. As mentioned in Section 1, Au was chosen due to its physical and chemical stability and availability in reliable standards. To solely assess centrifugal ultrafiltration with ICP-MS detection to differentiate nanoparticulate and ionic metals, and not be interfered by other chemical reactions, it was important to avoid metals subject to dissolution, reprecipitation, and/or oxidation. All nanoparticle solutions and dilutions were well mixed and bath sonicated for at least 15 min at room temperature prior to use and stored refrigerated for more extended periods.

2.3. Preparation of Au test solutions

Lab 1 prepared 4 L each of the following solutions containing ionic and/or nanoparticulate Au (Table 2) by spiking appropriate amounts of the concentrated stock solutions and diluting with the NSF Standard 61 exposure water in glass containers. Solutions A-E represent differing fractions of ionic vs. nanoparticulate metal to be tested with centrifugal ultrafilters and Solution X is the stock solution of ionic Au used to prepare ICP-MS standards by serial dilution. Solutions were well mixed with a magnetic stir bar for 30 min, divided evenly into 8 separate HDPE bottles for storage and shipping, and a package

Table 1

Nanomaterial	Approx. size	Concentration	Ultrafilter cut-off	References	Use of centrifugal ultrafiltration
Ag	1–10 nm, 20 nm, 40 nm, and 80 nm	50–500 nM	kDa	(Hadioui et al., 2013)	Exploring nanoparticle-membrane interaction mechanisms or ultrafiltration method development
Ag, Au, TiO_2	2–9 nm	120–760 ppb	kDa, 10 kDa, 20 kDa, 50 kDa, and 100 kDa	(Ladner et al., 2012)	
Zeolite	1–2000 nm	17–25 ppm	kDa and various others	(Tsao et al., 2009)	
Au	nm	mM	kDa	(Kokubo et al., 2020)	Separation or washing step in nanoparticle synthesis or coating
Fe_3O_4	nm	35,000 ppm	kDa	(Liu et al., 2006)	
Ag	25–44 nm	1–10,000 nM	kDa	(Navarro et al., 2008)	
Ag, Au, Cu	20–100 nm	0.3 %–66 % w/w%	kDa	(Nishida et al., 2009)	
Au	nm, 50 nm	ppm	kDa, 100 kDa	(Alele et al., 2016)	Size fractionation and discrimination of nano from ionic metals
Ag	1–30 nm	15.3–199 ppm	kDa	(Anders et al., 2012)	
Au, SiO_2, TiO_2, polystyrene	20–200 nm	1–200 ppm	kDa	(de la Calle et al., 2018)	
Ag	17–27 nm	ppm	kDa	(Dong et al., 2016)	
ZnO	17–21 nm	2.5 mM	kDa	(Gelabert et al., 2014)	
Ag, Ag_2S	34–91 nm for Ag2S	ppm Ag2S	kDa	(Li et al., 2016)	
Au	nm	20–40 ppm	kDa	(Louie et al., 2013)	
ZnO	nm, 40 nm	1–5 ppm	kDa	(Merdzan et al., 2014)	
Ag	2–10 nm	61–3040 ppb	kDa	(Peyrot et al., 2014)	
ZnO, SiO_2	15–26 nm	2.2–9.0 ppm	kDa	(Poynton et al., 2011)	
CeO_2	≥200 nm	10–100 uM	kDa	(Rohder et al., ¨ 2014)	
Cr, Ni, Zn, Cu, Cd, Pb	N/A	50–410 ppb (colloid fraction)	kDa	(Wang et al., 2003)	
Polyvinyl alcohol	nm	170–2500 ppm	kDa	(Marques et al., 2020)	Quantifying drug delivery agent on nanoparticle carrier
Fe_2O_3	3–7 nm	mM	kDa, 30 kDa	(Turiel-Fernandez ´ et al., 2021)	

Summary of conditions used in recent papers using centrifugal ultrafiltration to separate nanomaterials.

containing one of each solution type was shipped to all participating laboratories. Portions of 500 mL each were enough for many experiments.

Table 2
Conditions for preparing standard test solutions with ionic and nanoparticulate Au.

Solution code	Total Au concentration[a] (ppb)	Percentage ionic Au (%)	Percentage nanoform Au (%)
A	50	0	100
B	50	25	75
C	50	50	50
D	50	75	25
E	50	100	0
X	200	100	0

[a] As prepared in a 4-L volume.

2.4. Centrifugal ultrafilter conditions

Aliquots of initial samples for each solution type (A–E) were set aside for analysis (10 mL, referred to as "initial"). Next, 4-mL aliquots of each were added into the top compartment of pre-weighed ultrafilter tubes. Samples were centrifuged at 5000 ×*g* for at least 25 min. The filtrate volume was determined gravimetrically and quantitatively transferred from the tube (referred to as "permeate"). These two samples, initial and permeate, are measurements that can be used to estimate nanoparticulate vs. ionic metal. Initial and permeate samples were acidified with a 1-mL spike of 6 %:2 % $HCl:HNO_3$ aqua regia prepared from 18.2 MΩ·cm water and TraceMetal grade acids (Fisher Scientific). To further test the method, any captured Au nanoparticles on the ultrafilter were dissolved and extracted into a retentate sample using aqua regia solution to facilitate calculation of a mass balance (see Supporting Information). In total, three sample types (initial, permeate, retentate) were measured in triplicate for each of the 5 sample compositions (A–E) for a total of 45 samples per experiment. The general workflow for experiments is summarized in Fig. 1.

2.5. ICP-MS measurements and data analysis

Acidified Au solutions were analyzed by ICP-MS for ^{197}Au on Perkin Elmer NexION 1000 instruments (or similar). Each laboratory prepared their own 8-point calibration curve following in-house procedures with ionic Au standards from 0.5 to 100 ppb prepared in 2 % HCl from the Solution X, 200 ppb stock solution. Internal standards (In, Bi, or W) flowed through a T-joint into the sample introduction lines and tuning procedures were used to account for plasma instability and daily variation in instrument parameters. A method detection limit was determined by taking 10× the standard deviation for replicate measurements of the 1 ppb standard. Dilution-corrected Au concentrations determined by ICP-MS were converted to Au masses using the respective solution volume. All Au concentration and mass data (across different solutions types and laboratories) can be found in the Supporting Information, Tables S1-S10.

If all nanoparticulate Au is blocked by the ultrafilters and all ionic Au passes through, the ionic Au mass fraction (w_{ion}) can be determined by Eq. (1) and the nanoparticulate Au mass fraction (w_{nano}) can be determined by difference with Eq. (2), where m_{ini} is the mass of Au in the initial solution and m_{perm} is the mass of Au in the permeate. Percent accuracy for ionic and nanoparticulate mass fractions were calculated for initial and permeate solutions based on the stock solution compositions (Eq. (3) for ionic and Eq. (4) for nanoparticulate). The percent total Au recovery (%*R*) was determined by Eq. (5).

$$w_{ion} = \frac{m_{perm}}{m_{ini}} \quad (1)$$

$$w_{nano} = 1 - w_{ion} \quad (2)$$

$$\text{Ionic Mass Accuracy} (\%) = 100 \cdot \frac{w_{ion}(measured)}{w_{ion}(expected)} \quad (3)$$

$$\text{Nano Mass Accuracy} (\%) = 100 \cdot \frac{1 - w_{ion}(measured)}{w_{nano}(expected)} \quad (4)$$

$$\%R = 100 \cdot \frac{m_{perm} + m_{ret}}{m_{ini}} \quad (5)$$

All figure error bars represent ±1 standard deviation. To test for statistical significance between laboratory data sets, ionic Au mass fractions (w_{ion}) and nanoparticulate Au mass fractions (w_{nano}) for each solution composition were compared using a single factor ANOVA test at the 95 % confidence level in Excel. To test for statistical significance between measurements of differing solution compositions two-tailed, two-sample *t*-tests were performed at the 95 % confidence level in Excel for each pair of adjacent solution compositions (0 % ionic and 25 % ionic, 25 % ionic and 50 % ionic, etc.).

3. Results and discussion

3.1. Precision in discriminating between ionic and nanoparticulate Au

Laboratories were able to discriminate well between ionic and nanoforms of Au using centrifugal ultrafiltration as a separation technique and ICP-MS for quantification. Ionic Au mass fractions (Au that passed the ultrafilter) for centrifugal ultrafilter experiments across laboratories are shown in Fig. 2A, with the ionic fraction increasing from left to right. There was no statistical difference in results across laboratories for any given solution composition ($p \gg 0.05$), whereas there is clear statistical significance across measurements of different solution compositions ($p \ll 0.01$). Experimental mass fractions in Fig. 2A directly align with those prepared before ultrafiltration (25 %, 50 %, etc.), as addressed further in Section 3.2. The concentrations of Au in permeate samples (the quantity measured by ICP-MS) are shown in Fig. 2B. Unsurprisingly, these also follow the pattern expected based on the starting

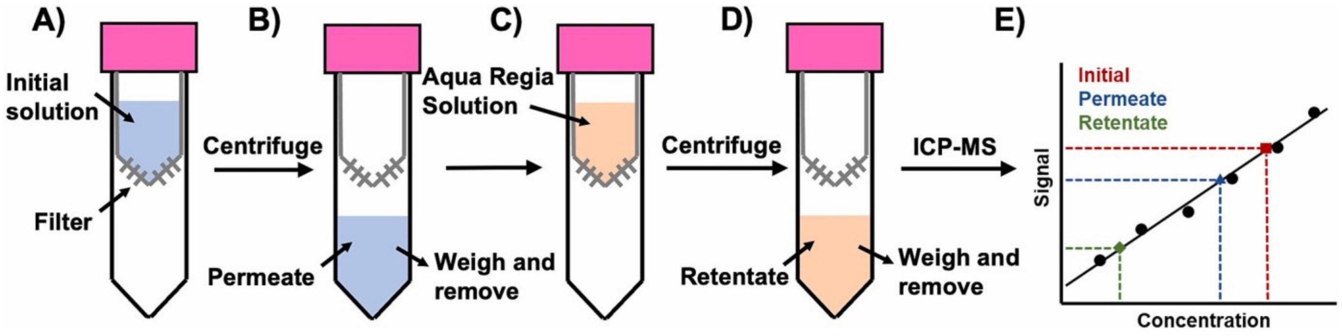
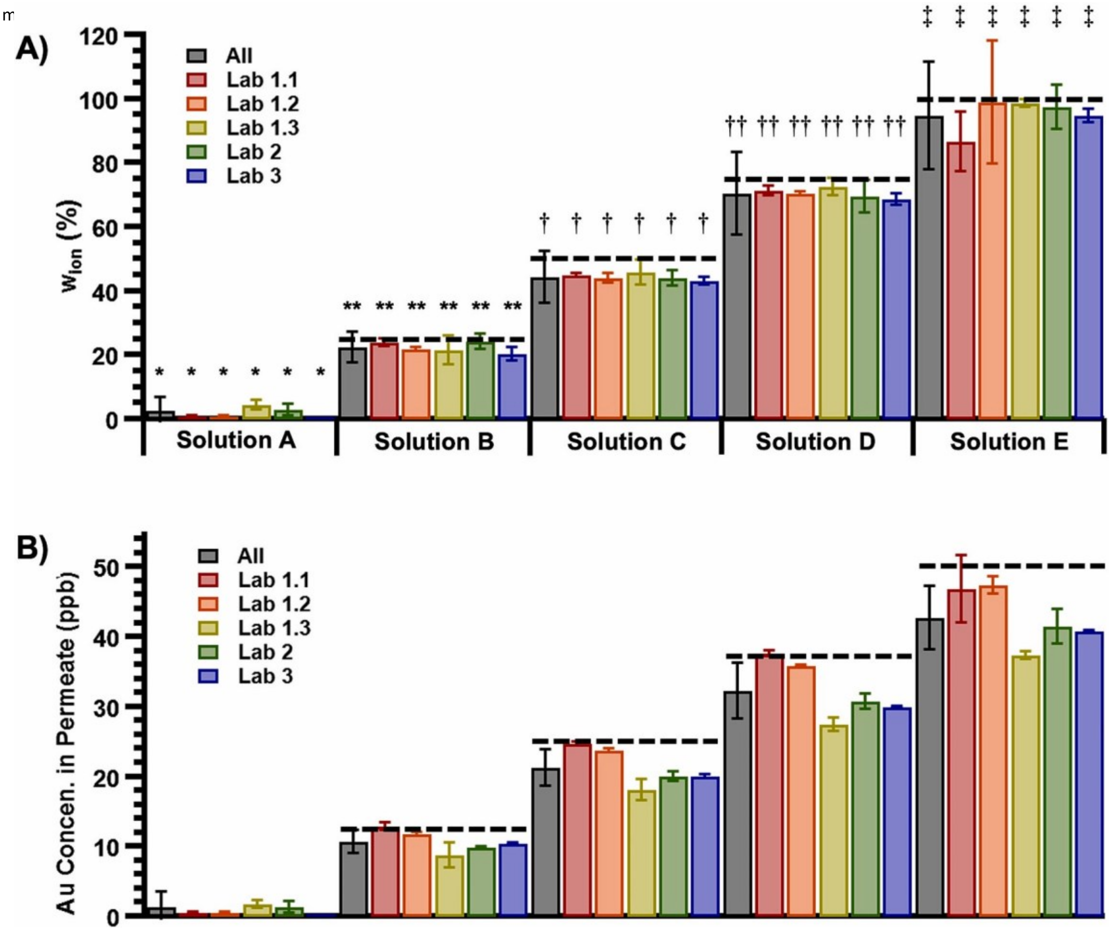


Fig. 1. Experimental summary for centrifugal ultrafiltration with ICP-MS detection. Steps A and B are the primary measurements determining nanoparticulate vs. ionic metal, and steps C and D are for dissolving retained particles and collecting the retentate to obtain mass balance. This workflow was performed for each solution type and each replicate.

Fig. 2. A) Percent m … bined in increasing



ionic fraction from left to right: Solution A 100 % nano, Solution B 75 %:25 % nano:ionic, Solution C 50 %:50 % nano:ionic, Solution D 25 %:75 % nano:ionic, and Solution E 100 % ionic. Dashed lines indicated the expected mass fraction (A) or concentration (B) for each solution type. Markers in A (*, **, †, ††, ‡) indicate statistically distinct groupings at confidence >95 %.

solution concentrations and compositions. However, the concentrations are biased low in concentration, particularly for experiments performed a longer time after the stock solutions were prepared (Lab 1.3, Lab 2, and Lab 3). This is addressed further in Section 3.4, as the *total* gold concentrations in stock solutions themselves decreased over time.

Uncertainty for individual experiments ranges from 1 %–16 % RSD, with higher errors present for samples with lower ionic Au concentration. This is increased slightly when combining all experiments (10 %– 16 % RSD) due to variability between laboratories. For specific measurements where either the ionic (solution A) or nanoparticulate (Solution E) concentration is intentionally ≈0 ppb, there is larger relative error, and the opposite measurement (with lower error) would be used to quantify the Au species in such a sample. Therefore, these were not considered in assessing precision. Since all laboratories reproduced results with no statistical differences in w_{ion} or w_{nano} and with %RSD typically <10 %, this indicates the method is both precise and reproducible.

3.2. Accuracy in discriminating between ionic and nanoparticulate Au

Across all solution compositions in Fig. 2, the interlaboratory average ("all") mass fractions match closely with the expected mass fractions of 0 %, 25 %, 50 %, etc. from Table 2. The permeate mass fractions assigned as ionic Au in Fig. 2 equally inform of Au *not* in the permeate by conservation of mass considering the initial Au content is included in the calculation. For example, if 49 % of Au is detected in the permeate and assigned as ionic Au, this also means that 51 % of Au in that sample is assigned as nanoparticulate Au. Thus, these measurements reaffirm the expected ratios of nano:ionic Au from our stock solutions even after ultrafiltration, now with added separation and assignment of Au into each fraction. By assigning ionic and nanoparticle fractions of Au and comparing to total Au in the initial, this culminates to a simple yet effective means for discriminating Au mass fractions. Accuracy for determining ionic and nanoparticle mass fractions were determined using Eqs. (3) and (4) and are expressed in Tables 3 and 4

Table 3

Percent accuracies for ionic Au mass fractions calculated using Eq. (3) for each experiment and all experiments combined.

Solution composition	All Labs	Lab 1.1	Lab 1.2	Lab 1.3	Lab 2	Lab 3
Solution A (100 % nano)	N/A	N/A	N/A	N/A	N/A	N/A
Solution B (75 %:25 % nano: ionic)	89 ± 15	95.8 ± 4.6	87.4 ± 2.0	87 ± 18	97.29 ± 0.50	82.1 ± 2.9
Solution C (50 %:50 % nano: ionic)	89 ± 11	90.1 ± 1.1	88.5 ± 1.1	92.0 ± 7.9	88.1 ± 2.7	86.3 ± 1.4
Solution D (25 %:75 % nano: ionic)	94 ± 12	95.2 ± 1.3	93.94 ± 0.57	97.0 ± 3.6	92.6 ± 3.9	91.8 ± 2.0
Solution E (100 % ionic)	94.9 ± 9.9	86.6 ± 9.4	99.0 ± 2.9	98.7 ± 1.1	97.6 ± 6.3	94.8 ± 1.7

Table 4

Percent accuracies for nanoparticulate Au mass fractions using Eq. (4) for each experiment and all experiments combined.

Solution composition	All Labs	Lab 1.1	Lab 1.2	Lab 1.3	Lab 2	Lab 3

Solution A (100 % nano)	94 ± 27	99 ± 22	99 ± 16	96 ± 27	97 ± 54	81 ± 21
Solution B (75 %:25 % nano:ionic)	98.4 ± 6.4	101.4 ± 4.8	104.2 ± 2.4	104 ± 22	100.9 ± 0.52	80.9 ± 2.8
Solution C (50 %:50 % nano:ionic)	110.0 ± 3.8	109.9 ± 1.3	111.5 ± 1.3	108.0 ± 9.2	111.9 ± 3.4	108.8 1.8
Solution D (25 %:75 % nano:ionic)	117.9 ± 3.3	114.4 ± 1.5	118.18 ± 0.71	109.0 ± 4.0	122.1 ± 5.1	125.8 ± 2.8
Solution E (100 % ionic)	N/A	N/A	N/A	N/A	N/A	N/A

(plotted in the Supporting Information, Figs. S2 and S3). As in Fig. 2, "All" refers to the interlaboratory average. These data represent the accuracy of how much ionic or nanoparticulate Au is assigned to a sample from centrifugal ultrafiltration relative to what is expected from the initial stock (with 100 % being perfect accuracy). Table 3 shows ionic Au mass accuracy in the permeate ranging from 82 %–99 %, with typical values >90 %. This indicates that for a given sample, this method could estimate ionic Au concentrations with approximately 90 % accuracy. As with Fig. 2, accuracy does not systematically depend on the experiment location.

Nanoparticulate Au mass accuracy in Table 4 shows very similar results in that accuracy is typically ±10 % within expected, though there is some dependance on solution composition. Interestingly, accuracy for nanoparticulate Au increases with ionic gold fraction and is >100 % for samples with a higher ionic Au fraction (Solutions C and D). This means a portion of the ionic fraction was blocked by the filters, or at least not collected in the permeate sample. Combined with the fact that ionic Au mass accuracies (Table 3) were all <100 %, this implies that false positive identification of ionic metals as nanoparticles by this method is more likely than false negative assignment of nanoparticles as ionic. One hypothesis to explain this is that the negatively-charged citrate coating on the Au nanoparticles for stability could attract Au ions from solution and retain them in the ultrafilter. Using a different nanoparticle chemistry or MWCO ultrafilter (compared to our 30 kDa) could change this behavior. For example, a centrifugal ultrafilter with larger pores (e.g., 100 kDa) may show even higher ionic Au in the permeate (closer to ~100 % accuracy for entirely ionic solutions), but also may allow some passage of Au nanoparticles (falsely classifying as ionic).

Relative errors are higher in solutions with a larger proportion of Au as nanoparticles since the permeate solution for those samples inherently have lower Au concentration, closer to method detection limit. It follows that there is a slight increase in accuracy when increasing the ionic Au fraction (e.g., E > D > C > B), since the permeate in those samples contains a higher concentration of Au and is further from the method detection limit. This agrees with the three possible situations for an unknown sample: 1) $w_{ion} \gg w_{nano}$ ($m_{perm} \approx m_{ini}$), 2), $w_{ion} \approx w_{nano}$ ($0 < m_{perm} < m_{ini}$) or 3) $w_{nano} \gg w_{ion}$ ($m_{perm} \approx 0$). In all three scenarios, at least two of the three measurements (m_{perm}, m_{ini}, and $m_{ini} - m_{perm}$) will be non- zero and provide accurate results, but if one of the parameters is ≈0, the correct measurement must be used. For example, for a sample that is clearly >99 % nanoparticulate by centrifugal ultrafiltration and ICP-MS measurements, it follows to use w_{nano} for ascribing accuracy and uncertainty, not w_{ion}. This also justifies why data for Solution A is not included in Table 3 and data for Solution E is not included in Table 4.

3.3. Analytical figures of merit

Table 5

Figures of merit for the centrifugal ultrafiltration with ICP-MS interlaboratory study within each laboratory's data set and for all data combined, averaged across all solution compositions and replicates. Where applicable, expressed uncertainty is ±1 standard deviation.

Parameter	All Labs	Lab 1.1	Lab 1.2	Lab 1.3	Lab 2	Lab 3
Initial Au concentration (ppb)	46.6 ± 7.1	54.4 ± 3.4	51.9 ± 5.0	38.5 ± 2.3	42.1 ± 2.8	46.3 ± 5.2
Average mass fraction RSD (%)	13.1	4.53	1.75	8.56	3.56	2.27
Ionic mass accuracy (%)	92.1 ± 4.9	91.9 ± 4.4	92.2 ± 5.4	93.6 ± 5.5	93.9 ± 4.5	88.7 ± 5.7
Nano mass accuracy (%)	105 ± 11	106 ± 7.2	108 ± 8.4	104 ± 6.1	108 ± 11.4	99 ± 22
Ionic Au (Solution E) recovery (%)	101 ± 18	87.3 ± 9.5	99 ± 19	102 ± 1.4	103 ± 7.4	97.3 ± 2.0
Calibration R^2	0.999	0.999	0.999	0.999	0.997	0.999
Method detection limit (ppb)	0.4 ± 0.2	0.5	0.4	0.6	0.3	0.2

Table 5 summarizes the metrics applied to findings on the centrifugal ultrafiltration with ICP-MS detection. Note that values for "All Labs" are obtained from all individual data points combined. The precision of the method can be assessed broadly in terms of uncertainty within each data set (repeatability) and uncertainty across all combined data sets (reproducibility). The individual average %RSDs for calculated Au mass fractions range from 1.75 %–8.56 %, averaging 4.13 %. The average % RSD comparing all laboratories to each other was 13.1 %. A higher value is expected due to inherent error added when the experiment is performed in different laboratories by different researchers. This indicates that uncertainty for a given experiment can be expected as ~5 % and uncertainty across institutions can be expected as ~10 %, under the conditions of this study.

The accuracy of the method can be assessed broadly through the ionic and nanoparticulate Au mass accuracies, when compared to expected Au masses from stock solution composition. Ionic Au mass accuracy and nanoparticulate Au mass accuracy are all within ±10 % of their expected values in all but one experiment. This indicates that concentration estimates for nanoparticle and ionic fractions in an unknown Au solution could be made within ~10 % error. Since ionic (permeate) mass accuracy was <100 % and nano (excluded) mass accuracy was >100 %, this means it is more likely for ionic Au to be retained by the ultrafilters and misattributed as nanoparticulate Au (false positive), rather than Au nanoparticles passing through and being misattributed as ionic Au (false negative).

Lastly, from the ICP-MS standards a method detection limit of 0.4 ± 0.2 ppb Au was obtained, averaged across all laboratories. In general, ICP-MS detection limits strongly depend on the instrument, analyte, operational parameters, and sample preparation. This can be considered as the absolute limit of what could be measured. However, in the experiments of this study and what is predicted for most others using this method, the ICP-MS analytical detection limit obtained from standards is not the limiting factor in accurately differentiating nanoparticle vs. ionic metals. Instead, measurements may be limited by A) the actual ratio of nanoparticle vs. ionic metal in the sample, B) matrix effects in complex water matrices, and C) uncertainty across replicate ultracentrifugation experiments.

3.4. Variability in Au concentration over time

To evaluate variation in Au concentration and subsequent masses over the extended time of the study, the experiments were repeated at Lab 1 over three months. Permeate Au concentrations (Fig. 2B) and even initial Au concentrations (first entry in Table 5) were different across laboratories and when measured on different days. Fig. 3 shows that the initial Au concentration in the stock solutions of every composition (100

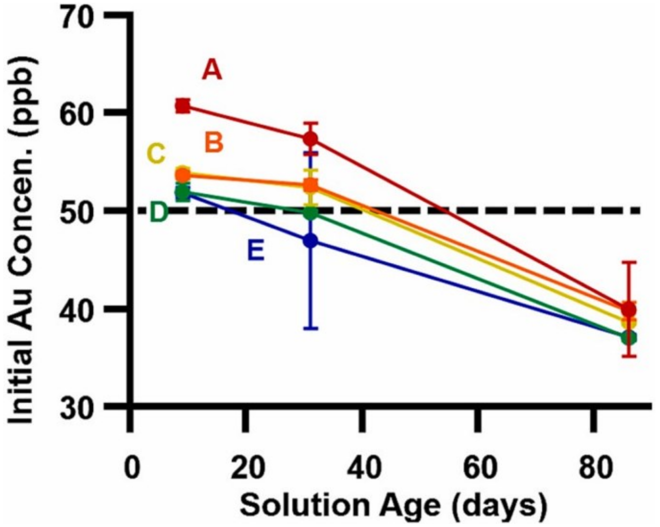


Fig. 3. Au concentration in initial stock solutions measured at the time of experiments vs. time since the solution was prepared for the three ASU experiments. The calculated nominal starting concentration was 50 ppb, shown in the black dashed line. Solutions were stored at 4 °C in HDPE bottles and well mixed and sonicated before each use.

% nano, 100 % ionic, or mixed) decreased when the stock solutions were stored in HDPE bottles for an extended period (~30 % over ~90 days), despite mixing and sonication prior to analysis. It is especially surprising considering it did not depend on the initial form of Au.

It is hypothesized that the loss of Au could be due to A) adhering of Au nanoparticles or ionic Au precipitates to the walls of the sample bottles, B) aggregation of Au nanoparticles, or C) precipitation and settling of the ionic Au in the test water. Precipitates of ionic Au^{+3} (from the source gold (III) chloride in the standard) could form by it reacting with hydroxide to form insoluble $Au(OH)_3$, given that the pH of 8 in the test water is much more basic than typical ionic Au solutions. For example, Macchione et al. (Macchione et al., 2018) found that moderately basic solutions of gold (III) at room temperature formed gold nanoparticle precipitates over extended periods (weeks to months). Further experiments would be required to test these hypotheses and explain why Au concentration decreased, as our study does not adequately address them. This decrease in both ionic and nanoparticle metal concentrations highlights the importance for future application of the ultrafiltration method to be performed immediately after the material extraction testing protocol. In our study, initial (total) Au concentrations were measured at the same time as centrifugal ultrafiltration samples for every solution composition and in every experiment, and are both integral in calculating metrics such as mass fraction or mass accuracy. Moreover, the lack of statistical significance across laboratories (Fig. 2) indicates that the changes over time did not impact the centrifugal ultrafilter's ability to discriminate ionic vs. nanoparticulate Au. This makes the change in Au concentration over time more relevant for sample preparation, rather than the analysis itself. Important to note is that NSF® testing waters are prepared fresh, right before testing with the target materials in leaching exposure tests or drinking water devices in continuous flow tests. Exactly how that water sample is obtained could be important to yield accurate results but is specific to the device or material in question. Ultimately, in a given water sample would be analyzed for initial "total metal concentration" and concurrently ultrafiltered for discriminating ionic vs. nanoparticulate through the permeate ionic mass fraction. So, these results do stress both A) the importance of measuring nanoparticle suspensions samples soon (within ~2 weeks) after preparing them, particularly with a material prone to dissolution and/or precipitation, and B) to use proper nanomaterial storage and handling practices (e.g., sonication, refrigeration). For the later, there is a need to optimize and establish standardized storage practices suitable not just for Au nanoparticles, but other inorganic nanomaterials as well (Jauregui-Gomez et al., 2017; Murphy and Buriak, 2015).

3.5. Total Au recovery

While only initial and permeate measurements are required to estimate both nanoparticle and ionic Au fractions by difference, the amount of Au captured in the filters ("retentate") was also measured by extracting with aqua regia (discussed further in the Supporting Information). This was to obtain a mass balance for Au. Fig. S1 contains total Au recoveries for all solution types and experiments, as calculated by Eq. (5), with 100 % recovery indicating the mass of permeate and retentate combined is the same as that in the initial test solution.

As discussed in Section 3.3, percent mass accuracies were excellent, typically >90 %. While ionic Au mass recoveries in the permeate were also exceptional, interestingly the retentate recoveries for nanoparticulate Au were low and had high relative errors. This is attributed to the retentate Au mass measurement and recovery of Au nanoparticles from the ultrafilters with aqua regia. The aqua regia solution concentration or exposure time used may not be sufficient to fully dissolve trapped nanoparticles and remove them from the filter. This may occur because the membranes are attached to plastic supports within the centrifuge tubes. It isn't viable to microwave or heat acid digest the entire membrane+plastic+tube without extensive modifications to standard water analysis techniques. After recognizing this and extended aqua regia exposure times to ~20 min, experiments for Lab 1.3 and Lab 2 show 80 %–120 % recovery on most solution compositions (Fig. S1 and Tables S8–9).

Because of these potential complications (depending on the material and particle size), it is not recommended to use extraction and measuring retentate to quantify nanoparticle vs. ionic fractions, but instead use centrifugal ultrafilter permeate and initial solution measurements only. The purpose of this study is to identify a means to conservatively discriminate ionic and nanoparticle metal fractions so that samples from water treatment materials or devices that are found to contain a detectable nanoparticle fraction can undergo further testing, which these two measurements do. Further experiments optimizing metal nanoparticle extraction from these filter membranes could improve retentate recovery, but that is beyond the scope of this study. The exceptional total Au recovery for the predominantly ionic Au solutions shows promise that permeate measurements for unknown samples would show similar recovery.

4. Summary and conclusions

Despite several studies into the application of centrifugal ultrafiltration as a separation strategy to aid in differentiating nanoforms from ionic forms of several metals (Table 1), there has been a general lack of controlled comparison studies on this methodology. This interlaboratory round-robin study has shown that the use of centrifugal ultrafiltration with ICP-MS can accurately and robustly differentiate between ionic and nanoparticulate Au in 100 % ionic Au solutions, 100 % nanoparticulate Au solutions, and in several mixtures at ≤50 ppb Au. Each laboratory reproduced statistically similar results, indicating this procedure could be performed more broadly and maintain efficacy. Typical mass accuracies were within ±10 % of expected from the initial stock solutions, and relative errors for a given experiment were typically within ±5 % (Table 5). Total Au recovery was excellent for initial and permeate solutions, which were used to determine the ionic vs. nanoparticle fractions. Retentate recovery (e.g., dissolving and extracting Au from the ultrafilters) varied across laboratories due to incomplete dissolution within the aqua regia extraction solution. Lastly, while elemental selectivity in ICP-MS for diverse water matrices was not assessed in this study, this largely depends on the analyte of interest and common best practices for ICP-MS (May and Wiedmeyer, 1998), rather than the centrifugal ultrafiltration separation step.

As represented in these findings, centrifugal ultrafiltration with ICP- MS detection can be used to discriminate between ionic and nanoparticulate Au and estimate concentrations. Centrifugal ultrafiltration provides >90 % effective separation in sample preparation, and ICP-MS provides element-specific, sensitive detection with our determined detection limit of 0.4 ± 0.2 ppb Au. Additionally, the relatively low combined cost of a centrifugal filter unit (~$10) and ICP-MS use time (~ $40 per sample) helps enable this method to be used by commercial labs. This method now represents the first part of a potential NSF® workflow to determine leaching of engineered nanomaterials from drinking water contact materials or devices, which rely upon well documented protocols (NSF International 53/61). Disclosure by any manufacturer would include precise composition and size of nanomaterials in their materials or devices. After subjecting the materials or devices to the extraction or release protocol, the workflow illustrated in Fig. 4 would determine if the engineered nanoparticle is released and, if so, at what potential concentrations. The work presented herein is intended to answer the question for Sample 2 in Fig. 4. In Fig. 4, a hypothetical 90 % non- nanoform threshold is applied, above which additional material characterization of the nanoform in extracted water from the material or device would not be required. NSF® will use the information herein in part to develop future nano-specific testing protocols, and this example threshold could change as standards are developed. It is important to recognize that the NSF International Standard 53/61 test solution represents one standard test solution and may not be representative of all drinking waters across the United States or internationally. The presence of chloramines instead of free chlorine could influence oxidation of chemicals or nanoparticles. Different salt matrices can also influence release of materials into extractant fluids. However, the purpose of a standard water chemistry is to provide a simple starting point for testing the method itself without interference from diverse water compositions.

The work presented in this study is for gold nanoparticles, which were selected for their chemical stability (i.e., low dissolution potential). Future work will be required with other nanoforms comprised of metals that may react more rapidly, and result in release of dissolved ions into water where they may persist or form secondary particles (e.g., silver chloride from Ag^+ released from Ag^0). Fig. 3 shows the potential for nanoparticle and dissolved gold concentrations to change over the course of 3 months, when no preservatives or acids are added. Recently presented and ongoing research is studying the need to select appropriate storage material, holding time, and preservatives. In the current work, adding preservatives was not desirable, because they could have impacted ultrafiltration results. The recommendation for the analytical workflow presented in Fig. 4 is to perform the ultrafiltration separation step within 1 day of conducting the surface contact NSF® testing. In applying the centrifugal ultrafiltration with ICP-MS approach to non-metallic based nanoforms (e.g., carbon nanotubes), it may be possible to build upon existing research that monitors their release into water using trace metal impurities in the catalysts used during their synthesis (Flores et al., 2022; Kidd et al., 2019; Lankone et al., 2017; Wang et al., 2016).

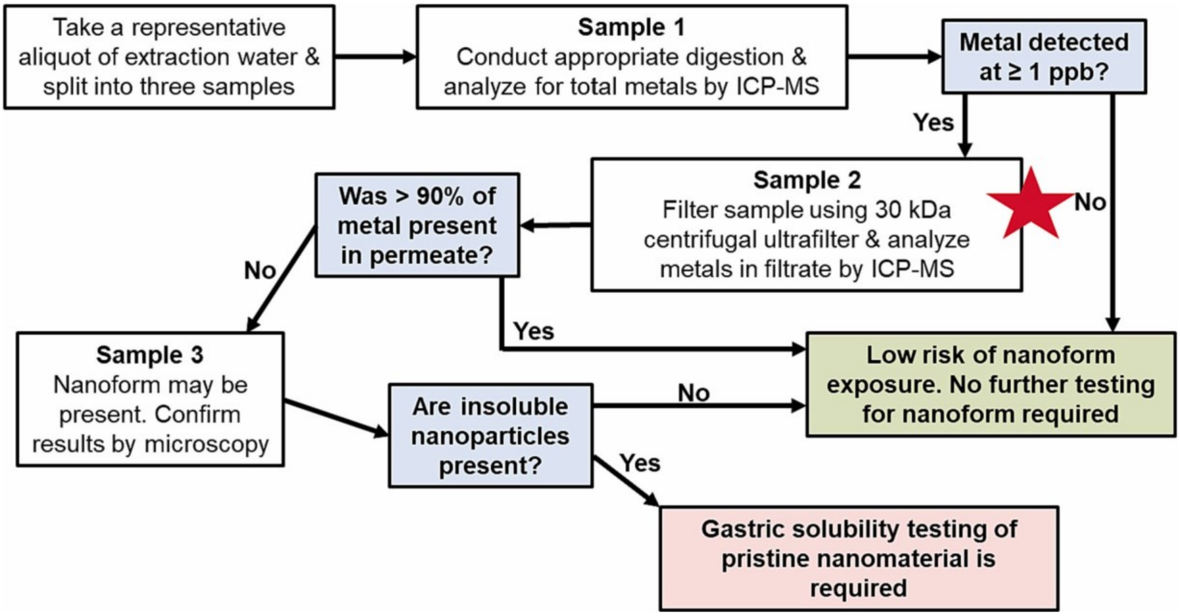


Fig. 4. Representative workflow to assess release of nanoforms into extractant test waters from drinking water contact materials or devices.

Overall, this work serves as a step towards having a simple and effective method for differentiating dissolved and nanoparticulate metals that could potentially be in water samples. This goal is intended to reduce barriers in implementing nano-technology enabled water treatment systems and water distribution products by providing simple and effective approaches for third-party safety assessments. The centrifugal ultrafiltration separation with metal quantification provides a robust, reliable, and readily applicable method to discriminate between nanoparticulate and ionic forms and estimate concentrations within a relevant range (ppb). This may be further improved in future studies to close the mass balance and improve quantification accuracy.

CRediT authorship contribution statement

Austin H. Henke: Investigation, Data curation, Writing – original draft, Visualization, Formal analysis. **Kenneth Flores:** Investigation, Data curation, Writing – original draft, Visualization, Formal analysis, Validation. **Aaron J. Goodman:** Data curation, Writing – review & editing, Validation. **Kelly Magurany:** Investigation, Writing – review & editing, Methodology. **Kerri LeVanseler:** Investigation, Writing – review & editing, Methodology. **James Ranville:** Validation, Writing – review & editing, Methodology. **Jorge L. Gardea-Torresdey:** Writing – review & editing, Methodology. **Paul K. Westerhoff:** Funding acquisition, Project administration, Supervision, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paul Westerhoff reports financial support was provided by National Science Foundation. Two co-authors are employed by the third-party certification entity mentioned in the paper (NSF®).

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.168686.

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