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Determination of trace level cadmium in SRM 3280 Multivitamin/Multielement Tablets via isotope dilution inductively coupled plasma mass spectrometry

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ABSTRACT

Cadmium was quantified at 80.15 ± 0.86 ng/g (mean ± 95% expanded uncertainty) in NIST SRM 3280 Multivitamin/Multielement Tablets, using isotope dilution mass spectrometry. The method described utilized various precipitation and solid-phase extraction separation methodologies to isolate Cd from Sn and Mo, present respectively, at 11.1 ± 0.9 mg/kg and 70.7 ± 4.5 mg/kg in the tablet matrix. This allowed for measurement of $^{111}Cd/^{113}Cd$ and $^{111}Cd/^{114}Cd$ isotope ratios using both quadrupole collision cell technology inductively coupled plasma mass spectrometry (Q-CCT-ICP-MS) and sector field (SF)-ICP-MS equipped with a desolvating nebulizer system to mitigate the MoO^+ and $MoOH^+$ molecular ion interferences that typically affect the envelope of Cd isotopes.

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1. Introduction

There are compelling reasons for the development of analytical methods and matrix-matched reference materials for the accurate determination of toxic analytes in foodstuffs and nutraceutical materials, especially for dietary supplement products, where national and international directives governing the regulation of these materials, in terms of their safety and efficacy, are in flux [1]. Dietary supplement products are not as tightly regulated as compared to pharmaceuticals, yet the active ingredients in these materials (e.g., vitamins and minerals, herbs, botanicals, enzymes, metabolites, etc.) can be very potent. In the United States, the Food and Drug Administration (FDA) is tasked with regulating dietary supplements through the Dietary Supplement Health and Education Act of 1994 (DSHEA) [2]. Within this framework, the dietary supplement manufacturer is responsible for ensuring that a dietary supplement product is safe and that health benefit claims are substantiated before a product is marketed. The FDA is ultimately responsible for taking action against any unsafe dietary supplement product after it reaches the market. To this end they have issued guidelines for good manufacturing practices (GMPs) that cover material packaging, labeling and custody, provenance and identity, strength, purity, chemical composition and contaminants. Good manufacturing practices require manufacturers to test products for contaminants before release, and new ingredients must be registered with the FDA if they are not Generally Regarded as Safe (GRAS)-listed. Here certified reference materials become valuable for GMPs through demonstration of method accuracy, and for conducting comparative measurements against products destined to enter the market. Typically, consumers are likely to be more familiar with the marketing claims and purported health benefits of dietary supplements, and less knowledgeable about material origin or possible safety concerns. Therefore rigorous quality assurance and product testing become important, with goals directed toward improving safety and labeling information, and thoroughly documenting a product's health benefits and risks.

The provenance of dietary supplement source materials (natural products, synthetic material or mineral blends), in addition to the preparation methods used to preserve or extract desired chemical constituents may influence the concentration and effectiveness of active ingredients. Also influenced are the amounts of concomitant toxicants, such as heavy metals. For example, Mindak et al. reported on Pb concentrations in 324 brands of women's and children's vitamins [3]. Most products presented low Pb mass fraction values (< 1 mg/kg), but a small number of products reflected Pb mass fraction values that were a concern for exposure

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risk in children. High levels of toxic metals such as As, Cd, Hg and Pb have been found in certain supplements, including ayurvedic medicines [4]. Exposure to heavy metals in dietary supplements is enough of a concern in Europe that legislative directives have been promulgated, setting maximum levels for elements such as Cd (1 mg/kg in non-seaweed supplements), Hg (0.1 mg/kg), and Pb (3 mg/kg) [5]. Exceedance of such levels could trigger a market or border notification through the European Commission Rapid Alert System for Food and Feed (RASFF). The RASFF recorded 855 notifications related to toxic metals (16% of total notifications) over a 4 year period (2003–2007) covering many categories, including dietary supplements [6].

Where contamination testing of products is required to demonstrate dietary supplement product safety, accurate trace analytical measurements are needed to assess the consistency and quality of natural products obtained from various suppliers, the repeatability of product preparation schemes, and country- or region-specific regulations that dictate lower maximum levels of toxic constituents. Reference materials certified for trace element content are needed to provide matrix-matched chemical measurement standards for validation of analytical methods and for laboratories pursuing various forms of accreditation or participating in proficiency testing programs, where traceability to higher order national or international metrological standards must be demonstrated and/or documented [7]. The National Institute of Standards and Technology (NIST) Chemical Sciences Division within the Material Measurement Laboratory is very heavily involved in developing analytical methods for dietary supplement products characterization and has produced many dietary supplement Standard Reference Materials (SRMs) certified for active ingredients and inorganic and organic chemical contaminants. NIST works closely with the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) and the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) on the production of these materials. A recent publication highlights NIST's inventory of dietary supplement SRMs that are certified for trace element content, including SRMs currently under development [8,9].

Isotope dilution quantification has been applied at NIST to assign Cd mass fraction values to plant-based and mineral-based dietary supplements and foods [10,11]. It is broadly applied by many research institutions to quantify Cd in environmental and biological samples [12–17], clinical samples [18,19], and utilized to monitor Cd in foodstuffs and agricultural products [20–23]. Cadmium isotope dilution ICP-MS measurements dictate monitoring of several isotope pairs to properly assess spectral interferences, regardless of the sample type, and often require implementing instrumental remedies and/or separation strategies to achieve accurate results. Pre-concentration and matrix reduction strategies can reduce the impact of interferences and matrix suppression effects when measuring Cd at trace levels using ICP-MS. In this report, we share the methodologies used for the assignment of a Cd mass fraction value to NIST SRM 3280 Multivitamin/Multielement Tablets using isotope dilution quantification.

2. Materials and methods

2.1. Samples and control materials

NIST SRM 3280 Multivitamin/Multielement Tablets is a material developed jointly between NIST and NIH ODS, intended for method validation for the determination of vitamins, carotenoids and trace elements. One unit of this SRM material consists of five bottles, with each bottle containing 30 tablets. The control materials used for verification of method accuracy were NIST SRM 3243 Ephedra-Containing Solid Oral Dosage Form and SRM 2709a San Joaquin Soil, with respective Cd mass fraction values (mean $\pm$ 95% expanded uncertainty) of 0.1218 $\pm$ 0.0033 mg/kg and 0.371 $\pm$ 0.002 mg/kg.

2.2. Sample preparation protocols

The microwave sample dissolution procedure involved pre-digestion spiking of nominal 0.25 g aliquots of ground SRM 3280 samples and SRM controls with ^{111}Cd for quantification of cadmium mass fraction by isotope dilution mass spectrometry (IDMS). All samples and spikes were weighed by difference into polytetrafluoroethylene (PTFE) vessels using a five-place balance that had been internally calibrated and checked using external weights (nominal 1 g check weight) prior to use. The microwave apparatus used was a CEM MARS5 equipped with Express vessels (CEM Inc. Matthews, NC). The method was programmed as follows: (1) ambient to 200 °C temperature ramp over 10 min at 1200 W, and (2) 60 min hold at 200 °C, 1200 W. The acid decomposition medium consisted of 9 mL of high purity (Optima grade, Fisher Scientific, Pittsburgh, PA) concentrated nitric acid (HNO_3) +3 mL of high-purity (Fisher Optima), concentrated hydrofluoric acid (HF). Precipitates, possibly titanium compounds (SRM 3280) or insoluble fluorides were present in the sample digests. Subsequently, samples were taken to near dryness on a hot plate in acid-leached perfluoroalkoxy beakers to remove HF. Additional HNO_3 (≈3 mL) and water (≈3 mL) were added after HF removal to redissolve the samples. The precipitates were eliminated and digests were clear after the entire procedure was completed.

The details and figures of merit for the separation methodology applied have been reported previously, and include discussion of column properties and technologies and specific procedures applied for matrix reduction, sample loading and Cd analyte elution [24]. The flowchart in Fig. 1 delineates the various method steps applied to isolate Cd from sample matrices containing mg/kg levels of Mo and Sn. Vacuum-assisted, solid phase extraction (SPE) cleanup was performed on all samples previously subjected to the hot plate procedure, in order to sequester Cd and remove Mo and Sn from the SRM 3280 samples and SRM control matrices, and establish procedural blanks. These elements are present at greater than tens of mg/kg in SRM 3280 and create known MoO^+ molecular ion interferences and Sn isobaric interferences that compromise the envelope of monitored Cd isotopes: ^{111,112,113,114}Cd. The samples were first passed (flow rate≈1 mL/min) through a 6 cm^3, 500 mg Agilent (Santa Clara, CA) thiourea solid phase extraction metal scavenger cartridge (high Cd selectivity). This step served to remove a significant quantity of non-complexing metals and Mo and Sn from the system. It should be noted that the thiourea support shows high selectivity for Pd, so the ^{110}Cd isotope (a potential candidate for IDMS measurement that would be subject to isobaric ^{110}Pd interference) was not considered in this study. The captured Cd was eluted with a 4% mass fraction reagent grade (99% purity) thiourea solution. Cadmium was precipitated from the thiourea solution in hydroxide and sulfide forms (isolating Cd from any residual Mo, which does not precipitate), through application of magnesium hydroxide co-precipitation. Residual Sn remained in the Cd sample fraction, but at a significantly reduced level. After precipitation, the samples were centrifuged at 58.33 Hz for 5 min and the thiourea-containing supernatant was discarded. The pellet was washed with water and then re-dissolved in high-purity, concentrated hydrochloric acid to facilitate loading of the Cd onto a water wettable, mixed-mode polymeric sorbent strong anion-exchange column (6 cm^3, 500 mg Waters (Milford, MA) Oasis MAX). The sample was washed with 5 mL of 0.6 mol/L HCl solution to remove residual cations, anionic Sn, and hydroxide from the system. Cadmium was eluted with 5 mL of 2% (volume fraction) HNO_3.

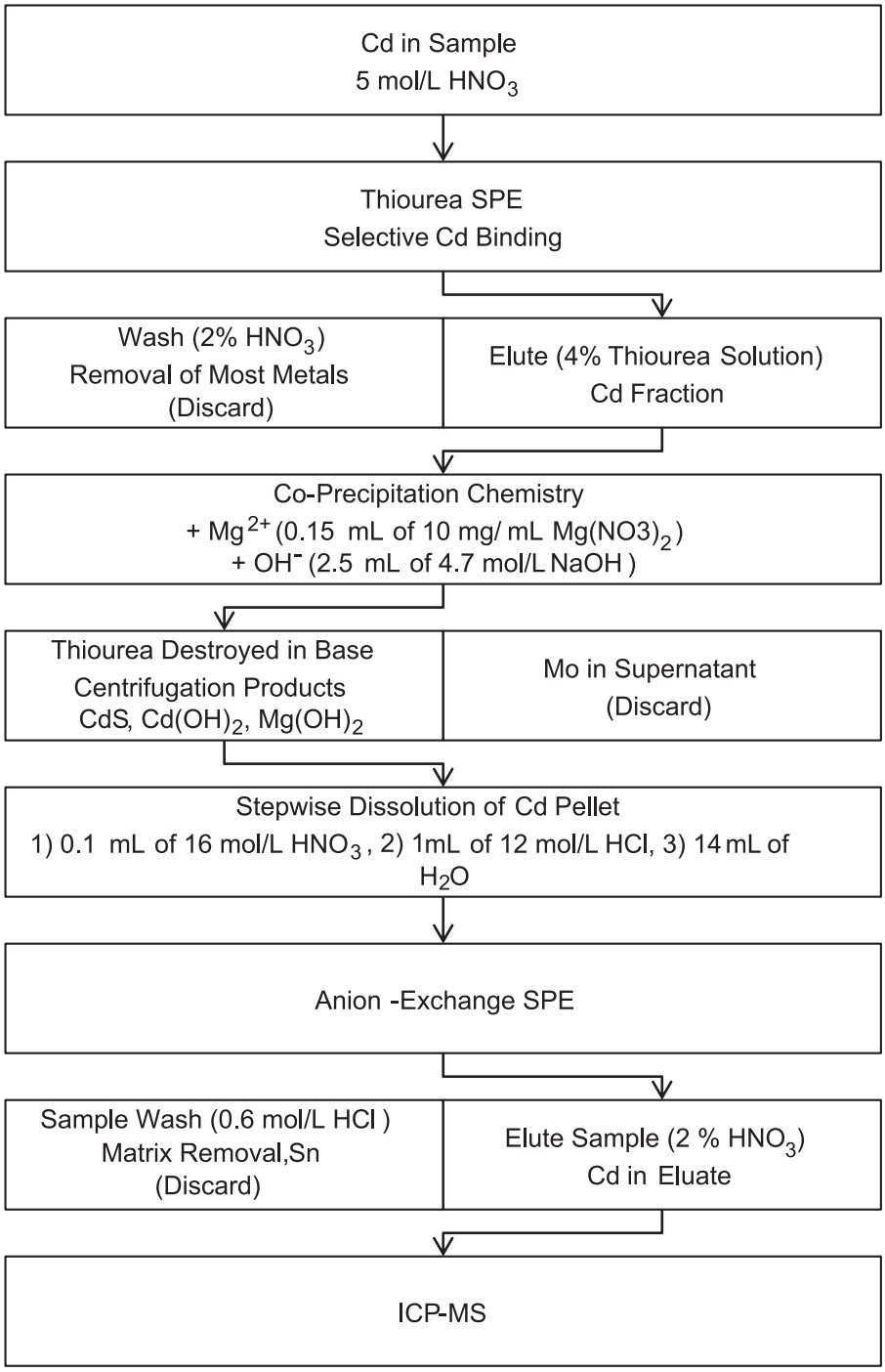

Fig. 1. Flow chart summarizing the matrix separation scheme for Cd in SRM 3280, and SRM 2709a and SRM 3243 control samples.

3. Spike calibration and sample spiking protocols for isotope dilution inductively coupled plasma mass spectrometry (ID-ICP-MS)

The calculations for the spike calibration and analytical samples were performed using the isotope dilution equation [25]. Standard Reference Material 3108 Cadmium (Lot. no. 060531) was used to calibrate the isotopic spike solution. The spike solution was prepared from a ^{111}Cd spike (95.29% abundance, ORNL Lot. 181201), obtained from the Oak Ridge National Laboratory (ORNL) Office of Isotopes Program (Oak Ridge, TN). Nominal 0.080 mg/kg natural (SRM 3108) and 0.080 mg/kg ^{111}Cd spike solutions were prepared, to facilitate calibration of the spike solution by reverse IDMS. Four gravimetric blends of the natural (0.25 g) and isotopic Cd (0.15 g) solutions were produced and measured (yielding approximate ^{111}Cd/^{113}Cd and ^{111}Cd/^{114}Cd isotopic ratios of 5.4 and 2.4, respectively).

The appropriate amount of spike to add to the spike calibration and SRM 3280 samples was determined by modeling error magnification factors for various ^{111}Cd/^{113}Cd and ^{111}Cd/^{114}Cd ratios in the spiked samples, and considering the optimum ratio of 1, which would yield the best ICP-MS measurement precision. The natural abundances of ^{111}Cd and ^{113}Cd are similar, so samples must be spiked such that resultant measured ^{111}Cd/^{113}Cd ratio is >1, in order to avoid inflated error magnification factors near this lower bound. A ^{111}Cd/^{113}Cd ratio of approximately 14 produces the lowest

error magnification factor, which is set by the natural sample and spike abundances for the $^{111}Cd/^{113}Cd$ system. A compromise $^{111}Cd/^{113}Cd$ ratio of 5.4 was chosen, yielding an approximate error magnification factor of 1.27, and correspondingly for the $^{111}Cd/^{114}Cd$ ratio, an approximate ratio of 2.4 with an error magnification factor of 1.25. Spiked samples and spike calibration blends were programmed to be similar in both concentration and measured isotope ratio. Approximately 0.58 μg of spike was added for every 1 μg of analyte to achieve the desired ratios in the analytical samples.

4. Instrumental measurement procedures

All samples were measured via quadrupole collision cell ICP-MS (Q-CCT-ICP-MS) on a quadrupole system and via sector field (SF)-ICP-MS equipped with a desolvating nebulizer system (Aridus II, Cetac, Omaha, NE). The quadrupole MS measurements were collected with a Thermo Scientific (Franklin, MA) X Series II inductively coupled plasma mass spectrometer, operating with a collision cell gas composition of 8% hydrogen in balance helium. The SF-ICP-MS measurements were collected with a Thermo Scientific (Bremen, Germany) Element XR ICP-MS system. The quadrupole MS routine utilized peak jumping, with each of five replicate runs consisting of 425 sweeps (59 s acquisition time), with dwell times of 15 ms for $^{111,112,113,114}Cd$, $^{118,120}Sn$ and ^{95}Mo, with one channel per peak monitored for each isotope. The same suite of isotopes plus ^{98}Mo was measured in low-, medium- and high-resolution modes via SF-ICP-MS, using electric sector scanning (ESCAN) and triple detector mode, with three runs and 30 passes per sample. Relevant instrument parameters for SF-ICP-MS in low resolution were 100 channels per peak, 1 ms sample time, 5% integration window and integration type set to average. Medium resolution settings were 30 channels per peak, 10 ms sample time, 60% integration window and integration type set to peak top. High resolution settings were 60 channels per peak, 10 ms sample time, 50% integration window and integration type set to peak top. The settings for the desolvating nebulizer system were 7.6 L/min sweep gas (Ar) and 8 mL/min addition gas (N_2), with factory preset temperature settings of 110 °C for the spray chamber and 160 °C for the desolvation region.

5. Results and discussion

The Mo/Cd mass fraction ratio in SRM 3280 is approximately 882, or 1036 on a mole fraction ratio basis. Similarly, the Sn/Cd mass fraction ratio in SRM 3280 is approximately 138, or 131 on a mole fraction ratio basis. The Mo- and Sn-based interferences that affect the Cd isotopes cannot be resolved by high-resolution ICP-MS. Although it may be possible to measure Cd isotope ratios in the presence of high amounts of concomitant Mo, it would be difficult to achieve the requisite oxide percentages using only instrumental remedies (collision cell or desolvating nebulizer and/or low oxide forming sampler and skimmer cones). Fig. 2 plots the expected $^{111}Cd/^{113}Cd$ ratio in a natural (unspiked) sample of SRM 3280, as a function of molybdenum oxide levels, considering the Cd/Mo mass fraction ratio in SRM 3280, and accounting for ionization potential and isotopic abundance differences in the elements and isotopes studied. The expected $^{111}Cd/^{113}Cd$ ratio data were generated using ionization energies of 684.3 kJ/mol for Mo and 867.8 kJ/mol for Cd [26], and isotopic abundances of 15.92% (^{95}Mo), 9.55% (^{97}Mo), 12.80% (^{111}Cd) and 12.22% (^{113}Cd) [27]. The data are compared to a theoretical $^{111}Cd/^{113}Cd$ ratio = 1.047, based on IUPAC isotopic compositions for Cd [27]. The vertical boundaries in Fig. 2 bracket the range of oxide conditions that can be considered routinely achievable using desolvation and or collision cell methodologies [28,29]. The theoretical isotope ratio is only achieved at molybdenum oxide levels on the order of 0.0001% or lower for the SRM 3280 sample. Without first employing a column-based matrix separation methodology [17], or other matrix separation means, for example, hydride generation ICP-MS [30], the Cd isotope ratio measurements would be relegated to occur in an oxide regime that would compromise accuracy and precision. One possible solution to measuring Cd in samples containing relatively higher amounts of Mo is to use O_2 as a collision cell gas to mass shift the MoO^+ and $MoOH^+$ molecular ion isobars to higher order oxides [29,31]. This strategy could be subject to problems associated with

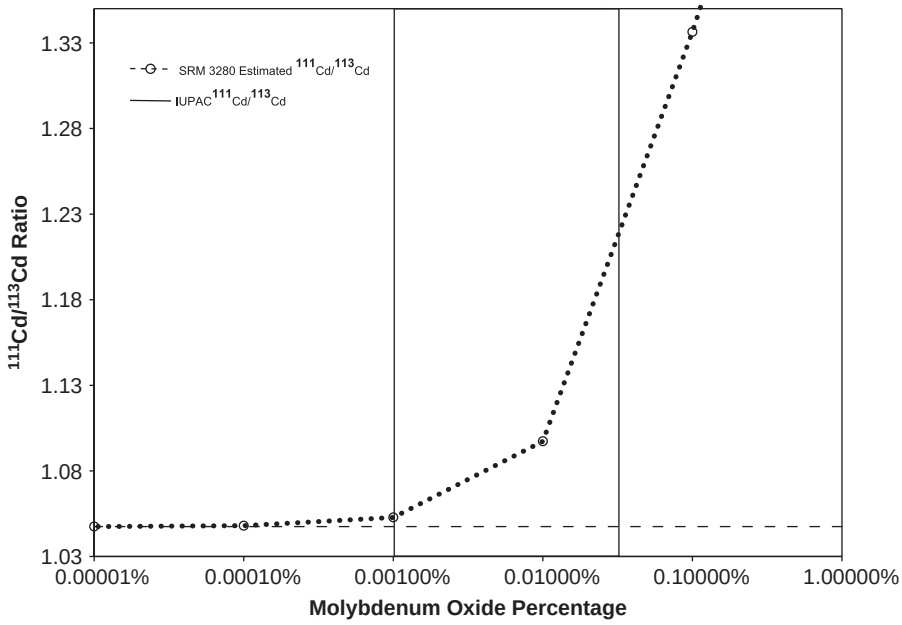

Fig. 2. Plot showing effect of Mo-oxide contributions on the estimated $^{111}Cd/^{113}Cd$ ratio for SRM 3280. The vertical boundaries between 0.001% and 0.05% bracket the range of oxide levels that are routinely achievable using desolvation nebulizer and collision cell technology.

introduction of high matrix samples that could cause ion suppression effects for trace-level analytes, and could compromise efficiencies of ion molecule reactions occurring inside most collision cells [32] (i.e., those operating without a Q1 quadrupole filter), wherein all ions are introduced into the pressurized collision cell without preselection of only Cd ions and their interfering Mo-based isobars.

Fig. 3 shows medium resolution ESCAN mass spectra (90% mass window for each isotope), comparing the relative amounts of Mo, Sn and Cd present in a ^{111}Cd-spiked analytical sample of SRM 3280 and a ^{111}Cd-spiked process blank taken through the matrix reduction, sample cleanup procedure. The Mo and Sn concentrations are clearly lower than the Cd concentration in the processed vitamin sample. The final samples as prepared for ICP-MS contained much lower amounts of Mo relative to Cd, with approximate Mo/Cd mass fraction ratios of 0.05, compared to an original mass fraction ratio of 882, and similarly, approximate Sn/Cd mass fraction ratios of 0.08, compared to an original mass fraction ratio of 138. The overall matrix reduction procedure coupled with low oxide ICP-MS conditions (through employment of either collision cell or desolvating nebulizer), effectively mitigated the MoO^+ and $MoOH^+$ molecular ion species that would otherwise compromise the accuracy and precision of measured ^{111}Cd/^{113}Cd ratios. The ^{111}Cd/^{114}Cd ratio still required correction for Sn interference at the 114 isotope, even though the Sn background was significantly reduced during the sample cleanup procedure. The goal emphasized during the development of the sample cleanup methodology was elimination of Mo to allow for measurement of ^{111}Cd/^{113}Cd ratios, in order to execute IDMS. The sample cleanup procedure favors rejection of Mo over Sn, because the magnesium hydroxide co-precipitation chemistry rejects Mo more strongly than Sn. The subsequent anion-exchange

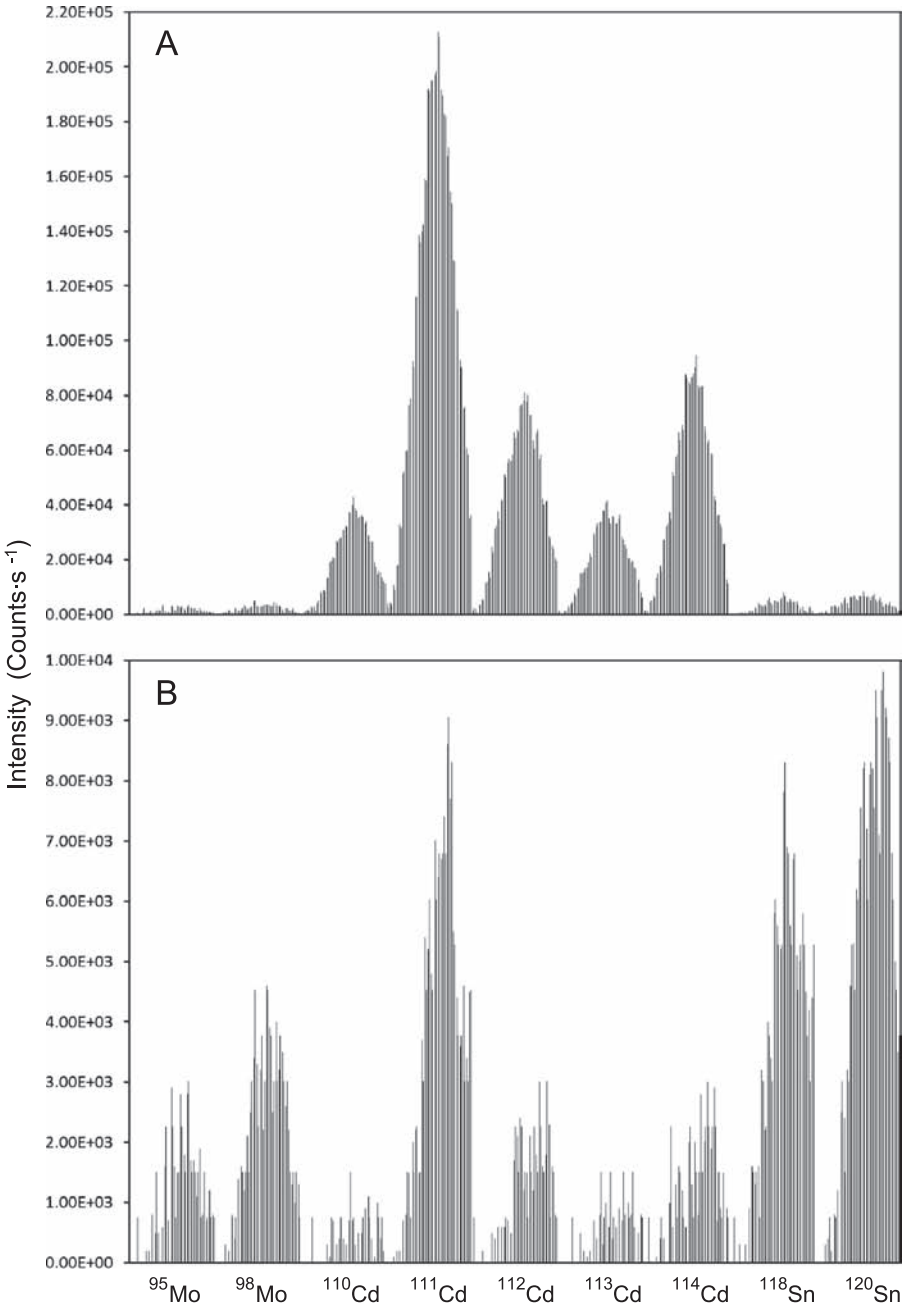

Fig. 3. Medium resolution SF-ICP-MS ESCANs (90% mass window) of Mo, Cd and Sn isotopes in a ^{111}Cd-spiked sample digest of SRM 3280 (A) and corresponding process blank (B), taken through the Mo and Sn reduction procedures.

step was executed using an aggressive hydrochloric acid gradient to eliminate salts from the co-precipitation reaction, with less emphasis placed on completely separating Cd and Sn fractions. The resolution of the Cd/Sn separation could be improved further by executing the anion exchange separation with a less aggressive (more time consuming) decrease in the hydrochloric acid elution gradient [33], which could potentially eliminate the need for mathematical Sn interference corrections for either the ^{112}Cd or ^{114}Cd isotopes.

5.1. Cd mass fraction results

The Cd mass fraction results obtained for the individual units of SRM 3280 tested are presented in Table 1, with associated summary statistics. The results obtained using either ^{111}Cd/^{113}Cd or ^{111}Cd/^{114}Cd ratios compare favorably across the Q-CCT-ICP-MS and SF-ICP-MS instrument platforms, and for the various modes of resolution employed. These data were used collectively to assign a Cd mass fraction and expanded uncertainty value to SRM 3280, after considering various sources of uncertainty using ISO guidelines. The Type A uncertainty contributions considered were sample repeatability, blank correction, spike calibration and mass bias correction. Type B uncertainty contributions included uncertainty in the certified moisture content for SRM 3280 and uncertainty in the certified S mass fraction value in the SRM 3154 calibrant solution. The uncertainty data are summarized in Table 2. The largest uncertainty factors for SRM 3280 were sample repeatability ($>35\%$ of the total uncertainty contribution) and moisture uncertainty ($>14\%$ of the total uncertainty contribution) for quadrupole, low and medium resolution SF-ICP-MS. The largest uncertainty factors for high resolution SF-ICP-MS were related to uncertainty parameters impacted by decreased isotope ratio measurement precision, such as the spike calibration and mass bias uncertainties, which combined, were responsible for $>80\%$ of the total uncertainty contribution. Typically NIST repeatedly measures a spike calibration solution as a surrogate to monitor drift in the mass bias correction factor over the sample measurement sequence. This prevents cycling of samples with natural and altered (spiked) Cd ratios. For ID-MS of Cd, a mass bias sample (SRM 3108 Cd Solution) is measured early in the experimental sequence and immediately calibrated with a spike calibration sample to establish a mass bias correction factor that needs to be applied to the measured isotope ratios of all subsequent samples. A spike calibration solution possessing a ^{111}Cd/^{113}Cd or ^{111}Cd/^{114}Cd ratio similar to the spiked SRM samples is interspersed between unknown samples and measured over the course of the experiment to monitor isotope ratio measurement repeatability. These repeated measures can be used to assess the drift in the isotope ratio used to calculate instrumental mass bias correction factors, and a drift function can be established (if necessary) to change the mass bias correction factor appropriately for each analytical sample. Isotope ratio repeatability data was collected for each mode of ICP-MS tested, over the course of a 9 h experiment and no drift corrections were applied to the mass bias correction factors, but the uncertainties were considered in the uncertainty budgets for the analytical samples. The Q-CCT-ICP-MS isotope ratio repeatability (expressed as percent relative standard deviation, % RSD) was minor (0.42% RSD for ^{111}Cd/^{113}Cd, $n=5$ repeat measures, and 0.36% RSD for ^{111}Cd/^{114}Cd, $n=5$ repeat measures). Similarly, the isotope ratio repeatability was (0.59% RSD and 0.68% RSD) for ^{111}Cd/^{113}Cd and (0.54% RSD and 0.36% RSD) for ^{111}Cd/^{114}Cd in low and medium resolution modes, respectively. The isotope ratio measurement repeatability was worse for the high-resolution mode of operation

Table 1
Cadmium mass fraction data (mg/kg) and summary statistics for individual units of SRM 3280 for Q-CCT-ICP-MS and SF-ICP-MS measurement modes.

SRM 3280 bottle no.	^{111}Cd/^{113}Cd Q-CCT-ICP-MS	^{111}Cd/^{114}Cd Q-CCT-ICP-MS	^{111}Cd/^{113}Cd SF-ICP-MS (LR)	^{111}Cd/^{114}Cd SF-ICP-MS (LR)	^{111}Cd/^{113}Cd SF-ICP-MS (MR)	^{111}Cd/^{114}Cd SF-ICP-MS (MR)	^{111}Cd/^{113}Cd SF-ICP-MS (HR)	^{111}Cd/^{114}Cd SF-ICP-MS (HR)
2	0.0802	0.0801	0.0798	0.0793	0.0799	0.0790	0.0806	0.0791
12	0.0803	0.0803	0.0795	0.0801	0.0802	0.0788	0.0807	0.0823
26	0.0795	0.0796	0.0799	0.0796	0.0799	0.0779	0.0811	0.0818
38	0.0808	0.0804	0.0809	0.0800	0.0799	0.0800	0.0815	0.0807
44	0.0802	0.0800	0.0806	0.0804	0.0801	0.0795	0.0812	0.0807
57	0.0806	0.0806	0.0810	0.0810	0.0805	0.0800	0.0791	0.0802
64	0.0797	0.0797	0.0799	0.0802	0.0803	0.0793	0.0783	0.0783
75	0.0817	0.0816	0.0834	0.0831	0.0834	0.0820	0.0820	0.0821
86	0.0794	0.0792	0.0797	0.0807	0.0796	0.0789	0.0771	0.0779
104	0.0796	0.0794	0.0806	0.0807	0.0794	0.0786	0.0780	0.0787
Mean	0.0802	0.0801	0.0805	0.0805	0.0803	0.0794	0.0800	0.0802
Standard deviation	0.0007	0.0007	0.0011	0.0010	0.0011	0.0011	0.0017	0.0016
% RSD	0.89	0.86	1.41	1.28	1.43	1.41	2.11	2.03

Table 2
Uncertainty budget data (mg/kg) for Cd in SRM 3280 Multivitamin/Multielement Tablets for Q-CCT-ICP-MS and SF-ICP-MS measurement modes.

SRM 3280 bottle no.	^{111}Cd/^{113}Cd Q-CCT-ICP-MS	^{111}Cd/^{114}Cd Q-CCT-ICP-MS	^{111}Cd/^{113}Cd SF-ICP-MS (LR)	^{111}Cd/^{114}Cd SF-ICP-MS (LR)	^{111}Cd/^{113}Cd SF-ICP-MS (MR)	^{111}Cd/^{114}Cd SF-ICP-MS (MR)	^{111}Cd/^{113}Cd SF-ICP-MS (HR)	^{111}Cd/^{114}Cd SF-ICP-MS (HR)
Measured Value	0.0802	0.0801	0.0805	0.0805	0.0803	0.0794	0.0800	0.0802
Type A	0.0003	0.0003	0.0005	0.0004	0.0005	0.0005	0.0015	0.0011
Type B	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
Combined uncertainty	0.0004	0.0004	0.0005	0.0005	0.0005	0.0006	0.0015	0.0011
Effective DF	43	46	25	31	28	19	9	12
Coverage factor	2.02	2.01	2.06	2.04	2.05	2.09	2.27	2.17
Expanded uncertainty (U)	0.0008	0.0007	0.0011	0.0010	0.0011	0.0012	0.0035	0.0024
Relative U (%)	0.96	0.91	1.40	1.26	1.38	1.46	4.39	2.98

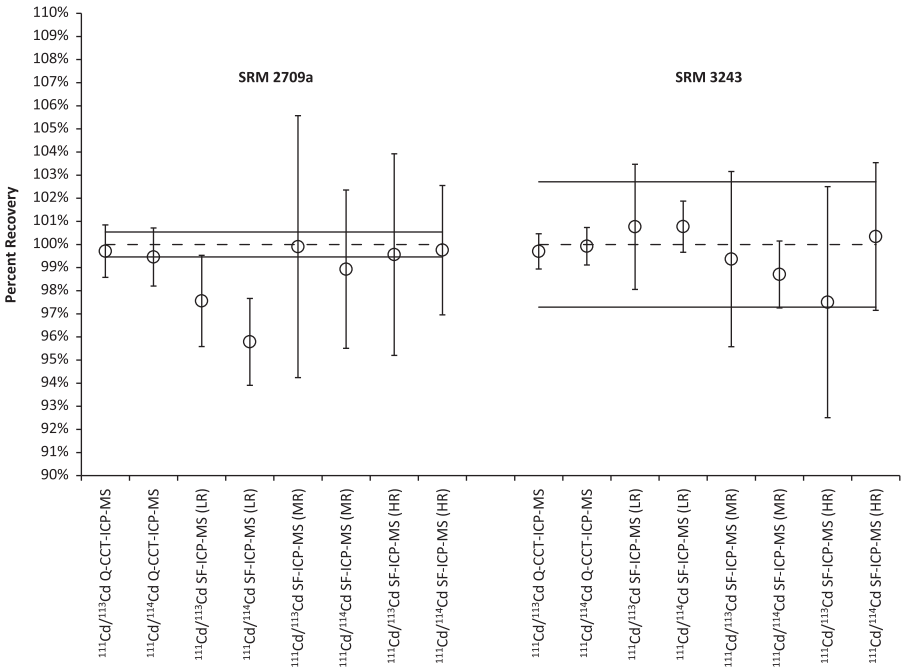

Fig. 4. Recovery plots for the SRM 2709a and SRM 3243 control materials as a function of Q-CCT-ICP-MS and SF-ICP-MS measurement modes. The data reflect the mean of three replicate samples taken through the sample cleanup and ICP-MS measurement procedures. The measured mass fraction data are normalized to the certified values for each control material, with uncertainty bars representing relative expanded uncertainties. Dotted (100% recovery line) and solid horizontal lines represent, respectively, the certified values and corresponding relative expanded uncertainties.

(approximately 2.70% RSD for $^{111}Cd/^{113}Cd$ and 1.90% RSD for $^{111}Cd/^{114}Cd$), with a random (not systematic) quality to the drift in isotope ratios. The SF-ICP-MS data could likely be improved further if the samples were measured as separate sequences in each mode of resolution, because this would prevent physical switching movement of the slits in between each analytical sample, however, at a significant cost of time and resources.

5.2. Control data

Recovery plots for the SRM 2709a and SRM 3243 control materials are shown in Fig. 4 for the various ICP-MS measurement modes. The data are normalized to the certified values of the respective control materials and presented with relative expanded uncertainties. The recoveries for both control samples are near 100% across the various ICP-MS measurement modes, except for the SRM 2709a low-resolution SF-ICP-MS data, where the artifact low recoveries result from high count rates for the measured Cd isotopes, in excess of 10×10^6 counts/s. One interesting trend that held for SRM 3280 and both control materials tested is that Q-CCT-ICP-MS data produced lower expanded uncertainties than any mode of SF-ICP-MS for the same samples (see relative expanded uncertainties in Table 2 or Fig. 4). This trend is most likely related to more stable conditions for the conventional nebulizer/Peltier cooled spray chamber and precise control of the collision cell gas pressure in the Q-CCT-ICP-MS system. The desolvating nebulizer interfaced to SF-ICP-MS is very sensitive to small changes in sweep gas and addition gas flow rates and environmental or laboratory factors such as static and temperature effects. The increased uncertainties for the medium- and high-resolution SF-ICP-MS data relative to the corresponding low-resolution data are most likely related to the increased isotope ratio precision achievable for flat-top peaks measured in low-resolution mode, higher uncertainties due to isotope ratio measurement repeatability in the medium and high resolution modes, and frequent changes in physical slit position required to capture Cd data in the three resolution modes.

5.3. Blanks

The absolute mean blank for Cd was 0.64 ± 0.06 ng ($n=6$ procedural blanks), based on calculating the grand mean of the absolute blanks obtained for each ICP-MS measurement mode for the $^{111}Cd/^{113}Cd$ and $^{111}Cd/^{114}Cd$ isotope ratios. Blank corrections were approximately 2.8%, 1.85% and 0.6%, respectively, for the SRM 3280, SRM 3243 and SRM 2709a materials. The Cd blanks are higher by approximately a factor of 36 compared to Cd blanks obtained using anion-exchange separations performed in a clean room at NIST in Gaithersburg, MD [10]. It is likely that the two-step SPE procedure using commercial (off the shelf) cartridges, the coprecipitation reagent purity of magnesium nitrate hexahydrate and purity of the thiourea used for elutant solutions, and performing laboratory operations in a positive pressure, HEPA filtered, general laboratory, versus true clean room laboratory conditions contributed to an overall higher blank. Improving the procedural blanks will be necessary for ultra-trace Cd determinations in the presence of high amounts of Mo and Sn, but the blank achieved was not prohibitive to assignment of the Cd mass fraction value to SRM 3280 at 80.15 ± 0.86 ng/g.

6. Conclusions

NIST has described the procedures applied to assign Cd mass fraction in a vitamin matrix, fortified in many trace elements including Mo present at 70.7 ± 4.5 mg/kg and containing Sn at 11.1 ± 0.9 mg/kg (mean $\pm$ 95% expanded uncertainty). The matrix separation procedure applied leveraged thiourea-based SPE to selectively bind Cd isotopes, in conjunction with a magnesium hydroxide co-precipitation chemistry and anion-exchange SPE to significantly reduce Mo and Sn levels to allow for quantification of Cd via isotope dilution mass spectrometry, measuring either the $^{111}Cd/^{113}Cd$ or $^{111}Cd/^{114}Cd$ isotope pairs via collision cell ICP-MS or desolvating nebulizer coupled to SF-ICP-MS.

NIST disclaimer

The commercial instruments and products utilized in this work are described only to communicate the details of the analytical procedures applied. These commercial items are not specifically endorsed or recommended by NIST. The described procedures required the use of concentrated nitric, hydrochloric and hydrofluoric acids; appropriate safety precautions were considered and requisite personal protective equipment were donned while performing the work.

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