# Simultaneous separation of arsenic and cadmium from interfering salt matrix of multivitamin/mineral supplements by sequential coprecipitation and determination by inductively coupled plasma mass spectrometry

**Ermira Begu**[a], **Brittney Snell**[a], and **Zikri Arslan**[a,*]

[a]Jackson State University, Department of Chemistry, Physics and Atmospheric Sciences, Jackson, MS 39217 USA

## Abstract

Multivitamin/mineral (MVM) supplements possess highly saline matrix which, unless eliminated, precludes accurate determination of trace amounts of toxic metal impurities by inductively coupled plasma mass spectrometry (ICP-MS). Multi-step separations (up to four-steps) are described in literature; often for single element determinations due to difficulties in removing the matrix components. In this study, we developed a three-step sequential coprecipitation procedure for simultaneous separation of As and Cd impurities from MVM supplements for determination by ICP-MS. The procedure provided effective elimination of salt matrix, including Ca, Mg and KCl along with the interfering molybdenum (Mo) and tin (Sn) from MVM solutions. KCl, Mo and Sn were removed by two-step $Mg(OH)_2$ coprecipitation to about 34 $\mu g\ mL^{-1}$ K (ca. 31 $\mu g\ mL^{-1}$ Cl) and 0.4 $\mu g\ mL^{-1}$ Mo. Levels of Sn and Na were not significant. A third coprecipitation of the resulting MVM solution with HF + $NH_4OH$ mixture precipitated virtually all Ca and Mg to as low as 1 and 10 $\mu g\ mL^{-1}$, respectively. The recoveries for As and Cd in the spiked MVM solutions were about 96% and 95%, respectively. The accuracy of the method was validated with analysis of multivitamin/multielement tablets certified reference material (SRM 3280). Experimental values were 112 ± 37 ng $g^{-1}$ for $^{75}$As, and 76 ± 5, 79 ± 5, and 78 ± 7 ng $g^{-1}$ for $^{110}$Cd, $^{111}$Cd and $^{114}$Cd isotopes, respectively, that were not significantly different from the certified values of As (132 ± 44 ng $g^{-1}$) and Cd (80.2 ± 0.9 ng $g^{-1}$) at 95% confidence level. Several commercially available MVM supplements were analyzed with the procedure. Mean As levels measured in the tablets varied between 24 and 128 ng $g^{-1}$ and that for Cd were between 28 and 125 ng $g^{-1}$ indicating total amount of As or Cd ingested per serving size were below the safe daily exposure limits. In addition, the results obtained for As and Cd with the procedure were lower in comparison to the values reported in literature indicating that ICP-MS analysis of complex MVM supplements could be prone to higher risks of inaccuracy without removal of interfering matrix.

*Corresponding author. Tel: +1 601 979 2072; Fax: +1 601 979 3674, zikri.arslan@jsums.edu (Z. Arslan).

**Keywords**

Arsenic; cadmium; multivitamin/mineral supplement; coprecipitation; matrix removal; ICP-MS

## 1. Introduction

Dietary multivitamin/mineral (MVM) supplements contain essential nutrients, such as vitamins, minerals, amino acids, and macro/trace elements that are intended to augment daily diets. Over the last two decades, their consumption has increased significantly and today they have been increasingly used among children and adults, including pregnant women to remedy inadequate macro-and micro-nutrient intake [1,2,3,4], although there is no conclusive evidence to their potential benefits in treating nutritional deficiencies and medical conditions [5,6,7]. MVM supplements are regulated under the Dietary Supplement Health and Education Act of 1994 by the US Food and Drug Administration (FDA) [8], but there are no clear regulations for monitoring the manufacturing and public safety of these products. Consequently, consumers often rely on the contents labels and do not accurately know benefits and possible health risks of the products [3,9–12].

Various MVM supplements are commercially available to consumers under different brands in the form of hard tablets, liquid-gels (soft gels), chewable jellies and liquid concentrates, yet they all contain similar organic micronutrients, such as vitamins (A, B, C, D, E and K), flavonoids, folic acid and biotin. Among the elemental nutrients, calcium (Ca), copper (Cu), magnesium (Mg), iron (Fe), potassium (K), manganese (Mn), phosphorous (P), and zinc (Zn) make up the majority of elemental nutrients of MVM supplements. Other trace element nutrients, such as boron (B), chromium (Cr), iodine (I), molybdenum (Mo), nickel (Ni), selenium (Se), tin (Sn) and vanadium (V) are added at microgram per gram (ppm) levels [9,12,13]. Ideally, MVM supplements should not contain any potentially toxic elements, such as arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb) that cause harmful effects on human health under chronic exposure. Nevertheless, they do contain toxic elements at varying levels depending on the raw minerals, their origin and chemical processes used in manufacturing [13–19].

In recent years, there has been an increasing interest in monitoring As and Cd impurities in dietary MVM supplements owing to their adverse effects on human health [4,9,12,13,15,16,20]. Arsenic is known to cause hepatic, renal, reproductive, and nervous systems disorders [21,22]. Cadmium is referred to as among the most toxic elements due to its long biological half-life (15–30 years). It largely accumulates in the kidneys in human body and hence chronic exposure to Cd could cause nephrotoxicity and kidney failure [23]. A number of studies have revealed that commercial MVM supplements contain both As and Cd impurities at varying levels [4,9,12,13,15,16,20]. Dolan et al. [15] reported as high as 4 $\mu g \ g^{-1}$ As and 0.4 $\mu g \ g^{-1}$ Cd in a number of dietary supplements. In another study, As levels from various MVM supplements were highly variable between 1 and as high as 16 $\mu g \ g^{-1}$ while that for Cd were between 0.5 and 3.8 $\mu g \ g^{-1}$ [20]. Evidently, As levels are in general an order of magnitude higher than Cd levels. Also, it should be noted that inorganic As species, As(III) and As(V), are more toxic than organic arsenic species, and hence speciation

of As is important to elucidate the health risks associated with As contamination in MVM supplements.

Chronic exposure to high levels of As and Cd are concerning for humans, especially for children and pregnant women, and thus development of appropriate methods is imperative to accurately monitor their levels in MVM supplements. Currently, inductively coupled plasma mass spectrometry (ICP-MS) is the most popular technique for testing the toxic elements impurities in MVM supplements due mainly to its excellent sensitivity [15,16,20,24–26]. Nonetheless, determination of trace As and Cd impurities is a difficult task due to the highly saline nature of MVM supplements. High salt content hampers the detection capabilities of ICP-MS instrument. In addition, potassium chloride (KCl) matrix of MVM solutions induces spectral interferences through $^{40}Ar^{35}Cl$ on monoisotopic $^{75}As$ while major Cd isotopes (e.g., $^{110}Cd$, $^{111}Cd$, $^{112}Cd$, $^{114}Cd$) suffer from the interferences of various molybdenum oxides, such as $^{94}Mo^{16}O$, $^{95}Mo^{16}O$, $^{96}Mo^{16}O$, $^{98}Mo^{16}O$. Tin (Sn) is also a common trace element nutrient of MVM supplements, which may confound the results of $^{112}Cd$ and $^{114}Cd$ isotopes due to overlaps of $^{112}Sn$ and $^{114}Sn$ respectively. To overcome such difficulties, high resolution (HR) ICP-MS and collision/reaction cell ICP-MS have been used in several studies [15,20], but it is hardly feasible to completely eliminate these spectral interferences even by using HR-ICP-MS instruments unless the interfering salt matrix (e.g., KCl, Mo and Sn) is removed prior to analysis.

Certified reference materials serve an indispensable role for quality assurance and development of suitable methods for elemental analysis of MVM supplements [16,27]. Recent reports, however, indicate that accurate measurements may not even be achieved with suitable reference materials owing to the fact that interferences of salt matrix could substantially confound the results from ICP-MS analysis. In their study, for instance, Avula et al. [20] used SRM 3280 (Multivitamin/Multielement Tablets standard reference material) in elemental analysis of various commercial MVM supplements by collision cell ICP-MS, but no values were reported for As and Cd, presumably chloride and molybdenum matrices of SRM 3280 precluded accurate measurements indicating the need for more sophisticated sample preparation tactics for analysis of complex MVM supplements.

In this study, we developed a sequential coprecipitation procedure for simultaneous separation of As and Cd from MVM matrix along with effective removal of salt matrix and interfering elements, including Na, K, Ca, Mg, Cl, Mo and Sn. Both As and Cd were quantitatively separated from the matrix of MVM solutions by sequential coprecipitations with triethylamine (TEA) and a mixture of hydrofluoric acid (HF) and ammonium hydroxide ($NH_4OH$). The procedure was validated with analysis of SRM 3280 (Multivitamin/Multielement Tablets) and applied to the determination of As and Cd impurities in various commercial MVM supplements by ICP-MS.

## 2. Experimental

### 2.1. Instrumentation

Measurements were made with a Varian 820MS inductively coupled plasma mass spectrometer (Varian, Australia). The ICP-MS instrument was equipped with collision

reaction interface (CRI) technology utilizing $H_2$ and He gases, a peltier-cooled double-pass glass spray chamber, an all-teflon Ari-mist nebulizer (SCP Science, Champlain NY), quartz torch, CRI-type Pt sampler and skimmer cones and all-digital detector (DDEM, Model AF250, ETP Australia). The instrument was optimized daily with 5 µg $L^{-1}$ solution of $^{138}Ba$, $^{25}Mg$, $^{115}In$, $^{140}Ce$, $^{208}Pb$ solution for optimal sensitivity, oxides ($^{156}CeO^+/$ $^{140}Ce^+ <$ 3%) and doubly charged ions ($^{138}Ba^{2+}/$ $^{138}Ba^+ < 2\%$). An internal standard (IS) solution was used for correcting the matrix effects and instrumental drift. The IS solutions contained 5 µg $L^{-1}$ of germanium (Ge), rhodium (Rh), rhenium (Re), and bismuth (Bi). $^{72}Ge$ and $^{185}Re$ were used for As and Cd, respectively. All standard and sample solutions were introduced to ICP-MS instrument manually. Data were acquired by ICP-MS Expert software package (Version 2.2 b126). Data were collected in mode peak hop mode using $^{75}As$, $^{110}Cd$, $^{111}Cd$ and $^{114}Cd$ isotopes. The concentrations of matrix elements, including Na, K, Ca, Mg, and P, and interfering Mo and Sn were measured simultaneously along with As and Cd. Measurements for $^{23}Na$, $^{25}Mg$, $^{26}Mg$, $^{31}P$, $^{39}K$, $^{43}Ca$ and $^{44}Ca$ were made with CRI mode. Hydrogen ($H_2$) was used as CRI gas (65 mL min-1) that was introduced through the skimmer cone. Mo and Sn determinations were made with $^{95}Mo$ and $^{98}Mo$, $^{118}Sn$ and $^{120}Sn$ isotopes using the same instrumental conditions for As and Cd. The operating conditions of the ICP-MS instrument are shown in Table 1.

## 2.2. Materials and solutions

All solutions were prepared with double deionized water (18.0 MΩ cm resistivity). Trace metal grade nitric acid ($HNO_3$, BDH Aristar Plus), hydrochloric acid (HCl, Fisher Scientific)) and hydrofluoric acid (HF, Fisher Scientific) were used in sample dissolution and/or preparation of standard solutions. They were obtained from Fisher Scientific. Hydrogen peroxide ($H_2O_2$, Sigma Aldrich, 99.99%) was used for digesting multivitamin/ mineral samples. Trace metal grade triethylamine (TEA, 99.8%, Acros Organics) and ammonium hydroxide ($NH_4OH$, BDH Chemicals, Aristar Plus) were used for coprecipitations. A 1.0 µg $mL^{-1}$ multielement standard solution was prepared in 5% (v/v) $HNO_3$ from 1000 µg $mL^{-1}$ single element stock solutions (High Purity Standards, Fisher Scientific). The standard solution contained Al, As, Ba, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Sb, Se, Sr, Tl, V and Zn and used for spike studies and preparing calibration solutions. A tin (Sn) standard solution (10 µg $mL^{-1}$) was prepared separately in 2% (v/v) HCl and 2% (v/v) $HNO_3$ from 1000 µg $mL^{-1}$ single element stock solution.

For method development, commercially available Rite Aid complete multivitamin/ multimineral supplements was used. A stock solution was prepared by acid dissolution and analyzed for elemental content. Details of preparation and analyses are provided in the next section. Method validation was performed with SRM 3280 (multivitamin/multielement tablets) standard reference material purchased from National Institutes of Standards and Technology (NIST). Several multivitamin/mineral (MVM) samples were purchased from local pharmacy stores and analyzed for As and Cd impurities. All MVM samples were in the form hard tablets with the following codes: Century Adults (MVM-1), Rite Aid MVM (MVM-2), Kroger Complete MVM Supplement (MVM-3), Centrum Adults MVM (MVM-4), Equate MVM (MVM-5), Walgreens MV (Adults 50+) (MVM-6), SpectraVite CVS (MVM-7) and One-a-Day Men (MVM-8).

### 2.3. Preparation and characterization of MVM stock solution for method optimization

For method development and optimization of experimental conditions, samples of Rite Aid MVM tablets were dissolved/digested in $HNO_3$ and $H_2O_2$. This brand was chosen as the contents label declared the closest essential and trace element nutrient composition to that of SRM 3280. In addition, Rite Aid MVM contained very high level of molybdenum (160 μg/tablet as sodium molybdate) along with typical chloride (72 mg/tablet as KCl) which were key elements to optimize the procedures for As and Cd determinations. A total of 24 g MVM sample (16 tablets) were digested. A sample of 3 g (2 tablets, total 8 sets) were digested in 5 mL $HNO_3$ and 4 mL $H_2O_2$ in teflon vessels (Savillex) on a digestion block (DigiPrep, SCP Science, Champlain, NY). The tablets were first digested in 5 mL $HNO_3$ at 120 °C for 3 h, and an additional 2 h at 140 °C. Then, vessels were briefly cooled, opened and 4 mL $H_2O_2$ was added slowly. The contents were digested at 140 oC for additional hour to destroy the organics. These temperatures were opted to avoid over-boiling and excessive pressure build-up in teflon vessels from large amount sample.

After digestion, the MVM solutions were heated to near dryness at 120 oC to evaporate $HNO_3$ The resulting residue/pellet was suspended in 10 mL of 1% (v/v) $HNO_3$ and centrifuged to remove undissolved $TiO_2$ and $SiO_2$. The supernatant solution was evaporated in the teflon vessels again. The residue was then dissolved and heated in 2 mL $HNO_3$ and 1 mL $H_2O_2$ for complete digestion until dryness. Finally, all digests were dissolved in 5 mL of 5% (v/v) $HNO_3$ and combined in a 50-mL test tube. This solution was centrifuged for 30 min at 10,000 rpm on a centrifuge (Thermo Scientific Sorvall ST 16) to remove the suspending particles. The supernatant solution was transferred to an acid-cleaned polypropylene bottle and completed to 500 mL with deionized water. The acid concentration of the MVM stock solution was around 0.4% (v/v) $HNO_3$.

For elemental analysis, 0.1 mL aliquots (n = 5) of the MVM stock were diluted to 2 mL with 5% (v/v) HNO3. They were then analyzed by ICP-MS. Determinations of $^{23}Na$, $^{25}Mg$, $^{26}Mg$ $^{31}P$, $^{39}K$, $^{43}Ca$, $^{44}Ca$, $^{56}Fe$ and $^{57}Fe$ were made with CRI mode (see Table 1), while $^{55}Mn$, $^{63}Cu$, $^{65}Cu$, $^{66}Zn$, $^{68}Zn$, $^{95}Mo$, $^{98}Mo$, $^{118}Sn$ and $^{120}Sn$ were measured using normal operating conditions (non-CRI, Table 1). For Zn determinations, $^{66}Zn$ results were not utilized due to interference of $^{26}Mg^{40}Ar$. The concentrations of the major matrix and interfering elements in 500 mL stock solution were as follows: Ca ($4.6 \pm 0.3$ mg $mL^{-1}$), Mg ($3.6 \pm 0.2$ mg $mL^{-1}$), P ($2.9 \pm 0.3$ mg $mL^{-1}$), K ($4.2 \pm 0.3$ mg $mL^{-1}$), Fe ($91 \pm 3$ μg $mL^{-1}$), Cu ($65 \pm 5$ μg $mL^{-1}$), Mn ($96 \pm 8$ μg $mL^{-1}$) and Zn ($532 \pm 30$ μg $mL^{-1}$). Mo and Sn concentrations were $4.0 \pm 0.3$ μg $mL^{-1}$ and $0.10 \pm 0.004$ μg $mL^{-1}$, respectively. The concentration of Sn was lower than the declared value (ca. 0.5 μg $mL^{-1}$ equivalent to 10 μg Sn/tablet). To compensate for this deficiency, Sn concentrations in experimental MVM solutions were adjusted to 0.5 μg $mL^{-1}$ from 10 μg $mL^{-1}$ Sn stock solution throughout the method development studies.

### 2.4. Dissolution of SRM 3280 and commercial MVM samples

A sample of 10 tablets of SRM 3280 (1.5 g per tablet) were ground and homogenized. About 0.125 g sub-samples (n = 5) were digested in 4 mL $HNO_3$ in teflon vessels for 3 h at 160 ˚C on a digestion block. Then, the vessels were carefully opened and 2 mL H2O2 were

added to samples. The samples were heated for another 3 h at 160 ˚C. The lids were opened and contents were heated to dryness at 120 ºC. The residue was dissolved with 2 mL of 0.5% (v/v) HNO$_3$ and transferred to 2-mL microcentrifuge tubes, and then centrifuged at 10,000 rpm for 15 min to remove undissolved material. The supernatant solution was transferred to new micro-centrifuge tubes and the volume was completed to 2 mL. For commercial MVM tablets, 5 tablets (ca. 6 to 7.5 g sample) for each brand were ground, homogenized and stored in plastic bottles. About 0.15 g samples (n = 5) were digested in HNO$_3$ and H$_2$O$_2$ digested and prepared similarly as for the SRM 3280. The solutions were then processed concurrently with the coprecipitation procedure for separation of As and Cd from the MVM salt matrix for ICP-MS analysis.

### 2.5. Optimization of coprecipitation procedure

Coprecipitations in stock MVM solution was carried out in a sequential manner starting with TEA-assisted Mg(OH)$_2$ of As and Cd and other trace element nutrients. The schematic of the coprecipitation procedure is outlined in Fig. 1. Initially, a one-step or two-step coprecipitation with TEA was examined for removal of matrix salts and interfering elements (e.g., Mo and Sn). A volume of 1.5 mL of MVM stock solution (n = 4) was placed into 2-mL micro-centrifuge tubes, and spiked with 30 μL of 1.0 μg mL$^{-1}$ multielement solution and 100 μL of 10 μg mL$^{-1}$ Sn solution to introduce a spike concentration for 15 μg L$^{-1}$ for As and Cd, and 0.5 μg mL$^{-1}$ for Sn in 2 mL volume. First precipitation was performed by adding 100 μL TEA to the solutions. An intense Mg(OH)$_2$ coprecipitation occurred due to high level of Mg in highly saline medium. The suspensions were allowed to wait for about 5 min and then centrifuged at 12,000 rpm for 15 min. After discarding the supernatant solutions, the pellets were dissolved in 0.75 mL of 10% (v/v) HNO3 and completed to 1 mL with water. A volume of 0.5 mL was pipetted out and completed to 1 mL with 5% (v/v) HNO3 to determine recoveries of As and Cd, and elimination profiles of the matrix elements.

The remaining 1.5 mL solution was further treated with 100–110 μL TEA for second Mg(OH)$_2$ coprecipitation, which occurred fast but not as intense as the first indicating partial removal of the salt matrix in first precipitation. Similarly, suspensions were allowed for completion of precipitation and then centrifuged. The pellets were dissolved in 0.6 mL of 10% (v/v) HNO$_3$ and completed to 1.5 mL with deionized water. A volume of 0.5 mL was taken and completed to 1 mL with 5% (v/v) HNO$_3$ to determine As and Cd recoveries and matrix removal efficiency as in the first precipitation.

The third step involved the removal of persistent Ca and Mg via simultaneous CaF$_2$ – Mg(OH)$_2$ coprecipitation. A volume of 30 μL HF was first added to the remaining 1 mL MVM solution to induce CaF$_2$ precipitation. This step was relatively slow due to partial removal of Ca in previous two steps; solutions showed faint turbidity (e.g., weak precipitation) in about 10 min. Then, the same solutions were treated with 50, 100 and 150 μL volumes of NH4OH that accelerated CaF$_2$ precipitation by inducing Mg(OH)$_2$ coprecipitation. After completion of precipitation, suspensions were centrifuged similarly. At this stage, the supernatant solutions were transferred to new 2-mL micro-centrifuge tubes

and completed to 2 mL with 5% (v/v) $HNO_3$. Solutions were analyzed for As and Cd and the remaining matrix components by ICP-MS.

## 3.    Results and discussion

### 3.1.    Elemental recoveries and matrix elimination via sequential TEA coprecipitations

Major nutrient elements including, Ca, Mg, K, P, Cl, and Na make up about 35% of salt matrix of most MVM supplements. This amount increases to about 37% when trace metal nutrients, Fe, Mn, Cu and Zn are added. Triethylamine (TEA) is an alkylamine (weak base, $pK_b = 3.25$) which readily generates a pH between 10 and 11 in its aqueous solutions. Unlike $NH_4OH$, TEA does not coordinate with divalent or trivalent metal ions; consequently it does not form any water-soluble complexes as $NH_4OH$ does (e.g., $Cd(NH_3)_4^{2+}$). With this feature, TEA has been shown to be a very valuable reagent providing robust and quantitative scavenging of various of trace transition elements and heavy metals, including As and Cd, in the presence of Mg matrix [28]. Nevertheless, Mg and Ca, the two major matrix elements of MVM solutions, are carried over substantially in TEA-assisted $Mg(OH)_2$ coprecipitations; it was not feasible to fully eliminate these elements despite three-step sequential coprecipitation with TEA [16].

Similar pattern was observed in this study for Mg, Ca, P, K and Na (Fig. 2) via one-step or 2-step TEA coprecipitation. As shown in Fig. 2A, single precipitation with TEA was not effective for removal of Mg, Ca and P although K matrix decreased to as low as 380 μg mL$^{-1}$ from 4,200 μg mL$^{-1}$ (ca. 91% K removal). With two-step coprecipitation with TEA (e.g., TEA-TEA), Mg levels dropped from 3,600 μg mL$^{-1}$ to 1910 μg mL$^{-1}$ (ca. 47% removal) while Ca was reduced from 4,600 μg mL$^{-1}$ to about 2350 μg mL$^{-1}$ (ca. 49% removal). In contrast, most Mo and Sn were eliminated from MVM solutions (Fig. 2B) via two-step coprecipitation; Mo concentration dropped from 4 μg mL$^{-1}$ to about 0.6 μg mL$^{-1}$, and Sn concentration was about 0.2 μg mL$^{-1}$.

The recoveries for As (128%) and Cd (116%) were significantly high from direct determinations (e.g., no TEA, Fig. 2C) indicating significant interferences of $ArCl^+$ and various $MoO^+$ on As and Cd. It should be noted these values are for the artificially spiked MVM solutions (15 μg mL$^{-1}$ As or Cd) and thus the interferences are expected to worsen for actual samples with lower As and Cd impurities. It is also evident from Fig. 2C that both As and Cd coprecipitated onto $Mg(OH)_2$ with one-and two-step coprecipitation. For one-step TEA coprecipitation, recoveries were 111% and 106% for As and Cd, respectively. In comparison to direct determination, interferences were alleviated but could not be fully eliminated since interring matrix levels were still significantly high; 380 μg mL$^{-1}$ K (equivalent to 725 μg mL$^{-1}$ KCl) and 1.9 μg mL$^{-1}$ Mo (Fig. 2A and 2B). After two-step (TEA-TEA) coprecipitation, K and Mo concentrations decreased to about 45 μg mL$^{-1}$ and 0.6 μg mL$^{-1}$ affording more accurate determinations; the recoveries for As and Cd were about 103% and 101%, respectively.

### 3.2. Removal excess Mg and Ca matrix with combined HF-NH4OH coprecipitation

Sequential coprecipitations with TEA were not effective for eliminating Mg, P and Ca matrices that consequently carried over into the analysis solutions. As a result, the salt matrix content was still high to cause significant suppression of sensitivity (ca. 35–40%) and salt deposition on the sample and skimmer cones of the ICP-MS instrument. To overcome this hurdle, we attempted to retain As and Cd as fluoride complexes in the solution while precipitating Ca and Mg as $CaF_2$ and $Mg(OH)_2$. It was previously reported that both As and Cd form fluoride complexes in acidic solutions [29]. Fluoride complexes of As (e.g., arsenic hexafluoride $AsF^{6-}$) appear to be highly stable. We verified this phenomenon with preliminary trials that once a small volume of HF (e.g., 20–30 μL) was added to stock MVM solutions, it was not feasible to fully scavenge As from solution, even with an excess volume of TEA (e.g., 200 μL). In contrast, $CdF^+$ is a weak complex ($K_q = 5.8 - 6.4$) [30], and thus coprecipitated with $Mg(OH)_2$ upon addition of TEA [16]. Here we utilized NH4OH instead of TEA to avoid precipitation of Cd from weak $CdF^+$ complex, since $Cd^{2+}$ forms cadmium ammonia complex, $Cd(NH_3)_4^{2+}$, in ammonical solutions.

The results for combined HF + $NH_4OH$ coprecipitation are illustrated in Fig. 3A-C comparatively for HF and HF + $NH_4OH$ treatments. The MVM solutions coprecipitated twice with TEA (e.g., TEA-TEA) were treated with either 30 μL HF only or a combination of 30 μL HF and 100 μL $NH_4OH$ (see section 2.5). It was evident that addition of HF resulted in significant removal of Mg (482 μg $mL^{-1}$) and Ca (963 μg $mL^{-1}$) via $CaF_2$ coprecipitation (Fig. 3A). However, a more drastic decrease occurred for Mg and Ca levels with HF + $NH_4OH$ treatment when the pH of colloidal solutions containing HF were raised to alkaline pH (ca. pH 10) with $NH_4OH$ resulting in coprecipitation of virtually all Mg and Ca (Fig. 3A). The analysis solutions contained about 7 and 1.5 μg $mL^{-1}$ Mg and Ca. The HF + $NH_4OH$ treatment also favored the removal of P to some extent in comparison to the levels with TEA-TEA coprecipitation; P concentration was reduced to about 615 μg $mL^{-1}$ from 1415 μg $mL^{-1}$ measured in TEA-TEA treatment (see Fig. 2A). As can be seen in Fig. 3C that As and Cd were in the solution after HF + $NH_4OH$ treatment; recoveries were $96 \pm 7\%$ for As and $95 \pm 6\%$ for Cd that were similar to those with HF treatments; $100 \pm 6\%$ for As and $95 \pm 5\%$ for Cd. Mo levels did decrease slightly (ca. to 0.4 μg $mL^{-1}$) with HF + $HN_4OH$ coprecipitation, but Sn was almost completely removed from MVM solutions; residual Sn concentration was as low as 0.019 μg $mL^{-1}$ (ca. 96.2% removal) (Fig. 3B).

In a separate trial, the volume of $NH_4OH$ was examined for HF + $NH_4OH$ coprecipitation step. Namely, the $NH_4OH$ volume added to the MVM solutions was increased from 50 to 150 μL. The results are summarized in Table 2 for As and Cd along with interfering elements. The recoveries for As and Cd were quantitative with up 100 μL NH4OH that was also adopted as optimum volume. With 50 μL $NH_4OH$, weak precipitation occurred which was not sufficient for eliminating Mg and Ca effectively. Adding 150 μL $NH_4OH$, on the other hand, caused intense precipitation that resulted in partial precipitation of As and Cd that decreased the recoveries to about 86% and 62%, respectively. Additional experiments performed also showed that a volume of NH4OH between 75 to 110 μL could be used without impacting As and Cd retention in solution. In case HF, the volume was kept at 30 μL since no significant improvement was observed in preliminary trials. Contrary, adding more

HF (ca. 50 μL) to solutions required more $NH_4OH$ to neutralize the acid and to initiate the precipitation without any improvement in the matrix removal.

### 3.3. Method validation with analysis of SRM 3280

Samples of SRM 3280 (multivitamin/multielement tablets) were analyzed using the optimized coprecipitation procedure. A sample of 10 tablets (15 g) of SRM 3280 was ground with agate mortar and mill to make a homogenized batch. About 0.125 g samples (n = 5) were weighed and digested in teflon vessels in 4 mL $HNO_3$ and 2 mL $H_2O_2$ and prepared as described in section 2.4. Blank solutions (n = 10) were prepared with 30 μL HF and 210 μL TEA in 2-mL centrifuge tubes. These solutions were first evaporated on a hot-block digester at 100 oC and then completed to 2 mL with 1% (v/v) $HNO_3$. Determinations were made using aqueous external standards from 0 to 20 μg $L^{-1}$ As and Cd. Limits of detection (LOD) were estimated as 0.013 μg $L^{-1}$ for As and 0.006 μg $L^{-1}$ Cd from the blank solutions using the $3\sigma$ method.

For SRM 3280, after removal of the undissolved material (e.g., TiO2 matrix), the supernatant solutions were treated according to the coprecipitation procedure described in Fig. 1. Namely, a volume of 0.5 mL solution was taken and completed to 1 mL with 1% (v/v) $HNO_3$ through Steps 1 and 2 to verify the effects of interfering salt matrix on As and Cd determination. The results for As, Cd and interfering matrix elements measured in SRM 3280 solutions are summarized in Table 3. The certified values of As and Cd in SRM 3280 are $132 \pm 44$ ng $g^{-1}$ and $80.15 \pm 0.86$ ng $g^{-1}$, respectively. As can be seen that both As and Cd values were inaccurately high at Step 1, about 38% for As and 45% to 56% for Cd, due to the presence of significant $Cl^-$ (e.g., KCl or K) and Mo matrices. Residual K concentration was around 461 μg $mL^{-1}$ that reflects about 419 μg $mL^{-1}$ $Cl^-$ or 880 μg $mL^{-1}$ KCl in SRM 3280 solutions. High As levels were indicative of significant contribution from $^{40}Ar^{35}Cl$ on monoisotopic $^{75}As$. For Cd, interfering Sn was removed mostly, but Mo concentration in analysis solutions was about 1.7 μg $mL^{-1}$ that caused significant interferences on $^{110}Cd$, $^{111}Cd$ and $^{114}Cd$ isotopes from $^{94}Mo^{16}O$, $^{95}Mo^{16}O$ and $^{98}Mo^{16}O$, respectively. These spectral interferences on As and Cd were mostly alleviated with second coprecipitation (Step 2) that substantially reduced the matrices of interfering $Cl^-$(80 μg $mL^{-1}$ K = 150 μg $mL^{-1}$ KCl) and Mo (0.42 μg $mL^{-1}$). Consequently the measured As and Cd values were in agreement with the certified values at 95% confidence level (Step 2). These results were also consistent with those obtained with the spiked stock MVM solutions for which quantitative recoveries for As and Cd were achieved after second $Mg(OH)_2$ coprecipitation (see Fig. 2C). Similarly, the SRM 3280 solutions possessed high levels of Mg, P and Ca as occurred for the stock MVM solutions (Fig. 2A). After the coprecipitation with HF – $NH_4OH$ (Step 3), the remaining Mg and Ca were effectively eliminated along with further reduction of P levels producing more conducive solutions for ICP-MS analysis. Concerning As and Cd, As concentration was slightly lower than that for at Step 2, however, both As and Cd concentrations were consistent with the certified values at 95% confidence level. It should be noted that SRM 3280 solutions contained substantial amount of Ca (2358 μg $mL^{-1}$) and P (2133 μg $mL^{-1}$) at Step 2. The decrease in measured As value at Step 3 could indicate a contribution from $^{44}Ca^{31}P$ on $^{75}As$ at Step 2, which was also eliminated when Ca matrix was reduced from 2358 μg $mL^{-1}$ to as low as 9 μg $mL^{-1}$.

### 3.4   Application to commercial MVM tablets

A sample of 5 tablets of commercial MVM were ground and homogenized. About 0.150 g samples (n = 5) were weighed and digested in teflon vessels in 4 mL HNO3 and 2 mL $H_2O_2$ as described for the SRM 3280 samples. Digests were diluted to 2 mL and treated entirely with the coprecipitation procedure. The results obtained after HF + $NH_4OH$ treatment (e.g., Step 3) are provided in Table 4. Arsenic concentration varied between 24 and 128 ng $g^{-1}$, and that for Cd were between 28 and 125 ng $g^{-1}$ in the tablets. These concentrations were equivalent to 0.031 – 0.180 μg As $day^{-1}$ (e.g. serving size) and 0.035 – 0.162 μg Cd $day^{-1}$. Both As and Cd are classified as toxic elements and thus their daily intake from MVM supplements is regulated. The minimum risk levels (MRLs) for adults under chronic exposure are estimated to be 21 μg $day^{-1}$ for As (e.g., 0.3 μg $kg^{-1}$ $day^{-1}$) [22] and 7 μg day $^{-1}$ for Cd (0.1 μg $kg^{-1}$ $day^{-1}$) [31]. The concentrations of As and Cd measured from the commercial MVM tablets were below the MRLs indicating that total amount of As or Cd ingested daily were within the safe exposure limits. In their survey of MVM supplements, Avula et al. [20] also reported As and Cd impurities below the MRLs, however, the measured concentrations were higher; As levels varied 0.6 and 15.9 μg $day^{-1}$ and that for Cd were between 0.3 to 3.8 μg $day^{-1}$. In contrast, both As and Cd levels determined in this study with the coprecipitation procedure were much lower indicating that ICP-MS analysis of complex MVM supplements for As and Cd impurities without implementing suitable analytical approaches could possess higher risks of inaccuracy.

## 4.   Conclusion

Despite the complex nature of MVM supplements, most studies concerning the safety of these products still rely on direct ICP-MS analysis to determine both essential elements and heavy metals. However, analysis of MVM supplements is a far more challenging task than it appears for accurate determination of toxic heavy metal impurities, even with highly sensitive ICP-MS technology. The results with MVM stock solutions and SRM 3280 samples showed that single step matrix elimination may not be sufficient to achieve accurate determinations. Here, a coprecipitation procedure is developed affording simultaneous determination of As and Cd impurities from MVM supplements with ICP-MS. Interfering salt matrix of MVM solutions comprising Mo, Sn, K, Cl, Ca and Mg were effectively eliminated through sequential coprecipitations. The mixture of HF-NH4OH was used judiciously to retain As and Cd in solution to eliminate predominant Ca and Mg. Analysis of commercial MVM supplements indicated lower As and Cd impurities in comparison to those reported in literature previously. It is therefore concluded that appropriate analytical methods should be developed to provide more accurate information on potential toxic element contamination in MVM supplements.

## Acknowledgements

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## Highlights

- Three-step sequential coprecipitation was developed to determine toxic metal impurities from multivitamin/mineral (MVM) supplements.

- The procedure is faster and allows simultaneous separation of As and Cd from MVM matrix.

- KCl matrix, and interfering Mo and Sn were effectively removed.

- Persistent Ca and Mg were completely eliminated from MVM solutions.

- The method is validated with analysis of SRM 3280 for As and Cd.

- Commercial MVM supplements contain lower As and Cd impurities than minimum risk levels (MRLs).
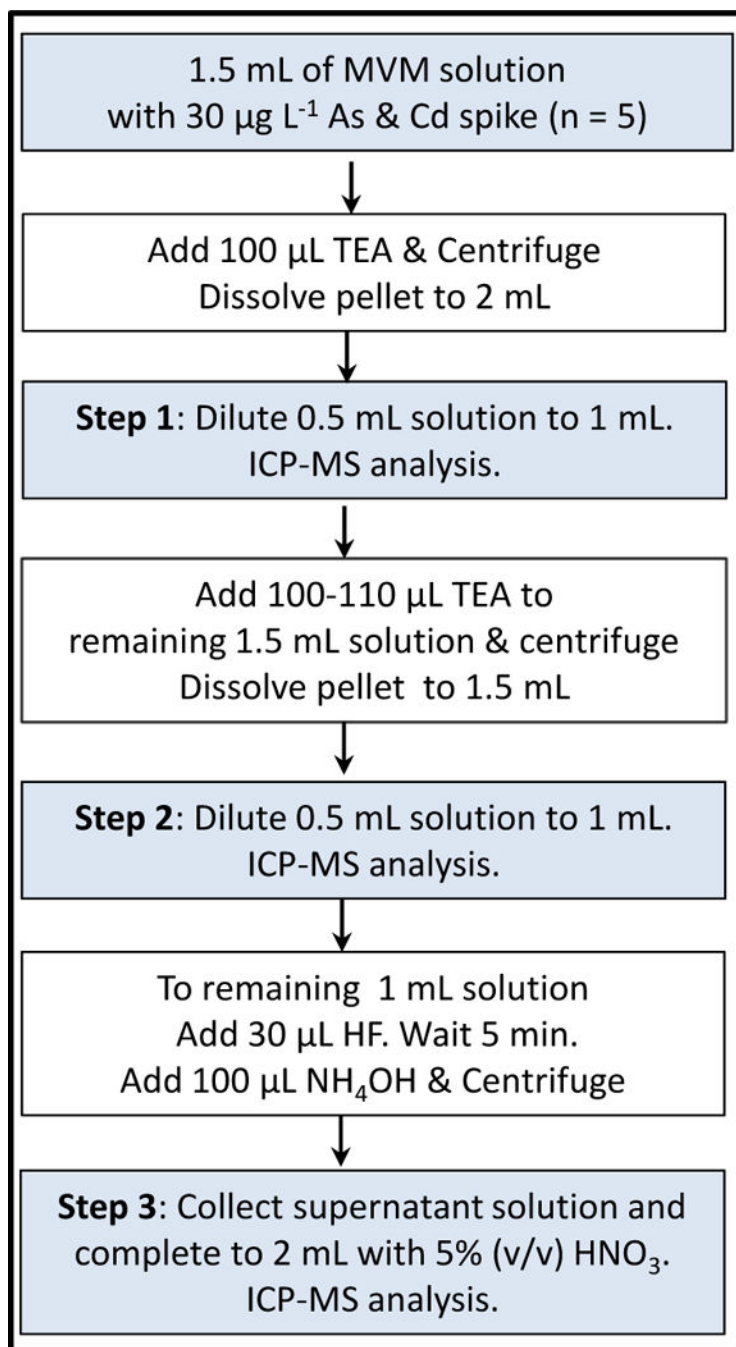
**Fig. 1.**
Coprecipitation scheme utilized for separation of As and Cd from MVM matrix. Steps 1, 2, and 3 refer to sampling after each treatment.
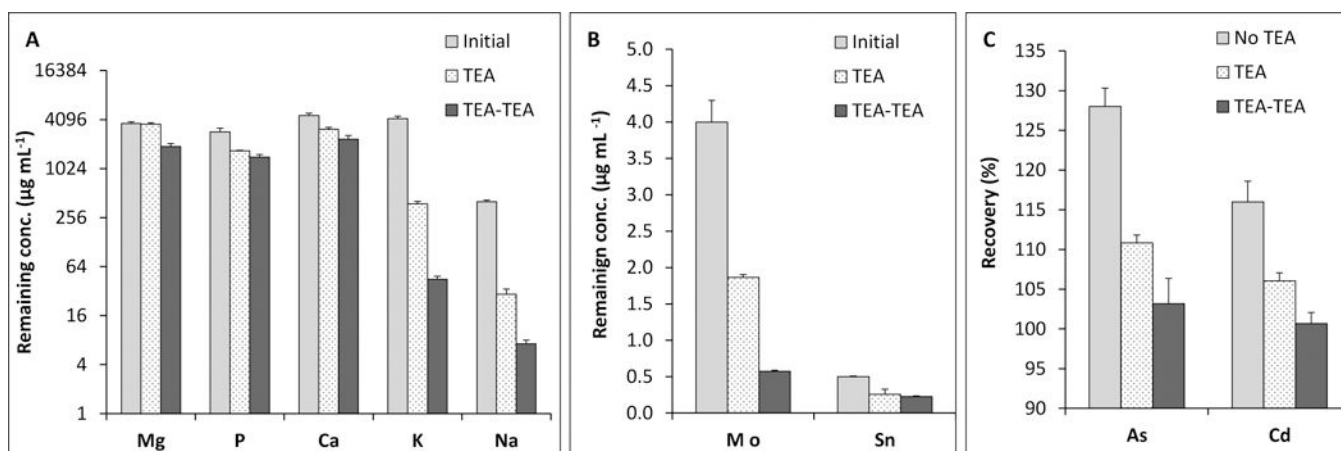
**Fig. 2.**
Recoveries for As and Cd, and the elimination profiles of interfering matrix elements with sequential coprecipitation with TEA in MVM solutions (n = 5). Initial values for the matrix elements refer to the concentrations in MVM stock solution. As and Cd recoveries without TEA are obtained with direct measurements of the MVM stock solutions spiked with 15 μg $L^{-1}$ As and Cd.
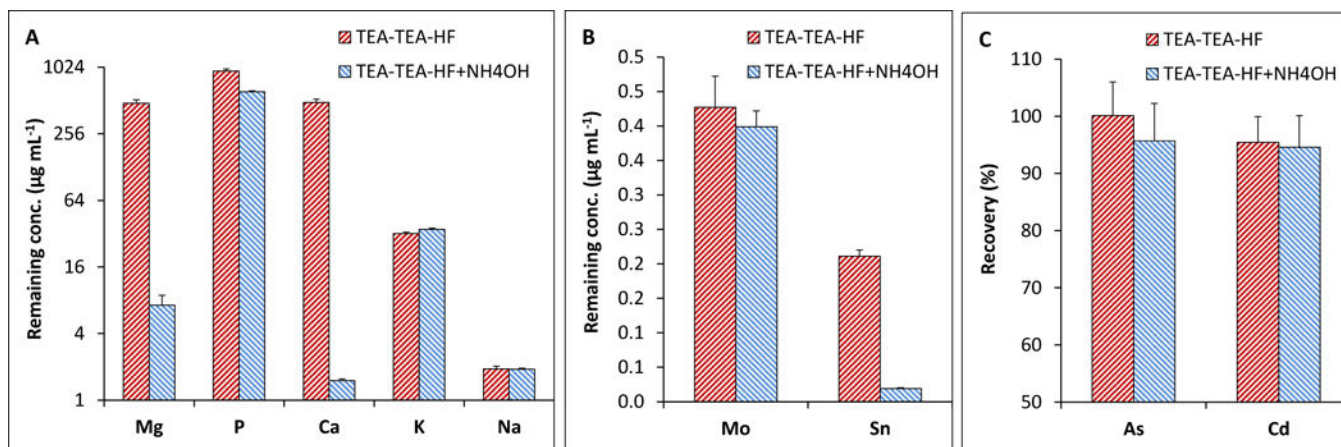
**Fig. 3.**
Recoveries for As and Cd, and the elimination profiles of interfering matrix elements with HF and HF + NH$_4$OH coprecipitation from MVM solutions after TEA coprecipitation.

**Table 1**

Operating parameters for Varian 820-MS ICP-MS instrument

| | |
|---|---|
| RF Power | 1.4 kW |
| Plasma argon flow | 17 L min-1 |
| Auxiliary argon flow | 1.7 L min-1 |
| Nebulizer argon flow | 1.1 L min-1 |
| Sheath argon flow | 0.2 L min-1 |
| Sampling depth | 6.5 mm |
| Pump rate | 6 rpm; 0.2 L min-1 |
| Stabilization time | 20 s |
| Spray chamber temperature | 4 oC |
| Scan mode | Peak hopping |
| Dwell time | 20 ms |
| Points/peak | 1 |
| Scans/peak | 5 |
| Scans/replicate | 3 |

*Normal mode (non-CRI)*

| | |
|---|---|
| Isotopes monitored | $^{55}$Mn, $^{63}$Cu, $^{65}$Cu, $^{66}$Zn, $^{68}$Zn, $^{75}$As, $^{95}$Mo, $^{98}$Mo, $^{110}$Cd, $^{111}$Cd, $^{114}$Cd, $^{118}$Sn, $^{120}$Sn |

*CRI mode settings*

| | |
|---|---|
| CRI gas/port | H2 / Skimmer cone |
| CRI gas flow rate | 65 mL min-1 |
| Isotopes monitored | $^{23}$Na, $^{25}$Mg, $^{26}$Mg, $^{31}$P, $^{39}$K, $^{43}$Ca, $^{44}$Ca, $^{56}$Fe, $^{57}$Fe |

**Table 2**

Effect of NH$_4$OH volume on the recoveries of As and Cd as well as the removal of interfering matrix elements from MVM stock solution with HF + NH$_4$OH coprecipitation. Values are mean ± standard deviation of five separate preparations (n = 5)

| Analyte (recovery) | NH4OH volume (µL) | | |
|---|---|---|---|
| | **50** | **100** | **150** |
| As (%) | 97 ± 3 | 99 ± 2 | 86 ± 2 |
| Cd (%) | 98 ± 7 | 95 ± 4 | 62 ± 4 |
| Matrix element (concentration) | | | |
| Mo (µg mL$^{-1}$) | 0.68 ± 0.06 | 0.43 ± 0.04 | 0.35 ± 0.04 |
| Sn (µg mL$^{-1}$) | 0.2 ± 0.04 | 0.05 ± 0.08 | 0.02 ± 0.02 |
| Mg (µg mL$^{-1}$) | 1283 ± 33 | 10 ± 2 | 4 ± 0.6 |
| P (µg mL$^{-1}$) | 1263 ± 136 | 812 ± 46 | 783 ± 34 |
| Ca (µg mL$^{-1}$) | 418 ± 41 | 1 ± 0.5 | 0.5 ± 0.2 |
| K (µg mL$^{-1}$) | 35 ± 3 | 34 ± 2 | 36 ± 3 |
| Na (µg mL$^{-1}$) | 4 ± 0.5 | 3 ± 0.7 | 4 ± 0.4 |

**Table 3**

Concentrations of As and Cd determined in SRM 3280 by ICP-MS along with residual solution concentrations of interfering matrix elements across each coprecipitation step. Values are mean ± standard deviation of five separate preparations (n = 5). Values in parenthesis indicate per cent deviation (inaccuracy) from the certified value of As and Cd.

| Analyte | Certified value (ng g$^{-1}$) | Step 1 | Step 2 | Step 3 |
|---|---|---|---|---|
| $^{75}$As (ng g$^{-1}$) | 132 ± 44 | 182 ± 22 | 141 ± 18 | 112 ± 37 |
| | | (+38%) | (+7%) | (−15%) |
| $^{110}$Cd (ng g$^{-1}$) | | 116 ± 14 | 77 ± 9 | 76 ± 5 |
| | 80.2 ± 0.9 | (+45%) | (−4%) | (−5%) |
| $^{111}$Cd (ng g$^{-1}$) | | 118 ± 15 | 78 ± 6 | 79 ± 5 |
| | | (+48%) | (−2%) | (−2%) |
| $^{114}$Cd (ng g$^{-1}$) | | 125 ± 14 | 88 ± 7 | 78 ± 7 |
| | | (+56%) | (+10%) | (−2%) |
| Residual concentration of the matrix and interfering elements | | | | |
| Mo (μg mL$^{-1}$) | 1.7 ± 0.1 | 0.42 ± 0.05 | | 0.37 ± 0.05 |
| Sn (μg mL$^{-1}$) | 0.10 ± 0.01 | 0.02 ± 0.005 | | 0.02 ± 0.003 |
| Mg (μg mL$^{-1}$) | 2331 ± 145 | 1224 ± 159 | | 21 ± 5 |
| P (μg mL$^{-1}$) | 2921 ± 280 | 2133 ± 190 | | 1451 ± 110 |
| Ca (μg mL$^{-1}$) | 3688 ± 262 | 2358 ± 200 | | 9 ± 3 |
| K (μg mL$^{-1}$) | 461 ± 28 | 80 ± 8 | | 55 ± 7 |
| Na (μg mL$^{-1}$) | 4 ± 1 | nd | | nd |

nd = not determined

**Table 4**

Arsenic and cadmium concentration determined in various multivitamin/mineral dietary supplements by ICP-MS using the developed coprecipitation. Values are mean ± standard deviation of five separate preparations (n = 5). Daily serving size is calculated as the average mass (μg) of As and Cd values per tablet.

| Sample | As (ng g$^{-1}$) | Average As (μg/serving size) | Cd (ng g$^{-1}$) | Average Cd (μg/serving size) |
|---|---|---|---|---|
| MVM-1 | 71 ± 8 | 0.089 | 28 ± 2 | 0.035 |
| MVM-2 | 100 ± 6 | 0.075 | 54 ± 6 | 0.081 |
| MVM-3 | 56 ± 5 | 0.068 | 67 ± 3 | 0.087 |
| MVM-4 | 63 ± 8 | 0.078 | 58 ± 7 | 0.076 |
| MVM-5 | 128 ± 11 | 0.180 | 97 ± 4 | 0.135 |
| MVM-6 | 44 ± 5 | 0.063 | 60 ± 7 | 0.087 |
| MVM-7 | 29 ± 4 | 0.038 | 125 ± 12 | 0.162 |
| MVM-8 | 24 ± 5 | 0.031 | 106 ± 16 | 0.138 |