Laboratory Procedure Manual

Analytes: **Antimony, Barium, Beryllium, Cadmium, Cesium, Cobalt, Lead, Molybdenum, Platinum, Thallium, Tungsten, and Uranium**

Matrix: **Urine**

Method: **Urine Multi-Element ICP-DRC-MS**
Renamed from "Inductively Coupled Plasma-Mass Spectrometry (ICP-DRC-MS)"

Method No: **3004.1**

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As performed by: Inorganic Radionuclides and Toxicology
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Important Information for Users

The Centers for Disease Control and Prevention (CDC) periodically refines these laboratory methods. It is the responsibility of the user to contact the person listed on the title page of each write-up before using the analytical method to find out whether any changes have been made and what revisions, if any, have been incorporated.

Urine Multi-Element ICP-DRC-MS

NHANES 2009-2010

Public Release Data Set Information
This document details the Lab Protocol for testing the items listed in the following table:

Data File Name	Variable Name	SAS Label
UHM_F	URXUBA	Barium, urine (ng/mL)
	URXUBE	Beryllium, urine (ng/mL)
	URDUCD	Cadmium, urine (ng/mL)
	URXUCO	Cobalt, urine (ng/mL)
	URXUCS	Cesium, urine (ng/mL)
	URXUMO	Molybdenum, urine (ng/mL)
	URXUPB	Lead, urine (ng/mL)
	URXUPT	Platinum, urine (ng/mL)
	URXUSB	Antimony, urine (ng/mL)
	URXUTL	Thallium, urine (ng/mL)
	URXUTU	Tungsten, urine (ng/mL)
	URXUUR	Uranium, urine (ng/mL)

1. Clinical Relevance & Summary of Test Principle

a. Clinical Relevance:

This method is used to achieve rapid and accurate quantification of thirteen elements of toxicological and nutritional interest including Antimony (Sb), Arsenic (As), Barium (Ba), Beryllium (Be), Cadmium (Cd), Cesium (Cs), Cobalt (Co), Lead (Pb), Molybdenum (Mo), Platinum (Pt), Thallium (TI), Tungsten (W), and Uranium (U). The method may be used to screen urine when people are suspected to be acutely exposed to these elements or to evaluate chronic environmental or other non-occupational exposure..

b. Test Principle:

Inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS) is a multi-element analytical technique capable of trace level elemental analysis. This ICP-DRC-MS method is used to measure either arsenic, a 12 element panel (Antimony, Arsenic, Barium, Beryllium, Cadmium, Cesium, Cobalt,

Lead, Molybdenum, Platinum, Thallium, Tungsten, and Uranium), or any subgroup of the 12 element panel.

Liquid samples are introduced into the ICP through a nebulizer and spray chamber carried by a flowing argon stream. By coupling radio-frequency power into flowing argon, plasma is created in which the predominant species are positive argon ions and electrons and has a temperature of 6000-8000 K. The sample passes through a region of the plasma and the thermal energy atomizes the sample and then ionizes the atoms. The ions, along with the argon, enter the mass spectrometer through an interface that separates the ICP (at atmospheric pressure, ~760 torr) from the mass spectrometer (operating at a pressure of 10^{-5} torr). The ions pass through a focusing region, the dynamic reaction cell, the quadrupole mass filter, and finally are counted in rapid sequence at the detector allowing individual isotopes of an element to be determined. The dynamic reaction cell operates in one of two modes. In 'standard' mode the cell is not pressurized and ions pass through the cell to the quadrupole mass filter unaffected. In 'drc' mode the cell is pressurized with a gas which will collide or react with the incoming ions to either eliminate an interfering ion or change the ion of interest to a new mass which is free from interference. In this method the instrument is operated in drc mode when analyzing for cadmium and arsenic, but in standard mode when analyzing for all of the other analytes. For arsenic, the reaction cell is pressurized with a mixture of hydrogen (10%) and argon (90%) which causes the breakup of the $^{40}Ar^{35}Cl^{+}$ ion which would otherwise interfere with detection of ^{75}As at m/z 75. When analyzing for cadmium, the reaction cell is pressurized with oxygen and the quadrupole mass filter in the reaction cell prevents ^{98}Mo from entering the oxygen-rich environment of the cell. The $^{98}Mo^{16}O^{+}$ ions which would normally interfere with detection of ^{114}Cd at m/z 114 react with the oxygen in the cell creating $^{98}Mo^{16}O_2{}^{+}$ and $^{98}Mo^{16}O_3{}^{+}$ at masses which no longer represent interference to ^{114}Cd analysis. Since the quadrupole in the reaction cell prevents $^{98}Mo^{+}$ from entering the cell, no additional interfering $^{98}Mo^{16}O^{+}$ is formed in the oxygen-rich environment of the cell. Electrical signals resulting from the detection of ions are processed into digital information that is used to indicate first the intensity of the ions and then the concentration of the element. This method was originally based on the method by Mulligan et al. [5]. The DRC portions of the method are based on work published by Tanner et al. Urine samples are diluted 1+9 with 2% (v/v) concentrated nitric acid (and 1.5% ethanol in the case of arsenic) containing iridium (Ir), rhodium (Rh), and gallium (Ga) for multi-internal standardization. Nitric acid is used for the purpose of solubilizing and stabilizing metals in solution. Internal standards are a constant concentration in all blanks, calibrators and samples. Monitoring the instrument signal ratio of a metal to its internal standard allows correction for instrument noise and drift, and sample-to-sample matrix differences. Ethanol is used in the case of arsenic for the purpose of providing a constant amount of signal enhancement (carbon effect) across all blanks, calibrators, and samples.

2. Safety Precautions

a. General Safety

i. Observe all safety regulations as detailed in the Division (DLS) Safety Manual. Additional information can be found in your lab's chemical hygiene plan.

ii. Observe Universal Precautions when working with urine.

iii. Wear appropriate gloves, lab coat, and safety glasses while handling all solutions. Consult the laboratory chemical hygiene plan.

iv. Exercise special care when handling and dispensing concentrated nitric acid. Add acid to water. Nitric acid is a caustic chemical that is capable of causing severe eye and skin damage. ***If nitric acid comes in contact with any part of the body, quickly wash the affected area with copious quantities of water for at least 15 minutes.***

v. Use secondary containment for containers of biological or corrosive liquids.

vi. The use of the foot pedal on the Micromedic Digiflex™ is recommended because it reduces analyst contact with work surfaces that have been in contact urine and also keeps the analyst's hands free to hold the specimen cups and autosampler tubes and to wipe off the tip of Micromedic Digiflex™.

vii. Training will be given before operating the ICP-DRC-MS, as there are many possible hazards including ultraviolet radiation, high voltages, radio-frequency radiation, and high temperatures. This information is also detailed in the PerkinElmer ELAN® ICP-DRC-MS System Safety Manual.

viii. Use flash arrestors on oxygen and argon / hydrogen gas cylinders and properly secure gas cylinders with safety harnesses.

ix. Wipe down all work surfaces at the end of the day with bleach-rite spray or freshly prepared 10% (v/v) sodium-hypochlorite solution.

b. <u>Radiation Safety</u>

i. All personnel performing this method must successfully meet requirements of a CDC-OHS radiation worker (RW) due to the use of natural uranium in this method and observe all necessary radiation safety considerations indicated in the CDC Radiation Safety Manual [9].

c. Waste Disposal: Operators of this method should take the CDC-OHS Hazardous Chemical Waste Management Course (initial and yearly refreshers).

i. Waste to be Placed Into Biohazard Autoclave Bags & Pans:

1. All biological samples and diluted specimens (after analysis run).

2. All disposable plastic and paper which contact urine (autosampler tubes, gloves, etc.).

3. Used non-glass/quartz ICP-MS consumables (i.e. probes, tubing, cones, and ion lenses).

ii. Waste to be Placed Into Sharps Containers: Pipette Tips, broken glass or quartz instrument consumables (broken spray chambers, torches, nebulizers, etc. . .). Large broken glass which will not fit in the sharps container should be placed in a separate autoclave pan from other waste and labeled as "broken glass" (see the "Autoclaving" section of the CDC safety policies and practices manual located in the laboratory).

iii. Liquid Waste

1. Waste discarded down sink: Only liquid waste from the ICP-DRC-MS instrument can be discarded at the sink. Flush the sink with copious amounts of water.

2. Waste to be picked up by the Radiation Safety Office: Contact the laboratory radiation inventory person and the CDC Radiation Safety Office for disposal of any single element uranium standard, intermediate stock standard, or intermediate working standard solutions.

3. Waste to be picked up by Hazardous Waste Program: Submit request for hazardous waste removal of all other liquid waste.

4.

3. Computerization; Data System Management

Calculation of Serum Ferritin values are accomplished with the software on the Hitachi Mod PE instrument. A backup copy of the generated data is copied onto the zip drive as a binary file. The data is also copied onto a floppy disk and archived to as an ASCII file.
Transmission of data from floppy disk A: to the Microsoft Access FrontEnds Database is described below:

Step 1 – Analyst – Import data file into FrontEnds.

Step 2 – Analyst – Review run in FrontEnds.

Step 3 – Analyst – Send email and run folder to QA Officer:

An e-mail is sent to the QA Officer including the following run information: Analysis date, Instrument, Study, Groups, File name, Batch ID, Run #, and QC Status. Noteworthy comments are included in the email. All printouts including raw data are submitted in a run folder to the QA Officer who reviews the Bench QC data via the FrontEnds database as described below.

Step 4 – QA Officer – Review Bench QC via FrontEnds.

Step 5 – Team leader – Review Blind QC and other parameters and set results ready in FrontEnds.

Step 6 – Supervisor – Approvals and Export of Results via FrontEnds.

For NHANES, data is transmitted electronically weekly to Westat's ISIS computer system and transferred from there to NCHS. Abnormal values are confirmed by the analyst, and codes for missing data are entered by the analyst and are transmitted as part of the data file to the Westat ISIS computer, and are eventually forwarded to NCHS. Westat also prepares the abnormal report notifications for the NCHS Survey Physician.

Files stored on the network or CDC mainframe are automatically backed up nightly by DLS LAN support staff and CDC Data Center staff, respectively. Backup of the daily data containing all raw data files and result files for each run are the responsibility of the analyst. Typically these files are backed up regularly onto a floppy disk or a CD-ROM using a CD writer.

Documentation for data system maintenance is contained in printed copies of data records, as well as in "system log" files on the local hard drives used for the archival of data.

4. Procedures for Collecting, Storing, and Handling Specimens; Criteria for Specimen Rejection; Specimen Accountability and Tracking

a. Procedures for Collecting, Storing, and Handling Specimens: Specimen handling conditions, special requirements, and procedures for collection and transport are discussed in the division (DLS) Policies and Procedures Manual [8]. Copies are available in branch, laboratory, and special activities specimen-handling offices. An electronic copy is available at:

In general,

i. No fasting or special diets are required before collection of urine.

ii. Use sterile, lot screened collectors for specimen acquisition.

iii. Urine specimens should be transported frozen (packed in dry ice during shipment is preferred when possible).

iv. Once received, store long term at ≤ -20°C until time for analysis. Short-term storage at 2-4°C is acceptable. Refreeze at ≤ -20°C portions of the sample that remain after analytical aliquots are withdrawn. Thawing and refreezing samples has not been found to compromise sample results.

v. Acceptable containers for analytical aliquots include lot screened polypropylene (PP) cryovials or tubes (i.e. 5 mL cryogenic vial or 15mL centrifuge tube).

b. Criteria for Specimen Rejection: Specimen characteristics that may compromise test results are indicated above. Reasons for rejection of a sample for analysis include

i. Low volume: Optimal amount of urine is 2+ mL. The volume of urine used for one analysis is 0.5 mL.

ii. Contamination: Improper collection procedures or collection devices can contaminate the urine by contact with dust, dirt, etc.

In all cases, request a second urine specimen.

c. Transfer or Referral of Specimens; Procedures for Specimen Accountability and Tracking: Location, status, and final disposition of the specimens will be tracked at least by paper document in the "Study Folder" (created before analysts receive the samples). Apart from this specimen tracking form, this folder will also contain the paper print outs of results from analysis of the specimens. Maintain records for a minimum of 3 years. Use only numerical identifiers for samples within the laboratory (e.g., case ID numbers) in order to safeguard confidentiality. Only the medical supervisor (MS) or project coordinator (PC) i.e. non CDC personnel should have access to the personal identifiers.

5. Procedures for Microscopic Examinations; Criteria for Rejection of Inadequately Prepared Slides

Not applicable for this procedure

6. Preparation of Reagents, Calibration (Standards), Controls, and All Other Materials; Equipment and Instrumentation

Instrument & Material Sources

a. Sources for ICP-MS Instrumentation

i. ICP-MS: Inductively Coupled Plasma Dynamic Reaction Cell Mass Spectrometer (ELAN® 6100 DRC^{Plus} or ELAN® DRC II) (PerkinElmer Norwalk, CT, www.perkinelmer.com).

ii. Recirculating chiller / heat exchanger for ICP-MS: Refrigerated chiller (PolyScience 6105PE for ELAN® 6100 DRC^{Plus} instruments) or heat exchanger (PolyScience 3370 for ELAN® DRC II instruments) (PerkinElmer Norwalk, CT, www.perkinelmer.com).

iii. Autosampler: ESI SC-4 autosampler (Elemental Scientific Inc., Omaha, NE) or equivalent.

iv. FAST Sample Introduction System (Elemental Scientific Inc., Omaha, NE).

1. FAST controller
2. FAST actuator: CTFE high-flow valve head like part number SC-0599-1210 (part number includes lines and probes).

b. Sources for ICP-MS Parts & Consumables

i. Adapter, PEEK: Securely connects 1.6mm O.D. PFA tubing to 0.03" I.D. peristaltic tubing. Composed of three PEEK parts.

1. Female nut for 1.6mm O.D. (1/16") tubing. Like part P-420 (Upchurch Scientific, Oak Harbor, WA, www.upchurch.com).
2. PEEK ferrule. Like part P-260x (10pk SuperFlangeless ferrule, Upchurch Scientific, Oak Harbor, WA, www.upchurch.com).
3. Conical Adapter Body. Like part P-692 (Upchurch Scientific, Oak Harbor, WA, www.upchurch.com).

ii. Coolant, for Polyscience chiller or heat exchanger: Only PerkinElmer part # WE01-6558 (PerkinElmer Norwalk, CT, www.perkinelmer.com) is approved for use by PerkinElmer. # *Spares = 6*.

iii. Cone, sampler (nickel/platinum): PerkinElmer part # WE021140/WE027802 (PerkinElmer Norwalk, CT, www.perkinelmer.com). Part # SC2011-Ni (Testing has also found Spectron, Ventura, CA, www.spectronus.com cones to be comparable). # *Spares = 4*.

iv. Cone, skimmer (nickel/platinum): PerkinElmer part # WE021137/WE027803 (PerkinElmer Norwalk, CT, www.perkinelmer.com). Part # SC2012-Ni (Testing has also found Spectron, Ventura, CA, www.spectronus.com cones to be comparable) # *Spares = 4*.

v. Connector (for tubing): Use to connect 1/8" I.D. PVC tubing to 0.125" I.D peristaltic pump tubing. Use part # 3140715 (PerkinElmer Norwalk, CT, www.perkinelmer.com) or equivalent. # *Spares = 4*.

vi. Detector, electron multiplier: Like part # N8125001 (PerkinElmer Norwalk, CT, www.perkinelmer.com). Available direct from manufacturer (part # 14210, SGE Incorporated, Austin, Texas, http://www.etpsci.com) or various distributors. # *Spares = 1*.

vii. Hose, for connection to chiller: Push on hose. I.D. = ½", O.D. = ¾". Use part # PB-8 (per inch, Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com) or equivalent. Do not normally need spare hose (unless moving instrument into a new location).

viii. Hose, for exhaust of ELAN: Available as part of ELAN installation kit from Perkin Elmer (PerkinElmer Norwalk, CT, www.perkinelmer.com). Available direct from manufacturer as part # S-LP-10 air connector (Thermaflex, Abbeville, SC, www.thermaflex.net). Equivalent part may be substituted. # *Spares = 10 feet of 4" diameter and 10 feet of 6" diameter hose.*

ix. Injector, quartz with ball joint: I.D. = 2.0 mm. PerkinElmer part # WE023948 (PerkinElmer Norwalk, CT, www.perkinelmer.com). Available direct from manufacturer as part # 400-30 (Precision Glass Blowing, Centennial, CO, www.precisionglassblowing.com) or from various distributors. # *Spares = 2.*

x. Injector support (for pass-through injector: PerkinElmer part # WE023951 (PerkinElmer Norwalk, CT, Available direct from manufacturer as part # 400-37 (Precision Glass Blowing, Centennial, CO, or from various distributors. # *Spares = 2.*

xi. Ion Lens: PerkinElmer part # WE018034 (PerkinElmer Norwalk, CT). # Spares = 3.

xii. Loop, for FAST valve: Default volume is 1.5mL Teflon sample loop with white nut connectors for high flow valve head of FAST sample introduction system. This volume loop can be created by cutting 25% off the length of a 2mL Teflon sample loop was cut to the 1.5mL length. Like part # SC-0315-20 (Elemental Scientific Inc., Omaha, NE.,. Volumes larger than 1.5mL can be used, but will require longer loop fill (ESI software) and sample flush (ELAN software) times, and proportionally larger volumes used in sample preparation.

xiii. Nebulizer: PolyPro-ST micro flow polypropylene nebulizer with external 1/4-28 threaded connector for liquid delivery, low pressure version or equivalent. Like part # ES-4040-7010 (Elemental Scientific Inc., Omaha, NE., # *Spares = 1*. Different nebulizers may be used, however, the nebulizer gas flow rate, sample flush time, read delay time, loop fill time, loop size, urine sample dilution

preparation volume, and sample-to-sample carry-over must be evaluated and optimized.

1. Gas connection:

   a. Teflon tubing: 4mm o.d., 2.4mm i.d. Teflon tubing (like part # ES-2502, Elemental Scientific Inc., Omaha, NE.,. # *Spares = 1*.

   b. Adapter kit: Plastic adapters to connect Teflon tubing (2.4mm i.d) to ¼" male Swagelok (compression) port on ICP-DRC-MS. Parts can be obtained as components in a "gas fittings kit for microflow nebulizer", kit part # ES-2501-1000, Elemental Scientific Inc., Omaha, NE.,. # *Spares = 1*.

2. Liquid connection: Connects nebulizer to port #3 of high flow FAST valve head with green, 1/4- 28 fitting. Like part # SC-0317-0250 (Elemental Scientific Inc., Omaha, NE.,. # *Spares = 2*.

xiv. Nut: (for flanged connections of 1.59mm (1/16") o.d. PFA tubing) Flanged, for 1/16" o.d. tubing, 1/4-28 threads. Use part # P-406x (pkg. of 10, Upchurch Scientific, Oak Harbor, WA, www.upchurch.com) or equivalent. Use a Teflon-coated Viton o-ring with this nut instead of the stainless steel washer that comes with part # P-406x*)*. # *Spares = 10.*

xv. Nut and Ferrule set, 1/8" Swagelok: Such as part # SS-200-NFSET (stainless steel) or part # B-200-NFSET (brass) (Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com) or equivalent. For part numbers listed here a quantity of 1 means 1 nut, 1 front ferrule, and 1 back ferrule. *Spares = 20.*

xvi. Nut and Ferrule set, 1/4" Swagelok: Such as part # SS-400-NFSET (stainless steel) or part # B-400-NFSET (brass) (Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com) or equivalent. For part numbers listed here a quantity of 1 means 1 nut, 1 front ferrule, and 1 back ferrule. *Spares = 20.*

xvii. Oil, Welch Directorr Gold: For roughing pumps. Available direct from manufacturer as part # 8995G-15 (1 gallon, Welch Rietschle Thomas, Skokie, IL, www.welchvacuum.com) or from various distributors. Equivalent oil may be substituted. # *Spares = 4.*

xviii. O-ring: (for sampler cone) PerkinElmer part # N8120511 (pkg. of 5, PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent. # *Spares = 20 o-rings.*

xix. O-ring: (for skimmer cone) PerkinElmer part # N8120512 (pkg. of 5, PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent. # *Spares = 20 o-rings.*

xx. O-ring: (for flanged connections of 1.59mm (1/16") o.d. PFA tubing) Teflon-coated Viton o-ring, i.d. = 1/16", thickness = 1/16", o.d. =

3/16". Such as part # V75-003 (O-rings West, Seattle, WA, www.oringswest.com) or equivalent. # *Spares = 20.*

xxi. O-ring: (for injector support).

1. Internal o-rings: ID = ¼", OD = 3/8", thickness = 1/16". Need 2 o-rings per injector support setup. PerkinElmer part # N8122008 (PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent (such as part # V75-010, O-rings West, Seattle, WA, www.oringswest.com). # *Spares = 20.*
2. External o-rings: ID = 3/8", OD = 1/2", thickness = 1/16". Need 2 o-rings for each injector support setup. PerkinElmer part # N8122009 (PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent (such as part # V75-012, O-rings West, Seattle, WA, www.oringswest.com). # *Spares = 20.*

xxii. O-ring: (for inside spray chamber at nebulizer port) Such as part # 120-56 (Precision Glass Blowing, Centennial, CO, www.precisionglassblowing.com). Additional o-rings can sometimes be obtained free of charge or at reduced price when acquired while purchasing spray chambers. # *Spares = 20.*

xxiii. O-ring: (for inside of torch mount): Part # WE017284 (PerkinElmer, Shelton, CT, www.perkinelmer.com). Do not substitute. The PerkinElmer o-ring is especially metal impregnated to minimize RF leakage though the torch mounts. # *Spares = 2.*

xxiv. Photon Stop: PerkinElmer part # WE018278 (PerkinElmer, Shelton, CT, www.perkinelmer.com). # *Spares = 1.*

xxv. Plugs, Quick Change for Roughing Pump Oil: These plugs will only work on the Varian roughing pumps which come standard on ELAN DRC II ICPMS instruments. These plugs will not fit the Leybold pumps which come standard on the ELAN DRC Plus instruments. Part # W1011013 (PerkinElmer, Shelton, CT, www.perkinelmer.com). No spares typically needed.

xxvi. Probes

1. for ESI autosampler: Teflon, carbon fiber support, 0.8mm i.d., blue marker, 1/4-28 fittings. Like part number SC-5037-3751 (Elemental Scientific Inc., Omaha, NE., # *Spares = 2.*
2. for carrier solution of FAST sample introducation system: Teflon, carbon fiber support, 0.5mm i.d., orange marker, 1/4-28 fittings. Like part number SC-5037-3501 (Elemental Scientific Inc., Omaha, NE.,. # *Spares = 2.*

xxvii. RF coil. PerkinElmer part # WE02-1816 (PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent. # *Spares = 2.*

xxviii. Screw, for Torch Mount: PerkinElmer part # WE011870. (PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent. # *Spares = 3*.

xxix. Spray chamber, quartz concentric: PerkinElmer part # WE025221 (PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent. Available direct from manufacturer as part # 400-20 (Precision Glass Blowing, Centennial, CO, www.precisionglassblowing.com) or from various distributors. # *Spares = 2.*

xxx. Torch, quartz: PerkinElmer part # N812-2006 (PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent. Available direct from manufacturer as part # 400-10 (Precision Glass Blowing, Centennial, CO, www.precisionglassblowing.com) or various distributors. Damaged torches can often be repaired for substantially lower cost than purchasing a new one by companies such as Wilmad LabGlass (Buena, NJ, www.wilmad-labglass.com) or Precision Glass Blowing (Centennial, CO, www.precisionglassblowing.com). # *New Spares = 2.*

xxxi. Tubing and adapter, for SC autosampler rinse station drain: Tygon tubing and adapter to attach to back of SC autosampler for draining rinse station waste (like part # SC-0303-002, Elemental Scientific Inc., Omaha, NE.,.

xxxii. Tubing and adapters, for SC autosampler rinse station filling: Teflon tubing and adapters (to attach to back of SC autosampler for filling rinse stations and to attach to rinse containers). Like part # SC-0302-0500, Elemental Scientific Inc., Omaha, NE.,.

xxxiii. Tubing and nut, for FAST carrier solution: 0.5mm i.d. Teflon tubing (orange marker) with red ¼-28 male nut. Connects to high flow FAST valve head, port #2. Like part # SC-0316-0500 (Elemental Scientific Inc., Omaha, NE.,.

xxxiv. Tubing, FAST vacuum: Vacuum line for SC-FAST high flow valve, connects to port #6, black nut for connection to valve head, natural brown color nut on other end for connection to SC autosampler vacuum port. Like part # SC-0321 (Elemental Scientific Inc., Omaha, NE.,.

xxxv. Tubing, main argon delivery to instrument: I.D. = 1/8", O.D. = ¼". Such as part # C-06500-02 (pkg. of 100ft, polypropylene, Fisher Scientific International, Hampton, NH, www.fishersci.com) or equivalent. # *Spares = 50ft*.

xxxvi. Tubing, PFA: I.D. = 0.5mm, O.D. = 1.59mm (1/16"). Used to transfer liquid between rinse solution jug and peristaltic pump tubing

The Perfluoroalkoxy (PFA) copolymer is a form of Teflon®. Such as part # 1548 (20ft length, Upchurch Scientific, Oak Harbor, WA, www.upchurch.com) or equivalent. # *Spares = 20ft.*

xxxvii. Tubing, peristaltic, 0.045" i.d. (rinse station feed): Standard PVC, 2-stop (red / red) peristaltic pump tubing, i.d. = 0.045". PerkinElmer part # N0680375, (PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent. # *Spares = 6 packs of 12 tubes.*

xxxviii. Tubing, peristaltic, 0.03" i.d. (carrier solution for ESI autosampler): Standard PVC, 2-stop (black / black) peristaltic pump tubing, i.d. = 0.03". PerkinElmer part # 09908587 (PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent. # *Spares = 6 packs of 12 tubes.*

xxxix. Tubing, peristaltic, 0.125" i.d. (spray chamber drain): Standard PVC, 2-stop (black / white) peristaltic pump tubing, i.d. = 0.125" or equivalent. PerkinElmer part # N812-2012 (PerkinElmer, Shelton, CT, www.perkinelmer.com) or equivalent. # *Spares = 6 packs of 12 tubes.*

xl. Tubing, PVC, i.d. = 1/8", o.d. = 3/16". May be used to transfer liquid

1. between spray chamber waste port and peristaltic pump
2. between peristaltic pump and liquid waste jug

Like part # 14-169-7A (pkg. of 50ft, Fisher Scientific International, Hampton, NH, www.fishersci.com) or equivalent. # *Spares = 20ft*.

xli. Tubing, Stainless Steel, o.d. = 1/8", wall thickness = 0.028": Used to connect DRC gas cylinders to ELAN DRC gas ports. Also used to replace plastic tubing in the DRC gas path within the ELAN. Like part # SS-T2-S-028-20 (20ft, Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com) or equivalent. *Spares = 20ft.*

xlii. Tubing, Teflon, corrugated, ¼" o.d.: Connects to the auxiliary and plasma gas side-arms of the torch. Part # WE015903 (PerkinElmer, Shelton, CT, www.perkinelmer.com). # *Spares = 2.*

xliii. Tubing, vinyl (argon delivery to nebulizer): Vinyl Tubing, 1/8" ID x 1/4" OD. Like part # EW-06405-02 (Cole Parmer, Vernon Hills, Illinois, www.coleparmer.com) or equivalent. Equivalent tubing material may be substituted. # *Spares = 10ft*.

xliv. Union Elbow, PTFE ¼" Swagelok: Connects argon tubing to torch auxiliary gas sidearm on bayonet mount ELAN ICPMS instruments. Like part # T-400-9 (Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com) or equivalent. *Spares = 2.*

xlv. Union Tee, PTFE, ¼" Swagelok: Connects argon tubing to torch plasma gas sidearm and holds igniter inside torch sidearm on

bayonet mount ELAN ICPMS instruments. Like part # T-400-3 (Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com) or equivalent. *Spares = 2.*

c. Sources for ICP-MS Maintenance Equipment & Supplies

i. Anemometer: Like digital wind-vane anemometer (Model 840032, SPER Scientific LTD., Scottsdale, AZ, www.sperscientific.com) or equivalent. Use to verify adequate exhaust ventilation for ICP-MS (check with hoses fully disconnected).

ii. Pan, for changing roughing pump oil: Like part # 53216 (United States Plastics Corporation, Lima, OH, www.usplastic.com) or equivalent. # On hand = 1.

iii. Container, to hold acid baths for glassware: Polypropylene or polyethylene containers with lids (must be large enough for torch, injector, or spray chamber submersion). May be purchased from laboratory or home kitchen supply companies. *# On hand = 4*.

iv. Cotton swabs: Any vendor. For cleaning of cones and glassware.

v. Cutter (for 1/8" o.d. metal tubing): Terry tool with 3 replacement wheels. Like part # TT-1008 (Chrom Tech, Inc., Saint Paul, MN, www.chromtech.com) or equivalent.

vi. Getter Regeneration Kit: Part # WE023257 (PerkinElmer, Shelton, CT, www.perkinelmer.com). Use this as needed (at least annually) to clean the getter in the pathway of channel A DRC gas.

vii. Magnifying glass: Any 10x + pocket loupe for inspection of cones and other ICP-MS parts. Plastic body is preferred for non-corrosion characteristics. Like part # 5BC-42813 (Lab Safety Supply, Janesville, WI, www.labsafety.com).

viii. Screw Driver, for Ion Lens Removal: Screw driver with long, flexible shaft, and 2mm ball-Allen end for removal of ion lens screws (if lens is not in quick-release mount), part # W1010620. Extra 2mm bits, part # W1010598 (PerkinElmer, Shelton, CT, www.perkinelmer.com).

ix. Toothbrush: Any vendor. For cleaning ion lens and glassware.

x. Ultrasonic bath: Like ULTRAsonik™ Benchtop Cleaners (NEYTECH, Bloomfield, CT, www.neytech.com) or equivalent.

d. Sources for General Laboratory Consumable Supplies

i. Bar Code Scanner: Like Code Reader 2.0 (Code Corporation, Draper, UT, www.codecorp.com) or equivalent. For scanning sample IDs during analysis setup. Any bar code scanner capable of reading Code 128 encoding at a 3 mil label density can be substituted.

ii. Carboy (for preparation of urine quality control pool and waste jug for ICPMS sample introduction system): Polypropylene 10-L carboy (like catalog # 02-960-20C, Fisher Scientific, Pittsburgh, PA, www.fischersci.com) or equivalent. Carboys with spouts are not advised due to potential for leaking.

iii. Containers for diluent and Rinse Solution: Two liter Teflon™ containers (like catalog# 02-923-30E, Fisher Scientific, Pittsburgh, PA., www.fishersci.com) and 4L polypropylene jugs (like catalog# 02-960-10A, Fisher Scientific, Pittsburgh, PA, www.fishersci.com) have both been used. Acid rinse before use. Equivalent containers may be substituted.

iv. Cups for urine collection: Like polypropylene 4.5 oz cup, catalog # 354013 (Becton Dickinson Labware, Franklin Lakes, NJ, www.bd.com) or equivalent. Each lot of cups used must be lot screened (tested to be free of trace metal contamination). Clear plastics tend to have lowest trace metal contamination.

v. Gloves: Powder-free, low particulate nitrile (like Best CleaN-DEX™ 100% nitrile gloves, any vendor). Equivalent nitrile or latex gloves may be substituted.

vi. Paper towels: For general lab use, any low-lint paper wipes such as KIMWIPES®EX-L Delicate Task Wipers or KAYDRY®EX-L Delicate Task Wipers (Kimberly-Clark Professional, Atlanta, GA, www.kcprofessional.com). For sensitive applications in cleanrooms, a wipe designed for cleanroom use may be desired such as the Econowipe or Wetwipe (Liberty, East Berlin, CT, www.liberty-ind.com).

vii. Pipette (for preparation of urine dilutions to be analyzed): Micromedic Digiflex-CX Automatic™ pipette equipped with 10.0-mL dispensing syringe, 2 mL sampling syringe, 0.75-mm tip, and foot pedal (Titertek, Huntsville, AL, http://www.titertek.com/).

viii. Pipettes (for preparation of intermediate stock working standards & other reagents): Like Brinkmann Research Pro Electronic pipettes (Brinkmann Instruments, Inc., Westbury, NY, http://www.brinkmann.com/home/). 5-100 ☐ L (catalog #4860 000.070), 20-300 ☐L (catalog #4860 000.089), 50-1000 ☐L (catalog #4860 000.097), 100-5000 ☐L (catalog #4860 000.100). Note: pipette catalog numbers are without individual chargers. Can purchase individual chargers (pipette catalog numbers will differ) or a charging stand that will hold four pipettes (catalog #4860 000.860). When purchasing pipette tips (epTips), purchase one or more boxes, then "reloads" for those boxes after that: 5-100 ☐L (box catalog # 22 49 133-4, reload catalog # 22 49 153-9), 20-300 ☐L (box catalog # 22 49 134-2, reload catalog # 22 49 154-7), 50-1000 ☐L (box catalog # 22 49 135-1, reload catalog # 22 49 155-5), 100-5000 ☐L (box catalog # 22 49 138-5, reload catalog # 22 49

198-9, bulk bag catalog # 22 49 208-0). Equivalent pipettes and tips can be substituted.

ix. Tubes for sample analysis (for autosampler): Like polypropylene 15-mL conical tubes, BD Falcon model #352097 (Becton Dickinson Labware, Franklin Lakes, NJ, www.bd.com). Equivalent tubes may be substituted which are shown by lot screening to be free of trace metal contamination. Clear plastics tend to have lowest trace metal contamination. Blue colored caps have also been used successfully for this method.

x. Tubes for storage of intermediate working stock standards: Like polypropylene 50-mL conical tubes, BD Falcon model #352098 (Becton Dickinson Labware, Franklin Lakes, NJ, www.bd.com). For use in storage of intermediate working stock standards. Equivalent tubes may be substituted which are shown by lot screening to be free of trace metal contamination. Clear plastics tend to have lowest trace metal contamination. Blue colored caps have also been used successfully for this method.

xi. Vortexer: Like MV-1 Mini Vortexer (VWR, West Chester, PA, www.vwr.com). Used for vortexing urine specimens before removing an aliquot for analysis. Equivalent item can be substituted.

xii. Water purification system: Like NANOpure DIamond Ultrapure Water System (Barnstead International, Dubuque, Iowa, www.barnstead.com). For ultra-pure water used in reagent and dilution preparations. An equivalent water purification unit capable of producing ≥18 Mega-ohm·cm water may be substituted.

e. Sources of Chemicals, Gases, and Regulators

i. Acid, Hydrochloric acid: Veritas™ double-distilled grade, 30-35% (GFS Chemicals Inc. Columbus, OH, www.gfschemicals.com). This is referred to as “concentrated” hydrochloric acid in this method write-up. For use in preparation of intermediate working stock standards. An equivalent hydrochloric acid product may be substituted, but it must meet or exceed the purity specifications of this product for trace metals content.

ii. Acid, Nitric acid: Veritas™ double-distilled grade, 68-70% (GFS Chemicals Inc. Columbus, OH, www.gfschemicals.com). For use in diluent, rinse solution, intermediate working stock standards, and QC pool preparations. This is referred to as “concentrated” nitric acid in this method write-up. An equivalent nitric acid product may be substituted, but it must meet or exceed the purity specifications of this product for trace metals content.

iii. Ethanol (EtOH): USP dehydrated 200 proof (Pharmco Products, Inc.) or equivalent.

iv. Argon Gas (for plasma & nebulizer) and Regulator: High purity argon (>99.999% purity, Specialty Gases Southeast, Atlanta, GA, www.sgsgas.com) for torch and nebulizer. Minimum tank source is a dewar of liquid argon (180-250L). Bulk tank (1500^{+}L is preferred).

1. Regulator for argon (at dewar): Stainless steel, single stage, specially cleaned regulator with 3000 psig max inlet, 0-100 outlet pressure range, CGA 580 cylinder connector, and needle valve shutoff on delivery side terminating in a ¼" Swagelok connector. Part number KPRAFPF415A2AG10 (Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com). An equivalent regulator from an alternate vendor may be substituted. # *Spares = 1*.

2. Regulator for argon (between bulk tank and PerkinElmer filter regulator): Single Stage 316SS Regulator, with 0-300 psi Inlet Gauge, 0-200 psi Outlet Gauge, Outlet Spring Range, 0-250 psi, ¼" Swagelok Inlet Connection, ¼ turn Shut off Valve on Outlet with ¼" Swagelok Connection and Teflon Seals. Part number KPR1GRF412A20000-AR1 (Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com). An equivalent regulator from an alternate vendor may be substituted. # *Spares = 1*.

3. Regulator for argon (PerkinElmer filter regulator on back of ELAN): Argon regulator filter kit. Catalog number N812-0508 (PerkinElmer, Shelton, CT, www.perkinelmer.com).

v. Argon / hydrogen: Argon (90%) / hydrogen (10%) for DRC channel A. Initial purity of argon = 99.9997^{+}% ("Research grade 5.7"). Initial purity of hydrogen = 99.9999^{+}% ("Research Grade 6.0"). Mixture is typically purchased in cylinder size 35 (6"x24") (Airgas South, Atlanta, GA, www.airgas.com).

1. Regulator for argon / hydrogen: Stainless steel, two stage, specially cleaned regulator with 3000 psig max inlet, 0-25 outlet pressure range, CGA 350 cylinder connector, and needle valve shutoff on delivery side terminating in a ¼" Swagelok connector. Like part number KCYADPF412A2AD10 (Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com). An equivalent regulator from an alternate vendor may be substituted. # *Spares = 1*.

2. Flash Arrestor (Stainless steel): Like part # 6104 (Matheson Tri Gas, Montgomeryville, PA, www.mathesontrigas.com) or equivalent.

vi. Disinfectant, for work surfaces: Bleach-rite spray (any distributor). On-site dilutions of bleach (1part bleach + 9 parts water) may be substituted, but must be re-made daily.

vii. Oxygen: Oxygen ("Research Grade Research Grade 5.0", 99.9999% purity) for DRC channel B. Typically purchased in cylinder size 300 (9.5" x 54") (Airgas South, Atlanta, GA, www.airgas.com).

1. Regulator for oxygen: High purity brass body with monel trim, two stage regulator. Stainless steel is not used for this application due to safety concerns of working with oxygen at high pressure [10]. For one regulator, order the following parts, and ask that they be tested and assembled (Engineered Specialty Products, Kennesaw, GA, www.espgauges.com).

a. Tescom part # 44-3410S24-555
Regulator body: Brass bar stock, two stage, Monel trim, TFE seats, Elgiloy diaphragms, Cv=0.05, 3000 psig max inlet, 1-25 psig outlet range, 1/4 FNPT inlet / outlet / gauge ports, O_2 cleaned to ASTMG93 and CGA4.1.

b. Tescom part # 60500-3000N
Inlet pressure gauge: 2" diameter, 0-3000 psig range , O_2 cleaned, ¼" MNPT bottom, brass.

c. Tescom part # 60500-0015N
Delivery pressure gauge: 2" diameter, 0-15 psig range , O_2 cleaned, ¼" MNPT bottom, brass.

d. Tescom part # 63842-540-B
NPT to CGA Adaptor: ¼" NPT to CGA 540 adapter, brass.

e. Swagelok part # B-200-1-4:
Adapter: Brass male connector, ¼" MNPT to 1/8" Swagelok (Georgia Valve and Fitting, Atlanta, GA, www.swagelok.com).

An equivalent regulator from an alternate vendor may be substituted.
 # Spares = 1.

2. Flash Arrestor (brass): Like part # 6103 (Matheson Tri Gas, Montgomeryville, PA, www.mathesontrigas.com) or equivalent.

viii. Standard, Gallium: Like 1,000 mg/L, item # PLGA2-2Y. (SPEX Industries, Inc., Edison, NJ, www.spexcsp.com). Used as an

internal standard in diluent. Any vendor whose standards are traceable to the National Institute for Standards and Technology may be substituted. The standard must have low trace metal contamination.

ix. Standard, Iridium: Like 1,000 mg/L iridium, item # PLIR3-2Y (SPEX Industries, Inc., Edison, NJ, www.spexcsp.com). Used as an internal standard in diluent. Any vendor whose standards are traceable to the National Institute for Standards and Technology may be substituted. The standard must have low trace metal contamination.

x. Standard, Multi-element intermediate stock standard: Item number SM-2107-003 (High Purity Standards, Charleston, SC, http://www.hps.net/). This is a custom mix solution. This solution is diluted to prepare the intermediate stock working standards, which are in turn diluted to prepare the working calibrators. This solution can be prepared in-house from NIST traceable single element stock solutions if necessary.

xi. Standard, Rhodium: Like 1,000 mg/L, item # PLRH3-2Y. (SPEX Industries, Inc., Edison, NJ, www.spexcsp.com). Used as an internal standard in diluent. Any vendor whose standards are traceable to the National Institute for Standards and Technology may be substituted. The standard must have low trace metal contamination.

xii. Standard, single element stock standards for preparation of urine quality control pools: National Institute of Standards and Technology (NIST) Standard Reference Materials (SRMs) 3103a (As), 3105a (Be), 3113 (Co), 3134 (Mo), 3108 (Cd), 3102a (Sb), 3111a (Cs), 3104a (Ba), 3163 (W), 3128 (Pb), 3140 (Pt), 3158 (TI), and 3164 (U) (National Institute of Standards and Technology (NIST), Office of Standard Reference Materials, Gaithersburg, MD, www.nist.gov). Other sources of standards can be used if they are NIST traceable.

xiii. Triton X-100™ surfactant: Like “Baker Analyzed” TritonX-100™ (J.T. Baker Chemical Co., www.jtbaker.com). Another source may be substituted, but it must be free of trace-metal contamination.

Preparation of Reagent and Materials.

f. Internal Standard Intermediate Mixture: Preparation of single intermediate solution containing all internal standards will simplify the addition of the internal standards into the final diluent solution. This solution can be purchased rather than prepared. To prepare 200 mL of the Intermediate internal standard solution

i. Partially fill a 200 mL acid-washed volumetric flask (PP, PMP, or Teflon™) with ≥18 Mega-ohm·cm water (approximately 100-150 mL).

ii. Carefully add 4 mL of double-distilled, concentrated nitric acid. Mix into solution.

iii. Add 0.8 mL of 10,000 ug/mL Rh standard. If initial Rh standard concentration is different, adjust volume proportionally.

iv. Add 0.8 mL of 10,000 ug/mL Ir standard. If initial Ir standard concentration is different, adjust volume proportionally.

v. Add 0.8 mL of 10,000 ug/mL Ga standard. If initial Ga standard concentration is different, adjust volume proportionally.

vi. Fill to mark (200mL) and mix thoroughly.

vii. Label should include "Internal Standard Intermediate Mixture. 40 ug/mL Rh, Ir, and Ga. 2% (v/v) HNO3", "Store at room temperature", preparation date, expiration date 1 year from preparation date, and preparer's initials.

g. Diluent and Carrier

i. Purpose: All samples (blanks, calibrators, QC, or patient samples) are combined with the diluent during the sample preparation step before analysis. This is where the internal standards are added which during the analysis will compensate for instrumental variations on the analyte signal. If using the FAST sample introduction system, the diluent is also used as the carrier solution.

ii. Preparation:

1. Diluent Preparation for 12 element method (***not including arsenic***)
– NO ETHANOL

a. Contents: An aqueous solution of 10 microgram/L Rh, Ir, and Ga in 2% (v/v) double-distilled nitric acid.

b. Preparation (4L) & storage: This solution does not have to be made up in a volumetric flask. The important thing about the concentration of the internal standards is that they be consistent within all samples in one run. To prepare different volumes of diluent, add proportionally larger or smaller volumes of the solution constituents.

i. Acid-rinse a 4 L container (material may be polypropylene (PP), polymethylpentene (PMP), or Teflon™).

ii. Partially fill the 4 L container with ≥18 megaohm·cm water.

iii. Carefully add 80 mL double-distilled, concentrated nitric acid and mix.

iv. Add 1 mL of the 40 ug/mL Rh, Ir, Ga internal standard solution. If other concentrations are used, the volume added should be adjusted proportionally.

v. Make up to volume (4 L) with ≥18 megaohm·cm water.

vi. Store at room temperature and prepare as needed.

vii. Label should include "10 µg/L Rh, Ir, and Ga", "2% (v/v) HNO_3", "Store at room temperature", preparation date, expiration date (1 year from prep), and preparer's initials.

2. Diluent Preparation ***for urine arsenic*** method – CONTAINS ETHANOL

   a. Contents: An aqueous solution of 10 microgram/L Rh, Ir, and Ga in 2% (v/v) double-distilled nitric acid and 1.5% (v/v) ethanol.

   b. Preparation (4L) & storage: This solution does not have to be made up in a volumetric flask. The important thing about the concentration of the internal standards is that they be consistent within all samples in one run. To prepare different volumes of diluent, add proportionally larger or smaller volumes of the solution constituents.

      i. Acid-rinse a 4 L container (material may be polypropylene (PP), polymethylpentene (PMP), or Teflon™).

      ii. Partially fill the 4 L container with ≥18 megaohm·cm water.

      iii. Carefully add 80 mL double-distilled, concentrated nitric acid and mix.

      iv. Carefully add 60 mL dehydrated 200 proof ethanol and mix.

      v. Add 1 mL of the 40 ug/mL Rh, Ir, Ga internal standard solution. If other concentrations are used, the volume added should be adjusted proportionally.

      vi. Make up to volume (4 L) with ≥18 megaohm·cm water.

vii. Store at room temperature and prepare as needed.

viii. Label should include “10 µg/L Rh, Ir, and Ga”, “2% (v/v) HNO_3”, “1.5% (v/v) Ethanol”, “Store at room temperature”, preparation date, expiration date (1 year from prep), and preparer’s initials.

h. Base Urine

i. Purpose: This urine pool material will be mixed with the intermediate working calibrators just prior to analysis to matrix-match the calibration curve to the urine matrix of the unknown samples.

ii. Contents: A mixture of multiple urine sources collected from anonymous donors are used to approximate an average urine matrix.

iii. Preparation & Storage:

1. Collect urine anonymously by placing screened containers and collection cups in the restrooms with a sign stating the reason the specimens are being collected, the name of the investigator to contact for additional information, and requesting that people provide a urine specimen (complete details can be found in CDC protocol #3994, ProTrack # DLSITN0313).

2. Once the urine is collected from donors, it should be analyzed to ensure that concentrations of the analytes in this method are relatively low, so as to not interfere with the proper measurement of calibrators.

3. Once screened, mix the urine collections together in a larger container (i.e. acid washed polypropylene (PP), polymethylpentene (PMP), or Teflon™) and stir for 30+ minutes on a large stir plate (acid wash large Teflon™ stir bar before use).

4. For short term storage, store at 2-4°C. For long-term storage, dispense into smaller-volume tubes (i.e., 50-mL acid-washed or lot screened polypropylene tubes) and store at ≤ -20°C.

5. Labels on 50mL tubes should include “Base Urine for Multi-element Method”, “Store Long Term at ≤ 20° C”, “Store Short Term at 2-4° C”, preparation date, expiration date 3 years from prep date, and preparer’s initials.

i. ICP-DRC-MS Rinse Solution

i. Purpose: Pump this solution into the sample introduction system between samples to prevent carry-over of the analytes of interest from one sample measurement to the next.

ii. Preparation:

1. Intermediate Triton X-100 Solution: To avoid the process of dissolving pure Triton X-100 on a daily basis, prepare an intermediate 2% Triton X-100™ / 5% (v/v) double-distilled, nitric-acid solution for daily use.

    a. To prepare 2L of Intermediate Triton X-100 Solution:

        i. Partially fill a 2 L acid-washed bottle (PP, PMP, or Teflon™) with ≥18 Mega-ohm·cm water (approximately 1-1.5 L). Use of volumetric flask is not required.

        ii. Add 20 mL of Triton X-100™ and stir until completely dissolved. Use a Teflon™ stir bar and stir plate if necessary (acid wash stir bar before use).

        iii. Carefully add 100 mL of double-distilled, concentrated nitric acid.

        iv. Fill to 2 L and stir thoroughly.

        v. Label should include "2% Triton X-100™ / 5% (v/v) HNO3", "Store at room temperature", preparation date, expiration date 1 year from preparation date, and preparer's initials.

2. Rinse Solution Preparation for 12 element method (***not including arsenic***) – NO ETHANOL

    a. Contents: A 0.002% Triton X-100™, 5% (v/v) double-distilled nitric acid solution.

    b. Preparation & Storage: To Prepare 4 L of the Final Rinse Solution,

        i. Partially fill a 4 L acid-washed bottle (PP, PMP, or Teflon™) with ≥18 Mega-ohm·cm water (approximately 2-3 L). Use of volumetric flask is not required.

        ii. Add 4 mL of the 2% Triton X-100™ / 5% (v/v) double-distilled, nitric-acid intermediate stock solution and mix well.

        iii. Carefully add 200 mL of double distilled concentrated nitric acid and mix well.

        iv. Fill to 4 L using ≥18 Megaohm·cm water.

v. Store at room temperature and prepare as needed. To prepare volumes other than specified here, add proportionally larger or smaller volumes of the solution constituents.

vi. Label should include "0.002% Triton X-100™ / 5% (v/v) HNO3", "Store at room temperature", preparation date, expiration date one year from preparation date, and preparer's initials.

3. Rinse Solution Preparation for arsenic method – INCLUDES ETHANOL

a. Contents: A 0.002% Triton X-100™, 5% (v/v) double-distilled nitric acid solution and 1.5% (v/v) ethanol.

b. Preparation & Storage: To Prepare 4 L of the Final Rinse Solution,

i. Partially fill a 4 L acid-washed bottle (PP, PMP, or Teflon™) with ≥18 Mega-ohm·cm water (approximately 2-3 L). Use of volumetric flask is not required.

ii. Add 4 mL of the 2% Triton X-100™ / 5% (v/v) double-distilled, nitric-acid intermediate stock solution and mix well.

iii. Carefully add 200 mL of double distilled concentrated nitric acid and mix well.

iv. Carefully add 60 mL dehydrated 200 proof ethanol and mix well.

v. Fill to 4 L using ≥18 Megaohm·cm water.

vi. Store at room temperature and prepare as needed. To prepare volumes other than specified here, add proportionally larger or smaller volumes of the solution constituents.

vii. Label should include "0.002% Triton X-100™ / 5% (v/v) HNO3, 1.5% (v/v) ethanol", "Store at room temperature", preparation date, expiration date one year from preparation date, and preparer's initials.

j. Standards and Calibrators

i. Multi-element Intermediate Stock Calibration Standard

1. Purpose: This master solution will be diluted to prepare five intermediate working calibrators.

2. Contents: An aqueous solution containing all 13 elements of interest (12 element panel analytes, arsenic, and elements for future R&D (see certificate of analysis), but does not include the internal standards). Matrix is 2% (v/v) HNO3 and 1% (v/v) HCl with traces of HF in ≥18 Mega-ohm·cm water.

3. Preparation (Purchase) & Storage:

   a. Purchasing from vendors: Either purchased as a NIST-traceable custom mixture, or prepared in-house.

Current vendor & preparation process: Currently purchased from High Purity Standards (Charleston, SC, part number SM-2107-003).

   b. In-house Preparation: Standard may be made in the lab from NIST-traceable single element standards.

   c. Storage: Store at room temperature. Label with additional information such as "store at room temperature", date received, date opened, and initials of person to first open.

ii. Multi-element Intermediate Working Calibration Standards

1. Purpose: Use each day of analysis to prepare the final five working calibrators that will be placed on the autosampler.

2. Content: Five aqueous dilutions of the multi-element intermediate stock calibration standard solution in 2% (v/v) double-distilled nitric acid and 1% (v/v) hydrochloric acid.

3. Preparation & Storage: Different volumes may be prepared by adding proportionally larger or smaller volumes of solution constituents.

   a. Cleaning flasks: Acid-rinse three 100-mL, one 200-mL, one 500-mL PP, and one 2 L PP (or PMP) volumetric flasks. Check their cleanliness by comparing the counts observed on the ICP-DRC-MS for 1% (v/v) HNO_3 before and after contact with the flasks. Mark each flask according to intended use. Dedicate to purpose.

   b. HNO_3 & HCl Diluent Preparation: In the cleaned 2L flask, add 1-1.5L ≥18 Megaohm·cm water, 40 mL high purity concentrated HNO_3, and 20 mL high purity concentrated HCl. Fill to the mark and mix thoroughly. Use this diluent to fill the remaining flasks during preparation of the intermediate working calibration standards.

   c. Dilutions & Storage:

i. Partially fill the 100 mL, 200 mL, and 500 mL flasks with the HNO_3 & HCl diluent (50-75% full).

ii. Pipette the appropriate volume of the multi-element intermediate stock calibration standard solution into each of the five volumetric flasks. Dilute each to the volumetric mark with the HNO_3 & HCl diluent using a pipette for the final drops. Mix each solution thoroughly. .

iii. Once mixed, transfer to acid-cleaned, labeled, 50-mL containers (PP, PMP, or Teflon™) for storage. Labels should include information such as "Multi-element Urine Working Calibrators", "2% (v/v) HNO3, 1% (v/v) HCl", date of preparation, expiration date (1 year from date of preparation), "store at room temperature", initials of preparer, and concentrations for each element.

iii. Working Multi-element Calibrators

1. Purpose: The working multi-element calibrators will be analyzed in each run to provide a signal-to-concentration response curve for each analyte in the method. The concentration of an analyte in a patient urine sample dilution is determined by comparing the observed signal from the dilution of the patient urine sample to the response curve from the working multi-element calibrators.

2. Content: Dilutions (1:100) of the corresponding five intermediate working calibration standards.

iv. Preparation & Use: Made immediately prior to analysis when the intermediate working calibration standards are mixed with base urine (Section 7.b) and diluent (Section 7.a) using a Digiflex automatic pipetter.

v. Multi-element Intermediate Stock Calibration Verification Standard

1. Purpose: This is the master solution from which all working calibration verification standards will be prepared. It will be diluted to prepare intermediate working calibration verification standards which are in turn diluted and used to verify the accuracy of instrument response to analyte concentrations greater than the calibration range. This stock solution contains all elements needed for both the arsenic and the 12 element panel.

2. Contents: For long shelf life, these four aqueous solutions have different matrices which are optimized to the elements

in each (this was recommended for the calibration verification stock standard solutions because the elemental concentrations were very high compared to the concentrations in the calibration stock standard solution.

a. Solution A: HNO_3 (10%), HF (0.5%)

b. Solution B: HCl (10%), trace HNO_3

c. Solution C: HCl (1%)

d. Solution D: HCl (2%)

3. Preparation (Purchase) & Storage:

a. Purchasing from vendors: The intermediate stock calibration verification standard solutions may be purchased as custom mixtures from any vendor which prepares multi-element solutions that are traceable to the National Institute for Standards and Technology (NIST) for their accuracy.

Current vendor & preparation process: Currently it is purchased from High Purity Standards (Charleston, SC, part number SM-2107-012, solutions A, B, C, and D).

b. In-house Preparation: If outside laboratories were not available to prepare the intermediate stock calibration standard solution, it is also possible to make it in the laboratory from single element standards which are NIST traceable.

c. Storage: Due to the uranium content, and in keeping with the guidance of the CDC radiation safety manual [9], the intermediate stock standards must be kept in a lockbox. Store the solutions at room temperature. Label these bottles from HPS with additional information such as “store at room temperature”, date received, date opened, and initials of person to first open.

vi. Multi-element Intermediate Working Calibration Verification Standards

1. Purpose: Verification of accuracy of instrument response to analyte concentrations greater than the calibration range

2. Content: The intermediate working calibration verification standard solutions used in this method are aqueous dilutions of the multi-element intermediate stock calibration verification standard solution in 2% (v/v) double-distilled nitric acid and 1% (v/v) hydrochloric acid containing all 13 elements of interest (does not include the internal standards).

a. Preparation & Storage: Prepare the Intermediate Calibration Verification Standards for analysis just as Intermediate Working calibrators are prepared.

vii. Internal Quality Control Materials ("Bench" QC)

1. Purpose: Internal (or "bench") quality control (QC) materials are used to evaluate the accuracy and precision of the analysis process, and to determine if the analytical system is "in control" (is producing results that are acceptably accurate and precise). They are included in the beginning and at the end of each analytical run.

2. Content: The internal (or "bench") quality control (QC) materials used in this method are pooled human urine, acidified to 1-2% (v/v) HNO_3, and may have been spiked to reach a desired concentration. The analyte concentrations in the "low QC" are in the low-normal concentration range. The analyte concentrations in the "high QC" are in the high-normal concentration range.

3. Preparation & Storage: Quality control materials can be either prepared by and purchased from an external laboratory or prepared within the CDC laboratories. Quality control must always be traceable to the National Institute for Standards and Technology (NIST). The CDC laboratory currently prepares its own bench QC materials using the following procedures:

a. Collection of urine: Collect urine anonymously by placing screened containers and / or collection cups in the restrooms with a sign stating the reason the specimens are being collected, the name of the investigator to contact for additional information, and requesting that people provide a urine specimen (complete details can be found in CDC protocol #3994, ProTrack # DLSITN0313). Volume of urine to collect is dependent on the desired pool size. This write-up will assume a 10-L pool size for both the low and high bench QC.

b. Screening Urine: Screen collected samples for metal content before mixing together to make 2 separate base urine pools (for preparing the low and high bench QC materials). Samples can be screened individually or after combining several together (reduces number of analyses).

i. Keep urine refrigerated whenever possible to minimize microbial growth.

ii. Because this is only a quick screen of the metal content, the number of replicates in the urine method can be reduced to one in order to reduce analysis time.

iii. Analyte concentrations in the final urine pool to be spiked for the low bench QC pool should be in the low-normal population range. Analyte concentrations in the final urine pool to be spiked for the high bench QC pool should be less than some pre-selected target concentration values in the high normal population range. See the Second National Report on Human Exposure to Environmental Chemicals for estimations of the normal population ranges for metals (http://www.cdc.gov/exposurereport/).

c. Combining Collected Urine: Be attentive not to combine only diluted matrix urine samples into the low pool and only concentrated matrix urine samples into the high pool. The goal is for combining samples is to approach an 'average' matrix for each pool.

i. Graduate four acid-washed 10-L carboys (PP or PMP) in 0.5 L increments (two will be used for decanting into).

ii. Combine collected urine samples into two separate acid-washed 10-L carboys (PP or PMP), according to their concentrations, for the low bench and high bench QC pools.

iii. Mix each urine pool using large acid washed, Teflon™ coated stir bars and large stir plates. Keep urine refrigerated whenever possible.

iv. Acidify each urine pool to 1% (v/v) HNO3 by adding the appropriate volume of double distilled HNO3. Stir for 30+ min on large stir plates.

d. Settling out of solids:

i. Refrigerate the urine (no stirring) for 1-3 days to allow for settling out of solids.

ii. For each urine pool, decant the urine into another of the acid-washed 10-L carboys to remove the urine from the solids settled out on the bottom of the carboy.

iii. Repeat steps (i) and (ii) until minimal solids are left at the bottom of the carboy after sitting overnight.

e. Spiking of urine

i. Analyze a sample of each urine pool. Record these results for future recovery calculations.

ii. Use these results to determine target analyte concentrations possible for the pools

iii. Calculate the volume of single element standards needed to spike each pool to the desired concentrations.

iv. While stirring the pools on large stir plates, spike each pool with calculated volumes of single element standards (all spiking standards used must be traceable to NIST).

v. Continue to stir pools for 30+ minutes after spiking, then reanalyze.

vi. Repeat steps 4 and 5 until all analytes reach target concentrations keeping track of the total volume of spiking solution added to each urine pool.

f. Dispensing and Storage of urine

i. Container Types: Dispense urine into lot screened containers (i.e. – 5 or 15 mL polypropylene tubes). If possible, prepare tubes of QC which have only enough volume for one typical run + 1 repeat analysis. This allows for one vial of QC to be used per day of analysis, reducing chances of contamination of QC materials due to multi-day use.

ii. Labels: Place labels on vials after dispensing and capping if the vials are originally bagged separately from the caps. This minimizes the chance for contamination during the process. Include at least the name of QC pool (text and bar code), date of preparation, and a vial number on the labels.

iii. Dispensing: Dispensing can be accomplished most easily using a Digiflex automatic pipetter in continuous cycling dispense mode. This process should be done in a clean environment (i.e. a class 100 clean room area or hood).

a. Allow urine pool to reach room temperature before dispensing (to prevent temperature gradients possibly causing concentration gradients across the large number of vials being dispensed and to prevent condensation problems during labeling of vials). This may require leaving the carboy of urine at room temperature overnight before dispensing.

b. Replace the tubing attached to the dispensing syringe (left when looking at front of Digiflex) with a length of clean Teflon™ tubing long enough to reach into the bottom of the 10L carboy while it is sitting on the stir plate.

c. Check cleanliness of Digiflex before use by analyzing 1-2% (v/v) HNO3 which has been flushed through the Digiflex with a portion of the same solution which has not been through the Digiflex.

d. Approximately one hour before dispensing begins,

   i. With the large stir plate close to the left side of the Digiflex, begin stirring the urine pool to be dispensed.

   ii. Also during this time, flush the Digiflex with urine from the pool to be dispensed. Place the ends of the tubing attached to both the sample and dispensing syringes into the carboy of urine so that urine won't be used up during this process. Be sure to secure both ends of tubing in the carboy with Parafilm so they will not come out during the flushing process.

e. After dispensing the urine into the vials, cap the vials and label them. Placing labels on vials after capping minimizes the chance for contamination during the process.

iv. Homogeneity Testing: After dispensing, check homogeneity of analyte concentrations in pool aliquots by analysis of every Nth sample dispensed (where N ~ 20 - 50 depending on the pool size). Sample more heavily from the beginning and the ending portions of the tubes dispensed (these are the regions where most homogeneity problems occur). Keep samples pulled for homogeneity analysis in the sequence that they were dispensed for the purpose of looking for trends in concentrations. Once dispensed and homogeneity has been shown to be good throughout the tubes of a pool, store tubes at≤ -20°C and pull tubes out as needed for analysis.

v. Storage: Urine pools should be stored long term at≤ -20°C. Short term storage (several days) at refrigerator temperature (~ 2-4°C).

Analytical Instrumentation & Parameters

k. Instrumentation & Equipment Setup:

ICP-DRC-MS: Inductively Coupled Plasma Dynamic Reaction Cell Mass Spectrometer ELAN® 6100 DRC^{Plus} or ELAN® DRC II.

1. Modifications made to ICP-DRC-MS

a. Plastic tubing for between mass flow controllers and dynamic reaction cell have been replaced with stainless steel. Stainless steel tubing is preferred between the reaction gas cylinder / regulator and the back of the ICP-DRC-MS instrument.

b. A second mass flow controller has been added (channel B) for use with oxygen.

2. Configuration of tubing for liquid handling:

a. Sample introduction system:

i. SC-FAST valve setup: Valve connections must match this description for urine total arsenic analysis.

ii. SC autosampler setup for non-FAST applications:

Tubing connection between autosampler rinse station and rinse solution reservoir: Tubing of different inner diameters can be obtained from Elemental Scientific, their distributors, or custom built in the lab to optimize the rinse station fill rate between samples. Rinse station should not go empty at any point.

Tubing for autosampler rinse station waste removal: Use minimum drain tubing to make this connection. If this tube is too long, the rinse station will not drain properly.

Rinse solution jug: Leave one of the caps on the top of the rinse jug loose to allow air venting into the jug as liquid is removed. Otherwise the jug will collapse on itself as the liquid is removed and a vacuum is created inside.

7. Calibration and Calibration Verification Procedures

1. Calibration Verification:

   Bi-annual tests as defined in the DLS Policy and Procedures manual: CLIA requires the verification of accuracy of instrument response to analyte concentration be completed at least every 6 months. NIST traceable calibrators are analyzed in each run to define this response up to the concentration of the highest calibrator in the run. To verify accuracy of instrument response at concentrations higher than the highest calibrator in each run, analyze a NIST traceable standard with very high concentrations . Prepare the Calibration Verification Standard for analysis just as a working calibrator is prepared. Use the “Urine Blank” as the blank when it is analyzed. If the observed concentrations for the Calibration Verification Standard are not within 10% of the target value the lab supervisor should be notified and the issue should be investigated. Do not substitute external reference materials (i.e. biological samples from a PT program) for the Calibration Verification Standard when performing this. Solutions needed for the Calibration Verification checks can be purchased from standards vendors (i.e.SPEX, High Purity Standards, etc . . .) or prepared in-house from NIST traceable single element standards. Always verify that normal background levels have been re-achieved through adequate rinse time following analysis of elevated standards for calibration verification.

   a. As-needed confirmations (per supervisor discretion): When a sample result is greater than the highest calibrator in the run, the supervisor may request that the result be confirmed in an analysis run which includes a standard or external reference material with equivalent (within 10%) or greater concentration than the sample. In order to avoid needless contamination of the instrument with high

concentrations of analytes, the analyst should use the lowest appropriate calibration verification solution concentrations to meet the need.

For *infrequent* verification needs, the calibration verification stock solutions can be used to prepare verification standards to appropriate concentrations. This will, however, introduce elevated concentrations of all elements in the method to the sample introduction system. Frequent measurement of these very high concentrations can result in high background levels in the instrument which are difficult to rinse out and which may limit the ability to measure low concentrations.

For frequent verification needs (i.e. when certain studies have many elevated results on particular elements), use NIST-traceable single element stock standards to prepare single element verification standards. This will limit the exposure of the instrument to elevated concentrations of only the elements needing verification.

Always verify that normal background levels have been re-achieved through adequate rinse time following analysis of elevated standards for calibration verification.
An external reference material (i.e. historical proficiency testing sample) can be substituted in place of the Calibration Verification Standard sample in these situations IF The target value has been assigned by an external source (i.e. NIST, or the proficiency testing program).

b. The concentration of the external reference material is within 10% or is higher than the concentration of the material you need it to confirm.

c. There is confidence that there is no contamination of previously used external reference material.

d. A note to file is made that this was done.

e. If the observed concentrations are not within 10% of the target value the lab supervisor should be notified and the issue should be investigated.

8. Procedure Operating Instructions; Calculations; Interpretation of Results

a. Daily Analysis of Samples

i. Preparation of the Analytical Equipment

For further details on any part of this description, see the ITN Daily Startup SOP for ELAN ICPMS instruments.

1. Power on the computer, printer, and autosampler, and log into the operating system.

2. Peristaltic pump: Set up the peristaltic pump tubing with proper tension for the sample rinse station.

3. Software: Starting the ESI software before starting the ELAN software may improve stability of software.
4. Daily Pre-Ignition Maintenance Checks: Perform daily maintenance checks as described in the IRAT Daily Startup SOP for ELAN instruments (i.e., Ar supply pressure, interface components cleanliness and positioning, interface pump oil condition, vacuum pressure, etc.). Make appropriate notes in the Daily Maintenance Checklist and Instrument Log Book.
5. Start the Plasma: In the INSTRUMENT window of the software (or on the front of the ELAN), press the "Start" button to ignite the plasma.
6. Aspirate rinse (multi-element method) or carrier (arsenic method) solution: Send Probe to Rinse Station (multi-element method) or manually place carrier probe into carrier solution (arsenic method).
7. Start the peristaltic pump: *S*tart the peristaltic pump by pressing the appropriate arrow in the DEVICES window (make sure that the rotational direction is correct for the way the tubing is set up in the peristaltic pump). Set the pump speed to a slow speed in the DEVICES window during warm-up.
8. Warm-up time: Allow approximately 30 to 45 minutes warm-up time for the ICP-DRC-MS after igniting the plasma. This warm-up time is for the RF generator. There will be another "Stability time" for the DRC later in this procedure.
9. Optimizations and Daily Performance Check: After this warm-up time, perform a daily performance check and any optimizations necessary (as described in the ITN Daily Startup SOP for ELANs). Include Be (m/z 9) in the daily performance check. Fill in the Daily Maintenance Checklist according to the optimization procedures performed.
    a. Magnesium (^{24}Mg) may have high RSDs due to the use of Triton-X100 in the rinse solution. Avoid this problem by either temporarily using non-Triton-containing rinse solution during the daily check, or repeating the daily check multiple times in succession with no rinse time between.
        i. Saving the Files: Save new tuning (mass calibration) parameters to the file "default.tun." Save new optimization parameters (i.e., detector voltages, autolens values, nebulizer gas flow rate) to the file "default.dac."

10. Software setup for Analysis:
    a. Workspace (files & folders): Click on "Open Workspace" from the "File" menu. Select the workspace file "CDC_urine multi-element.wrk" (or one customized for user preferences).
    b. Samples / Batch Window: Update the window to reflect the current sample set. The only fields which need to be filled in include the autosampler location, sample identification (id), measurement action, method, sample flush time, sample flush speed, read delay time, read delay & analysis speed, wash time, wash speed. Use a bar code scanner to input data whenever possible. Save the Sample window file and re-use it on other days by simply replacing the sample IDs for the patient samples.

11. DRC Stability Time: Best analyte-to-internal standard ratio stability is obtained after 1-1.5 hrs of analysis of urine samples using the DRC method. Analyze enough "dummy" urine sample dilutions prior to any DRC analysis run to fill 1-1.5 hours of analysis time (not necessary if analyzing only a subgroup of the method containing no DRC analytes). If analyzing the full set of method analytes, 10 samples will be sufficient. .

12. Urine vs. Aqueous Method Files:
    a. The difference: There are two method files for this one method. It is necessary to use both to accomplish each run because the current PerkinElmer software will not allow for more than one blank per method file. The ONLY DIFFERENCE between these two files is on the Sampling tab where one lists the autosampler positions of the urine blank and urine calibrators (the "urblk" method file) and the other lists the autosampler position of the aqueous blank (the "aqblk" method file).
    b. Use: The ONLY TIME when it matters which of these files is used is when the measurement action *includes* "Run blank" or "Run standards". When the measurement action is only 'run sample', it does not matter whether the "urblk" or "aqblk" method file is used. Analysts typically follow the pattern below, however, for the sake of consistency and as a reminder of which blank must be used for which type of sample.

i. The *"urblk" method file:* Use to analyze the initial urine blank (blank for the calibration curve), the urine calibrators, and the urine blank checks (urblkchk1 & urblkchk2) at the very beginning of the run. The urine blank method defines the autosampler location of the urine blank and the urine calibration standards.

ii. The "*aqblk*" method file must be used to analyze all QC materials and patient samples. The aqueous blank method defines the aqueous blank in autosampler.

ii. Preparation of Samples for Analysis

1. Thaw the frozen urine specimens; allow them to reach ambient temperature.
2. DRC stability "dummy urine matrix". Prepare 50+mL of standard 2 or standard 3 to be analyzed for 1-1.5 hr before the beginning of the run. This can be prepared using 50mL polypropylene tubes or a wide-mouth bottle (which can be put on the autosampler in place of one of the tube trays).
3. Set up a series of 15-mL polypropylene tubes corresponding to the number of blanks, standards, QCs, and patient samples to be analyzed.
4. Prepare the following solutions in the 15-mL falcon tubes using the Micromedic Digiflex™ .
    a. *Aqueous Blank*: Prepare two aqueous blanks consisting of 1,000□L of ≥18 Mega-ohm·cm water and 9,000□L of diluen t. One will be the actual aqueous blank and the other will be a backup ("Aqueous Blank Check") in case the original aqueous blank gets contaminated.
    b. *Urine Blank*: Prepare two urine blank dilutions consisting of 900□L of base urine (same material used to prepare the urine calibration standards), 100 □L of ≥18 Mega-ohm•cm water, and 9,000 □L of diluent. One of these urine blanks will be the blank for the calibration standards; the other will be analyzed twice after standard 5 as UrBlkChk1 and UrBlkChk2, respectively. Results from the UrBlkChks will be used to determine the method limit of detection.
    c. *Calibrators*: Prepare the working calibration standards as 100 μL of the appropriate aqueous intermediate working calibration standard, 900 μL of base urine, and 9,000 μL of diluent.

d. *Patient & QC Samples*: Before taking an aliquot for analysis, mix the sample so that no particulates remain on the bottom of the tube. Prepare urine sample dilutions as 4,500 μL of diluent and 500 μL of the urine sample.

e. Cap all of the blanks, standards, and samples and mix them well. Uncap them and place them in the autosampler of the ELAN® ICPMS in the order that was entered in the Samples / Batch window of the ELAN software.

iii. Specimen Storage and Handling during Testing: Specimens may be left at room temperature during analysis in case confirmation analyses must be made. Take stringent precautions to avoid external contamination by the metals to be determined. Specimens may be stored short term at refrigerated temperatures, but should be stored long term (>4 weeks) at ≤ -20 °C.

iv. Starting the Analysis: To begin analysis, highlight (click and drag with the mouse) the table rows of the samples that should be included in the run, and then click on "Analyze Batch."

v. Monitoring the Analysis: Initiate work in a timely manner so that the run may be monitored. Make every effort to complete analysis within the work day so that the entire run can be monitored. If it is not possible to complete the analysis by the end of the work day, the run may be left to complete itself unattended as long as appropriate planning is made for either overnight operation or Auto Stop (see below).

Monitor the analysis for the following:

1. *DRC stability (analyte / internal standard ratio stability)*

After the analysis of the DRC stability "dummy" samples, these results can be reviewed to determine if sufficient stability of the analyte-to-internal standard ratio was reached before beginning analysis. Importing data into an MS Excel template file is useful to visualizing magnitude of drift.

2. *Proper operation of the instrument.*
3. *Contaminated blanks*.
4. *Linear calibration curves*.

a. Typical correlation coefficients will be 0.999 to 1.000.

b. The ELAN software generates a "simple linear" calibration curve (using a least squares calculation) for each of the 13 elements in this method. The curves are generated using the results from analysis of the urine blank and the 5 external urine calibrators whose concentrations are defined in the Calibration

tab of the Method file. Specifically, the software plots the "net intensity" (y-axis) versus the analyte concentration (x-axis).

5. *Bench QC results within the acceptable limits*.

   If an analyte result for the beginning QC material(s) falls outside of the 99% limits, then the following steps are recommended:

   a. If a particular calibration standard is obviously in error, remake a new dilution at the Digiflex of that working calibrator, reanalyze it, and reprocess the sample analyses using this new result as part of the calibration curve.

   b. Prepare a fresh dilution of the failing QC material and reanalyze it.

   c. Prepare fresh dilutions at the Digiflex of all of the calibration standards (working urine multi-element standards) and reanalyze the entire calibration curve using the freshly prepared standards.

   If these three steps do not result in correction of the out-of-control values for QC materials, consult the supervisor for other appropriate corrective actions. Do not report analytical results for runs that are not in statistical control.

6. *Good precision among replicates*.

7. *Consistent measured intensities of the internal standards*.

   Some sample-to-sample variations are to be expected. However the intensities should be within a few percent of one another, and should fluctuate around an average value (not drift continuously in one direction).

8. Elevated patient results.

vi. Records of Results: Run results will be documented daily in both electronic and paper form.

1. Electronic Records:

   a. Transfer of Results to the Laboratory Information System / Database: Transfer data electronically between computers or software to reduce errors. When keyboard entry must be used, proofread transcribed data after entry.

   b. Long-Term Storage of ELAN software files: Files used and produced by the ELAN software in

analyzing samples will be backed up long term on compact disk and kept a minimum of three years.

2. Paper Records: The paper copy of the results from the run should be put into the study folder(s) and should include
    a. A summary of the calibration curve statistics.
    b. A printout of analysis of each measurement made during the run.
    c. Optional, but helpful, is a printout of the DRC stability check measurements in graphical form.
    d. On the front sheet of the printed records, write the following
        i. Analyst initials
        ii. Instrument ID
        iii. Date of Analysis
        iv. Run # for the day on this instrument
        v. Study ID and Group Number
        vi. Database batch ID (Not known until the run is imported into the database)

vii. Transfer of Results to the Laboratory Database: Every analytical run performed for the analysis of patient samples should be entered into the laboratory results database unless the run is not useable for obvious reasons (i.e. the run is stopped for some reason before ending QC is analyzed, no internal standard spiked into the diluent, etc. . .).

1. Data Export Process (from ELAN® software to .TXT file): If the data file was not created during the initial analysis, reprocess the data of interest either with “original conditions” option, or by loading the files and folders used during the analysis. In the ELAN® ICP-DRC-MS software, select “Review Files” from the “File” menu. From this window, you must open the files and directories that were used when collecting the data of the run that you wish to export. (If the analysis has just ended, all of these files and directories will still be open.) NOTE: A second copy of the ELAN® software can be run as an Edit/Reprocess copy without affecting an ongoing analysis by the first copy of the software running in Windows. After you open the relevant files, go to the “Report” page in the METHOD window. Deselect the box that prints a paper copy of data and select the box that sends data to a file. Select the “Report Options Template” named “CDC_Database Output.rop” and type in a report filename using a format such as “2005-

0714a_group55.txt" to designate data from analysis of group 55 from July 14, 2005, run #1. Under "Report Format", choose the "Use Separator" option, and under the "File Write" section choose "Append." Finally, reprocess the data of interest. (See PerkinElmer ELAN® ICPMS Software Manual.) Make sure you apply the aqueous blank to all sample and quality control material analyses.

2. Data Import Process (from .TXT file to Microsoft Access™ database):

    a. Move the .TXT file to the appropriate subdirectory on the network drive where exported data are stored. Directories for data storage are named according to instrument \ year \ month\, such as I:\Instruments\ELANDRC2A\2005\07\.

    b. Using the ITN Database Frontends, import the instrument file into the database. On the GoTo window, click on "Add Sample Results to Database", then "Import Instrument Data File".

    c. Enter the appropriate information to identify the instrument, assay, analysis date & time, run number, analyst, calibrator lot number and prep date used (use the "IS Lot Number" field) and study. If other than default values for Method LOD, High Calibrator, Rep Delta Limit, and units were used in the run, document what was used by clicking on the "View/Set Batch Parameters" button, changing the appropriate values, and then clicking "Back".

    d. Press the "Import" button, then browse to the correct network folder to select the file which contains the results from the run. Select the file and click "OK".

    e. In the "Import Instrument Results" table, pressing the "Find X's" button will show only those samples whose sample ID is not recognized as a valid QC pool ID or sample ID for this study. (Sample IDs are set up when the study is logged into the database.) Corrections to sample IDs and dilution factors can be made in this table (e.g., correction of transcription errors and adjustment for level of dilution). If samples were diluted for analysis, both the sample ID and the dilution factor need to be edited in this table before the values are transferred to the database (the Replace command under the Edit window is helpful in this case). When corrections to sample IDs are made, press the "Check IDs" button to re-evaluate the sample IDs. Any sample or analyte row marked "Not

Recognized" will not be transferred to the database when the "Transfer" button is pressed. Once transferred into the database, the data should be evaluated for QC pass / fail, then set with the appropriate settings for QC accept / reject, final value status, and comment(s). See the database programmers for more detail on working in the database.

viii. Submitting Final Work for Review: Once results have been imported, reviewed, and set as final in the database by the analyst,

1. Submit an email to the QC reviewer informing them of the readiness of the data for final review. The email should include
    a. Instrument ID, run Date, run number, study ID, group ID.
    b. Any bench QC failures (include reasons if known).
    c. Anything out of the ordinary about this analytical work which could have a bearing on the availability (i.e. insufficient sample to analyze), accuracy, or precision of the results.
2. Include all items called for by the study folder cover sheet in the study folder (i.e. printouts from the ICP-MS, bench QC evaluation) together in the study folder before submitting the folder for review when analysis is complete.

ix. Overnight Operation or Using Auto Stop: Make every effort to complete analysis within the work day so that the entire run can be monitored. If it is not possible to complete the analysis by the end of the work day, the run may be left to complete itself unattended as long as appropriate planning is made for either overnight operation or Auto Stop.

1. *24 hrs / day operation in DRC mode*:
    a. To reduce startup time in the mornings, the analyst is encouraged to operate the ELAN in DRC mode 24hrs/day during the work week. This eliminates the need for daily 45 minute RF generator warm-up, and possibly the need for DRC stability time (if the DRC gas is not off for extended periods of time before analysis). To maintain the instrument in DRC mode when not analyzing patient samples, setup multiple sample rows in the Samples / Batch window with autosampler position n zero (rinse station of autosampler) and wash time of 1800s (30 minutes). Repeat this sample row enough times to keep the

instrument in analysis mode overnight (1 sample with 15 minute wash will take ~ 25 minutes).

2. *AutoStop*: If 24 hrs / day ELAN operation is not desired, the instrument can shut the plasma off unattended after analysis. Setup this as follows:

    a. On the "Auto Start / Stop" tab of the Instrument window, enable the Auto Stop feature.

    b. Press the "Change" button within the Auto Stop box and set the Delayed shutdown time to 5 minutes. This will rinse the sample introduction system of urine matrix before turning off the plasma.

    c. It will be necessary to replace the sample peristaltic pump tubing the next day since it will have been clamped shut overnight.

Equipment Maintenance: Analysts are expected to follow a 4-day analysis / 1-day maintenance schedule in the laboratory.

i. ICPMS Maintenance: On the maintenance day, perform all maintenance per the Inorganic Toxicology and Nutrition Branch ELAN ICP-MS Weekly Maintenance SOP. All equipment maintenance should be documented in the instrument logbook.

Interpretation of the Results

Action Levels: Due to the uncertainty of the health implications of elevated concentrations of many of the elements determined with this method, there is no routine notification for elevated levels of every analyte determined with this method. The present NRC standard for workplace removal is 15 □g/L of U in urine [11]. Other action levels for reporting to supervising physicians are determined on a study-by-study basis.

Method Calculations

Results:

Elevated Results:

I Boundaries Requiring Confirmatory Measurement:

1. Results Greater than the First Upper Boundary (1UB): Concentrations observed greater than the "first upper boundary" (defined in the laboratory database as the "1UB") should be confirmed by repeat analysis of a new sample preparation. Report the original result, as long as the confirmation is

within 10% of the original. Continue repeat analysis until a concentration can be confirmed.

2. Results Greater Than Highest Calibrator: When a sample result is greater than the highest calibrator in the run, the supervisor may request that the result be confirmed in an analysis run which includes a standard or external reference material with equivalent (within 10%) or greater concentration than the sample.
3. Results Greater Than Range of Linearity Tested: Perform an extra dilution.
4. Uranium Isotope Ratio Measurement for Elevated Uranium Concentrations: A uranium 235/238 isotope ratio analysis is performed for all urine uranium samples where the urine total uranium concentration is greater than the 2UB boundary.

ii. Inadequate Precision in Confirmation of a Measurement: If a sample is reanalyzed to obtain a confirmation of an initially elevated result, the confirmation should be within 10% of the original result.

iii. Analyst Reporting of Elevated Results: Concentrations observed greater than the "second upper boundary" (defined in the laboratory database as the "2UB") should be reported to the QC reviewer as an "elevated result". The concentration assigned to the 2UB for an element is determined by study protocol. The analyst should report any patient results confirmed to be greater than the second upper boundary to the QC reviewer as an "elevated result". There is no routine notification for elevated levels for the metals determined in this method. The protocol for supervisors reporting elevated results to medical personnel is defined according to the study protocol.

d. Inadequate Precision within One Measurement: If the range of the three replicate readings (maximum replicate concentration value - minimum replicate concentration value) for a single sample analysis is

greater than the criteria l***and*** the range of the three replicate readings is greater than 10% of the observed concentration, do not use the measurement for reporting. Repeat the analysis of the sample.

b. Method Limit of Detection (LODs): The detection limits for elements in urine specimens are based on 3 times the concentration standard deviation of urine blanks (named UrBlkChk1 or UrBlkChk2) analyzed in at least 20 separate runs. Method LODs are re-evaluated periodically.

c. Method Limit of Quantitation (LOQ): The Division of Laboratory Sciences does not currently utilize limits of quantitation in regards to reporting limits.

9. Reportable Range of Results and Dilutions

a. Urine multi-element values are reportable in the range between the method LOD. For example, if a urine cadmium value is less than the method LOD of 0.042, report it as < 0.042 μg/L). Above the highest concentration verified, extra dilutions are made of the urine sample to bring the concentration within the verified range.

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10. Quality Control (QC) Procedures

a. QC Limits: Quality control limits are calculated based on concentration results obtained in at least 20 separate runs. It is preferable to perform separate analyses on separate days and using multiple calibrator lot numbers, instruments, and analysts to best mimic real-life variability. The statistical calculations are performed using the SAS program developed for the Division of Laboratory Sciences.

b. Quality Control: Quality control procedures implemented in this method are defined by the Division Procedures and Practices Guidelines and include two types of QC systems which are both subjected to the complete analytical process. The data from these materials are then used to estimate methodological imprecision and to assess the magnitude of any time-associated trends. The concentrations of these materials should cover the expected concentration range of the analytes for the method. Before QC materials can be used to judge patient analytical runs, acceptable QC concentration limits must be calculated from the concentration results observed in at least 20 characterization runs. During the 20 characterization runs, previously characterized QCs or pools with target values assigned by outside laboratories should be included to evaluate the analysis. The process of limits calculation is performed using the laboratory database and the SAS division QC characterization program.

i. Types of Quality Control:

1. "Bench QC": The bench QC pools used in this method comprise two levels of concentration spanning the "low-normal" and "high-normal" ranges of the analyte of interest. The intent of bench QC is for the analyst to evaluate the performance of the analytical system on the day of analysis. The analyst inserts both the "low" and the "high" bench QC specimens two times in each analytical run (a set of consecutive assays performed without interruption) so that judgments may be made on the day of analysis. The first analysis of the two bench QC pools is done after the calibration standards are analyzed but before any patient samples are analyzed (so that judgments on the calibration curves may be made before analysis of patient samples). The second analysis of the two bench QC pools is done at the end of the run (approximately 20 patient samples total). If more patient samples are analyzed on the same calibration curve after the second run of the bench QC, both the low-normal and high-normal bench QC must be reanalyzed before and after the additional samples.

2. "Blind QC": When possible, "blind" QC samples are QC materials placed in vials, labeled, and processed so that they are indistinguishable from the subject samples handled by the analyst. Ideally, the supervisor decodes and reviews the results of the blind specimens without the analyst knowing of their presence in the runs. When it is not possible to have blind QC materials processed so that they are indistinguishable by the analyst from the patient samples, it is acceptable for the analyst to randomly insert into the run a QC material which only the QC reviewer knows the acceptable concentration limits for. At least one low-normal concentration and one high-normal concentration QC material should be kept in the laboratory for this purpose.

3. Analyst Evaluation of Run Results:

Bench Quality Control: After completing a run, and importing the results into the database, export the QC results to the SAS program where the run will be judged to be in or out of control. The QC limits are based on the average and standard deviation of the beginning and ending analyses of each of the bench QC pools, so it will not be possible to know if the run is *officially* accepted or rejected until it is completed.

a. Quality Control Rules: The SAS program applies the division QC rules to the data as follows:

i. If both QC run means (low & high bench QC) are within 2Sm limits and individual results are within 2Si limits, then accept the run.

ii. If 1 of the 2 QC run means is outside a 2Sm limit - reject run if:

1. Extreme Outlier – Run mean is beyond the characterization mean +/- 4Sm
2. 1 3S Rule - Run mean is outside a 3Sm limit
3. 2 2S Rule - Both run means are outside the same 2Sm limit
4. 10 X-bar Rule – Current and previous 9 run means are on same side of the characterization mean

iii. If one of the 4 QC individual results is outside a 2Si limit - reject run if:

1. R 4S Rule – Within-run ranges for all pools in the same run exceed 4Sw (i.e., 95% range limit)

Note: Since runs have multiple results per pool for 2 pools, the R 4S rule is applied within runs only.

Abbreviations:

Si = Standard deviation of individual results (the limits are not shown on the chart unless run results are actually single measurements).

Sm = Standard deviation of the run means (the limits are shown on the chart).

Sw = Within-run standard deviation (the limits are not shown on the chart).

Implications of QC Failures: If the division SAS program declares the run out of control" for any analyte, use the following to determine the implications on usability of the data from the run.

For 1 or 2 analytes: ONLY the analytes which were "out of control" are invalid for reporting from the run. Set all run results for those 1 or 2 analytes as "QC Rejected" in the database.

For 3 or more analytes: All results, regardless of analyte, are invalid for reporting from the run. Set all run results for all analytes as "QC Rejected" in the database. Note in the batch comment field why all results were marked QC rejected.

External Reference Materials: Materials produced by laboratories outside of the CDC which have assigned target concentrations can be helpful in verifying method performance. Some examples include Standard Reference Materials (SRM) from the National Institute of Standards and Technology (NIST) (i.e. SRM 2670a low & 2607a high) and samples from previous challenges of proficiency testing programs (i.e. Centre de Toxicologie du Quebec (CTQ)). However, only the results for the bench and blind QC materials are used to determine if the run results can be used.

11. Remedial Action if Calibration or QC Systems Fail to Meet Acceptable Criteria

Check to make sure that the hardware is functioning properly.
Recalibrate the instrument.
If the steps outlined above do not result in correction of the "out of control" values for QC materials, consult the supervisor for other appropriate corrective actions.
Do not report analytical results for runs not in statistical control.

12. Limitations of Method; Interfering Substances and Conditions

a. Interferences Addressed by This Method

i. Breakup of Argon Chloride ($^{40}Ar^{35}Cl$) Interference on Arsenic (^{75}As) Using DRC: The dynamic reaction cell of the ELAN ICP-DRC-MS is used in this method to break apart the argon chloride ($^{40}Ar^{35}Cl$) interference on arsenic at m/z 75 [6] which is common to urine analysis by ICP-MS (see Section 1.b for an explanation of this process).

ii. Correction & Elimination of Interferences (^{114}Sn, $^{98}Mo^{16}O$) on Cadmium (^{114}Cd).

1. Mathematical Correction for Tin (^{114}Sn) Interference:
The correction equation (-0.026826*Sn118) is used in the “Equations” tab of the method to correct the counts observed as m/z 114 to exclude counts due to ^{114}Sn.

2. Elimination of Molybdenum Oxide ($^{98}Mo^{16}O$) Interference Using DRC:
The dynamic reaction cell of the ELAN ICP-DRC-MS is used in this method to eliminate interference from molybdenum oxide ($^{98}Mo^{16}O$) onto cadmium at m/z 114 [7]. See Section 1.b for an explanation of this process.

iii. Matrix Enhancement of Arsenic Signal:
Matrix induced signal enhancement in ICP-MS analysis from carbon on arsenic has been previously reported in the literature [17, 18]. When arsenic is being determined by this method, ethanol

(1.5% v/v) is added in the diluent and rinse solutions to "normalize" the arsenic signal enhancement in all blanks, calibrators, and samples.

b. Limitations of Method (Interferences Remaining in Method)

i. Calcium Chloride ($^{40}Ca^{35}Cl$) Interference on Arsenic (^{75}As):
It has been determined that a small interference remains at m/z 75 when the urine matrix contains ***both*** high chloride ***and*** high calcium levels [6]. Even at extreme calcium and chloride levels, this interference is has not been found to be significant (approximately 0.4 μg/L).

13. Reference Ranges (Normal Values)

In this method the 95% reference ranges.

14. Critical Call Results ("Panic Values")

For NHANES 1999+, since data are transmitted weekly to the Westat ISIS computer, Westat automatically notifies the NCHS survey physician.

15. Specimen Storage and Handling during Testing

Specimens are allowed to reach room temperature during preparation. The unused portion of the patient specimen is returned to the freezer.

16. Alternate Methods for Performing Test and Storing Specimens If Test System Fails:

If the analytical system fails, the analysis may be setup on other ELAN DRC instruments in the laboratory. If no other instrument is available, store the specimens at ~4°C until the analytical system can be restored to functionality. If interruption longer than 4 weeks in anticipated, then store urine specimens at ≤ -20°C.

17. Test Result Reporting System; Protocol for Reporting Critical Calls (If Applicable)

The collaborating agency with access to patient identifiers or the responsible medical officer is notified by email

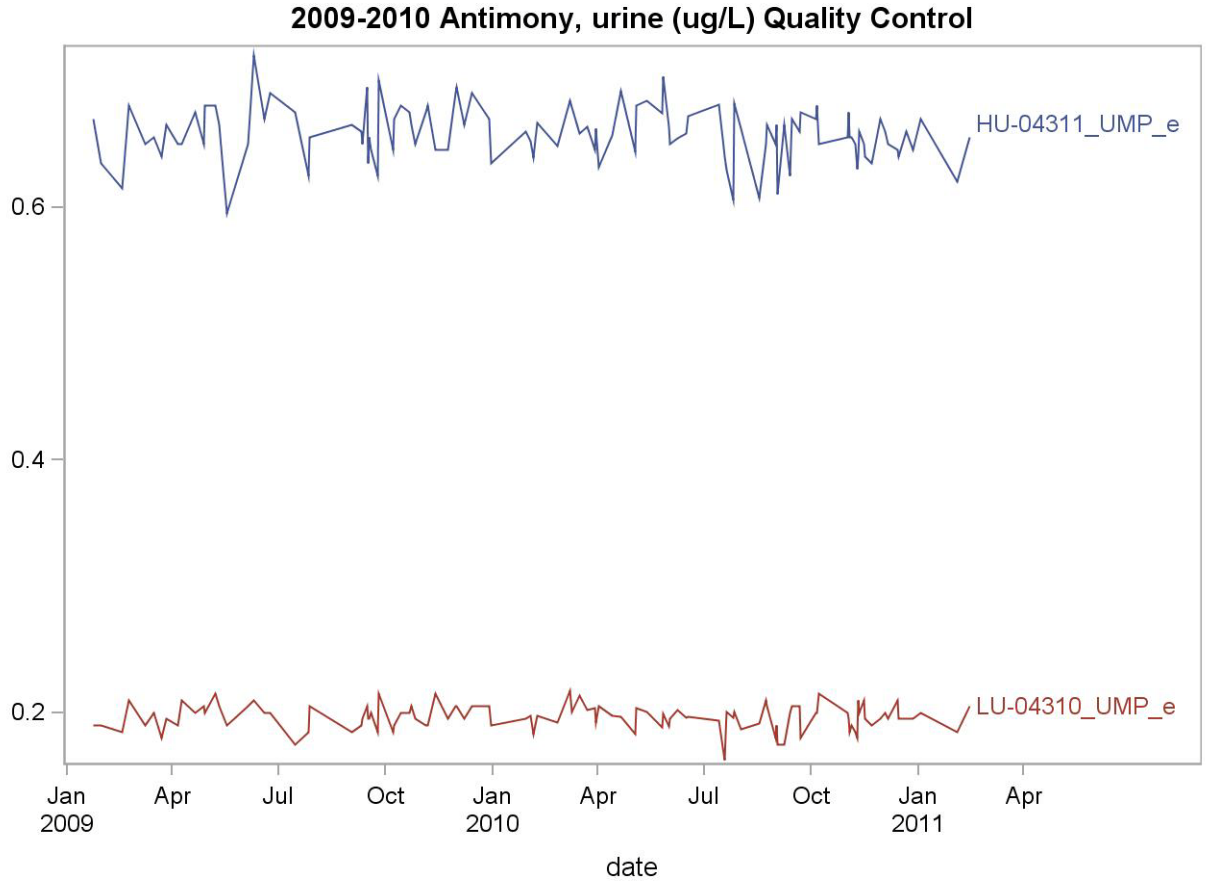
18. Transfer or Referral of Specimens; Procedures for Specimen Accountability and Tracking

The specimens are tracked in the electronic data base.

19. Summary Statistics and QC Graphs

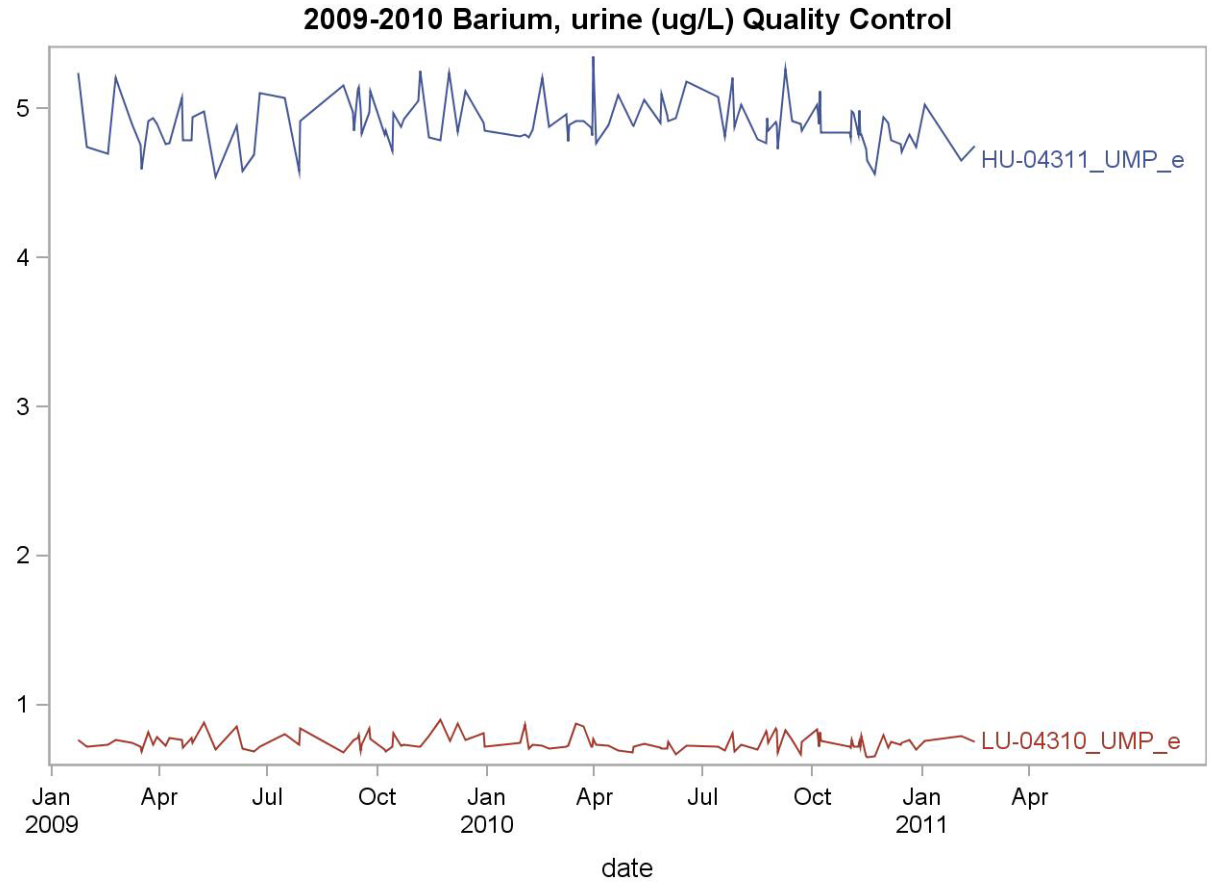
A. Antimony

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	164	23JAN09	14FEB11	0.6538	0.0217	3.3
LU-04310_UMP_e	160	23JAN09	14FEB11	0.1939	0.0107	5.5



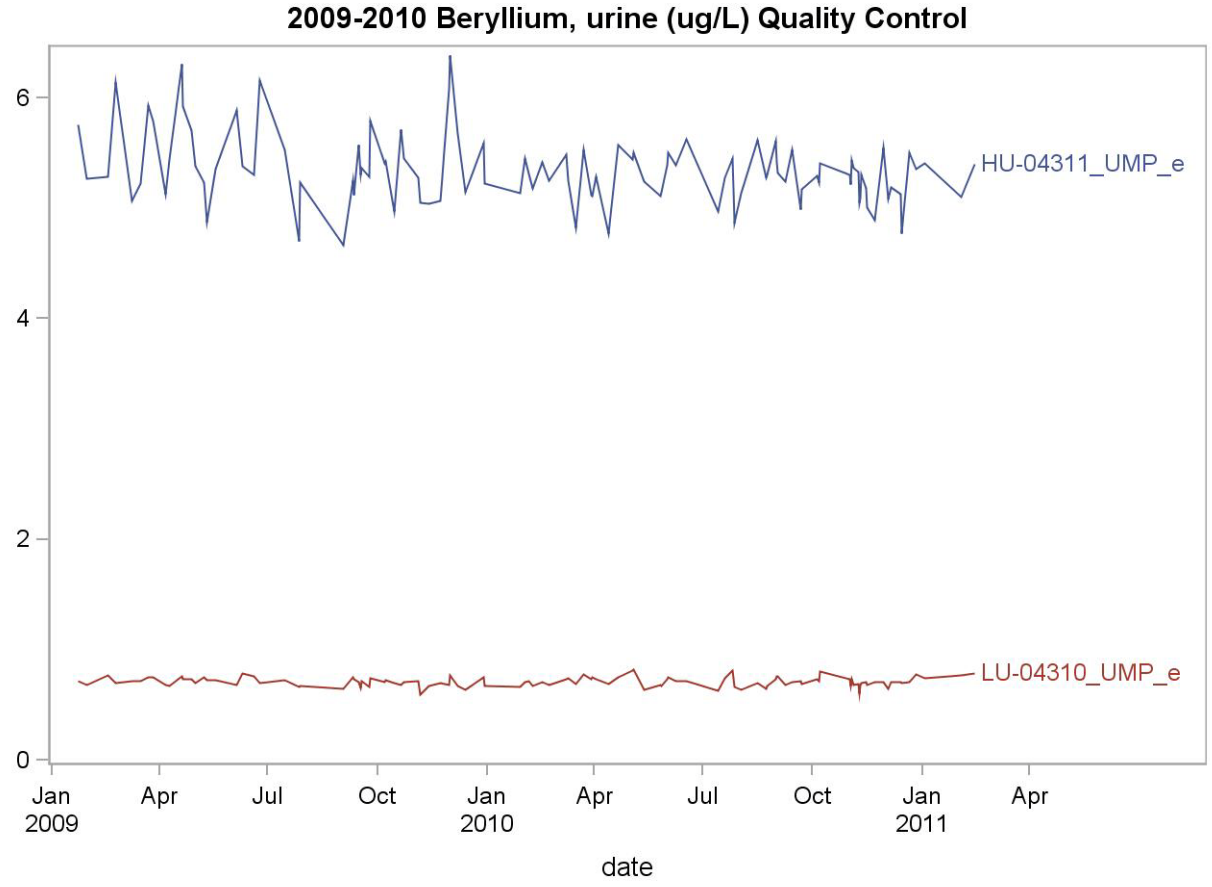
B. Barium

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	171	23JAN09	14FEB11	4.886	0.159	3.3
LU-04310_UMP_e	171	23JAN09	14FEB11	0.740	0.053	7.2



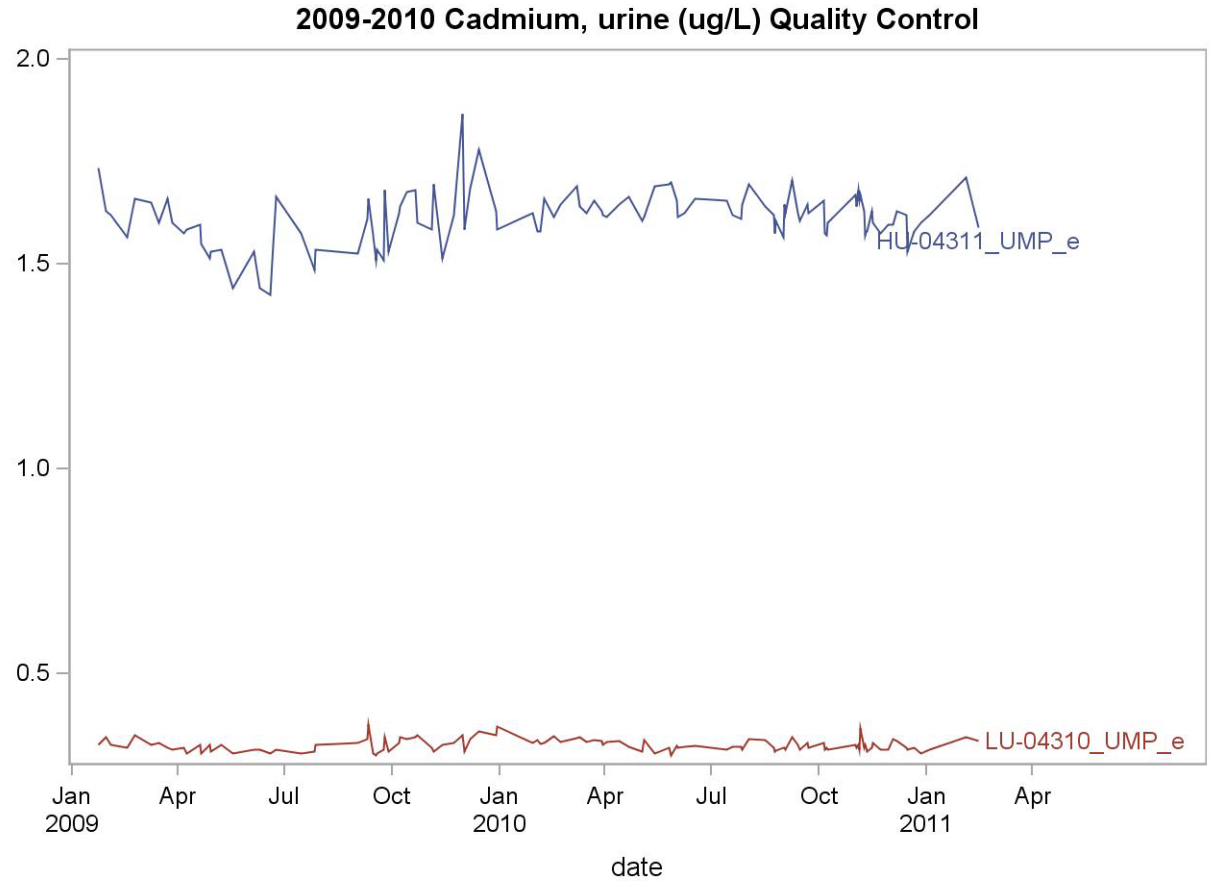
C. Beryllium

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	165	23JAN09	14FEB11	5.2801	0.3178	6.0
LU-04310_UMP_e	164	23JAN09	14FEB11	0.7009	0.0443	6.3



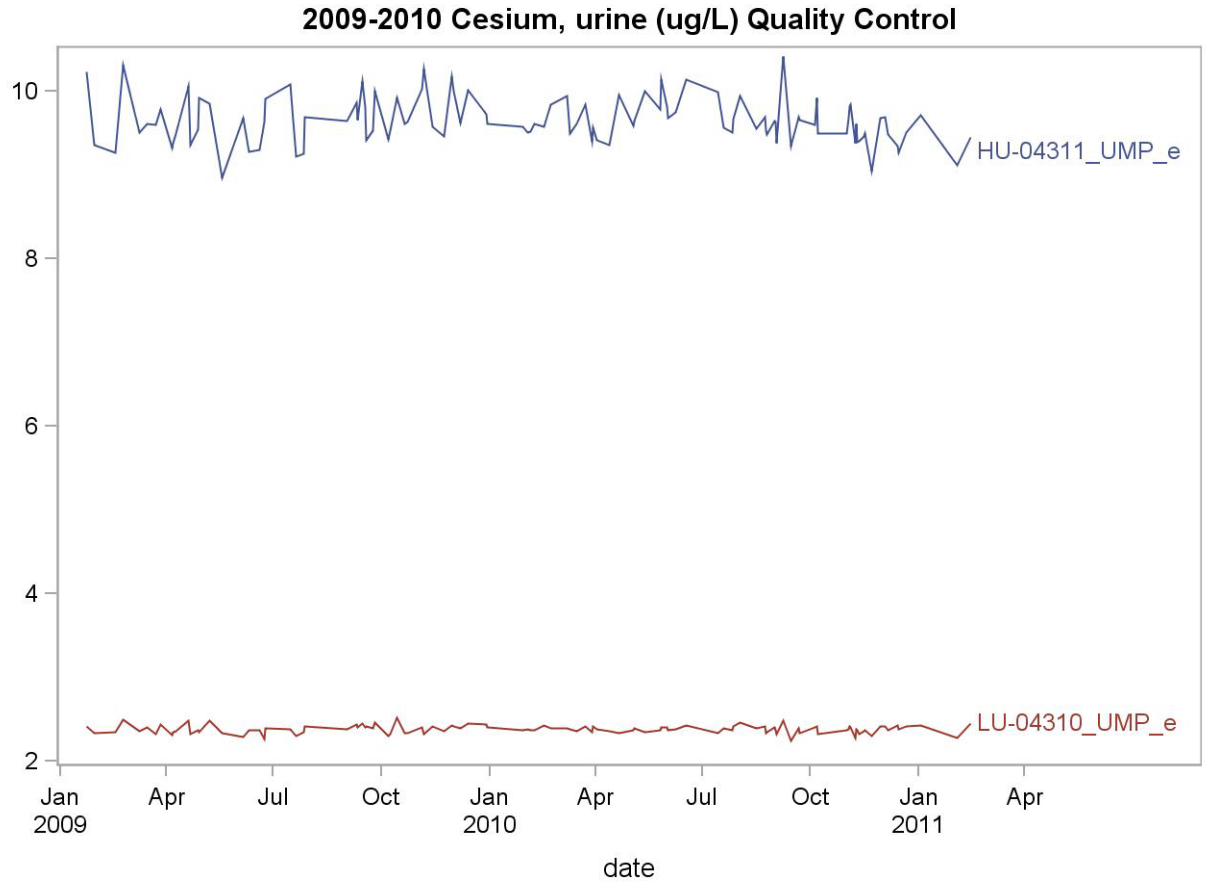
D. Cadmium

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	165	23JAN09	14FEB11	1.6033	0.0676	4.2
LU-04310_UMP_e	167	23JAN09	14FEB11	0.3230	0.0153	4.7



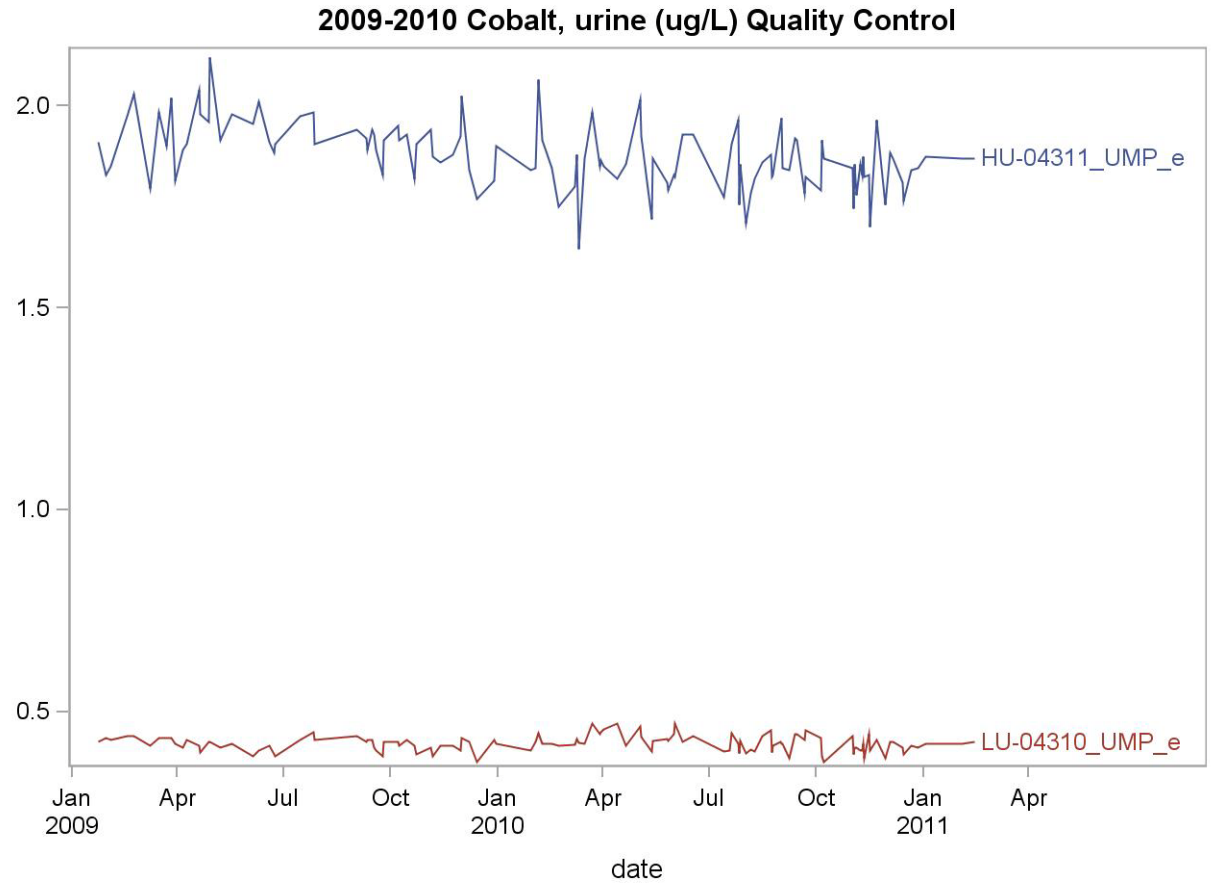
E. Cesium

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	168	23JAN09	14FEB11	9.6218	0.2664	2.8
LU-04310_UMP_e	168	23JAN09	14FEB11	2.3707	0.0506	2.1



F. Cobalt

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	175	23JAN09	14FEB11	1.8680	0.0779	4.2
LU-04310_UMP_e	175	23JAN09	14FEB11	0.4164	0.0202	4.8



Urine Multi-Element ICP-DRC-MS

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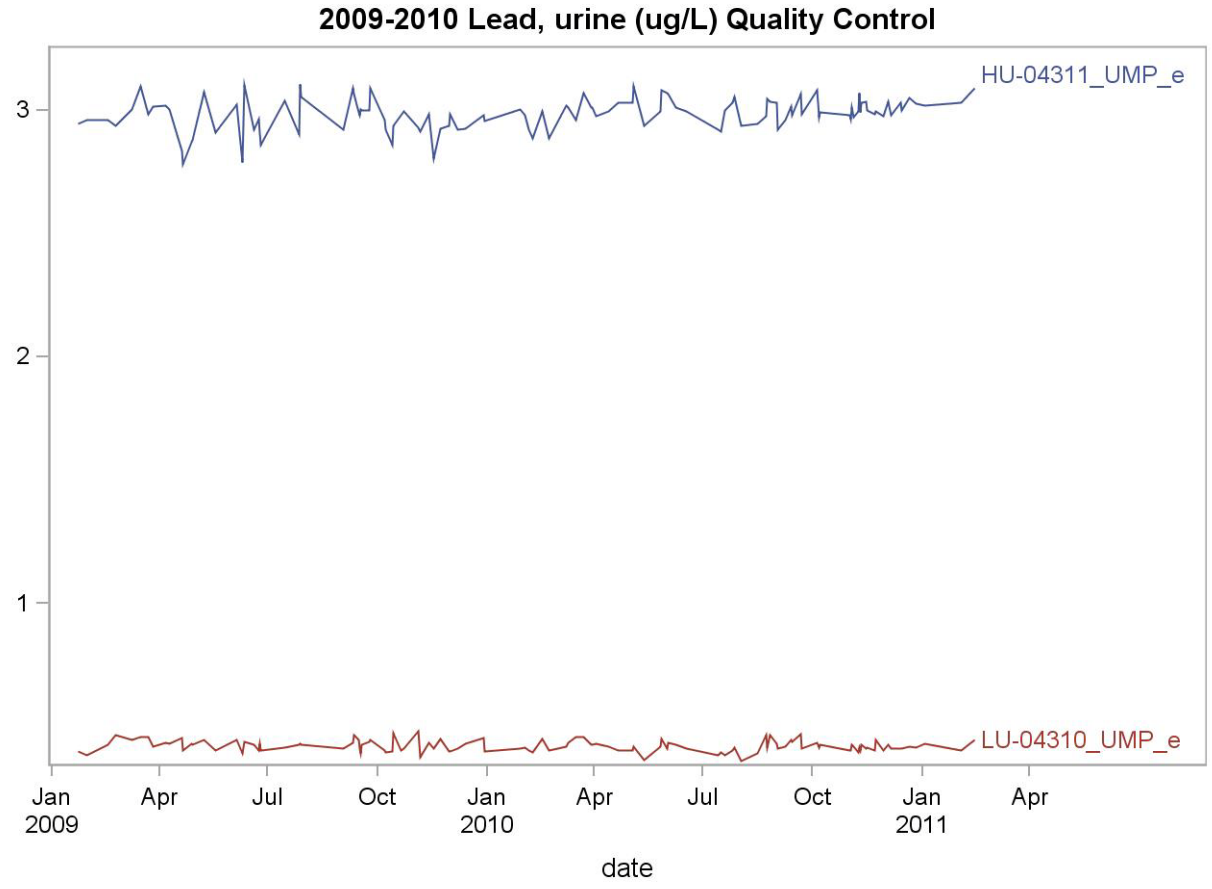
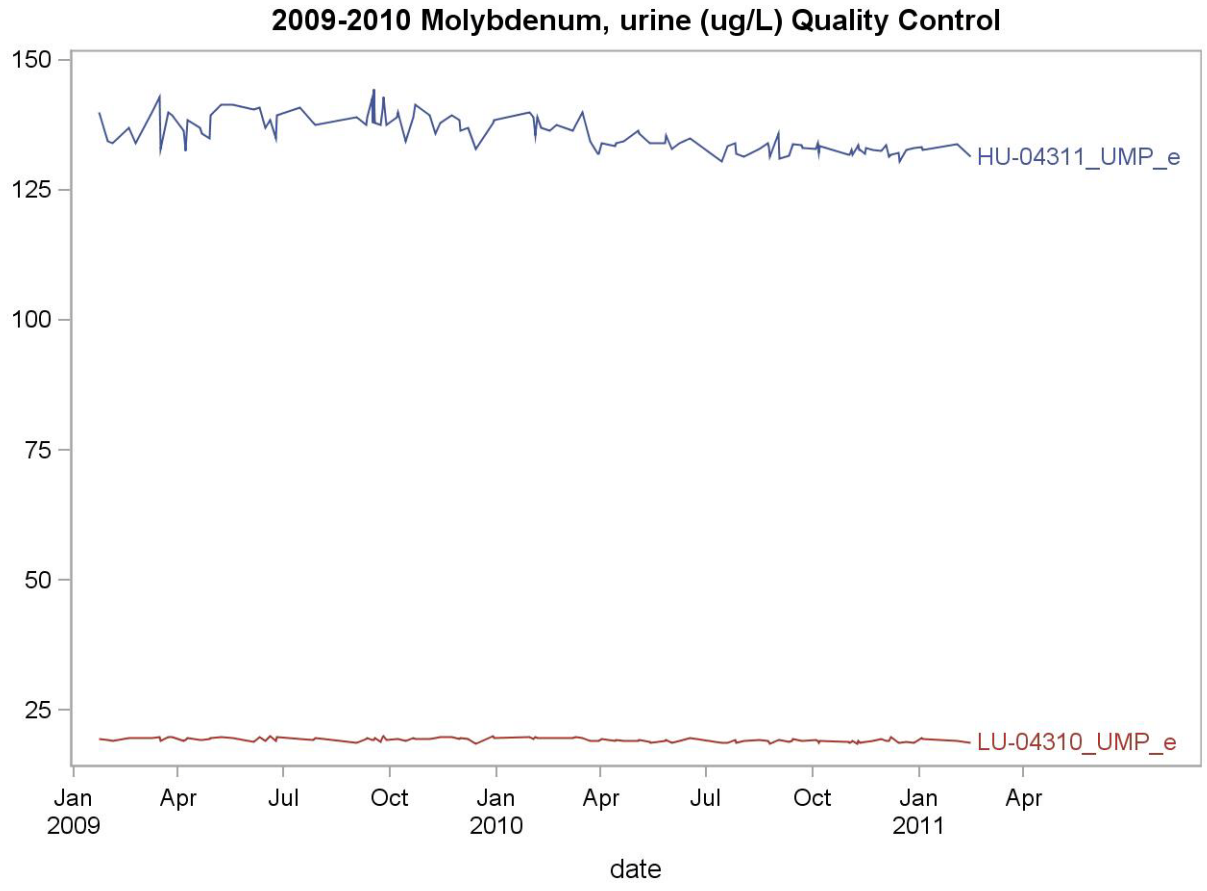
G. Lead

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	172	23JAN09	14FEB11	2.978	0.062	2.1
LU-04310_UMP_e	166	23JAN09	14FEB11	0.418	0.023	5.5



H. Molybdenum

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	162	23JAN09	14FEB11	135.916	3.210	2.4
LU-04310_UMP_e	169	23JAN09	14FEB11	19.247	0.363	1.9

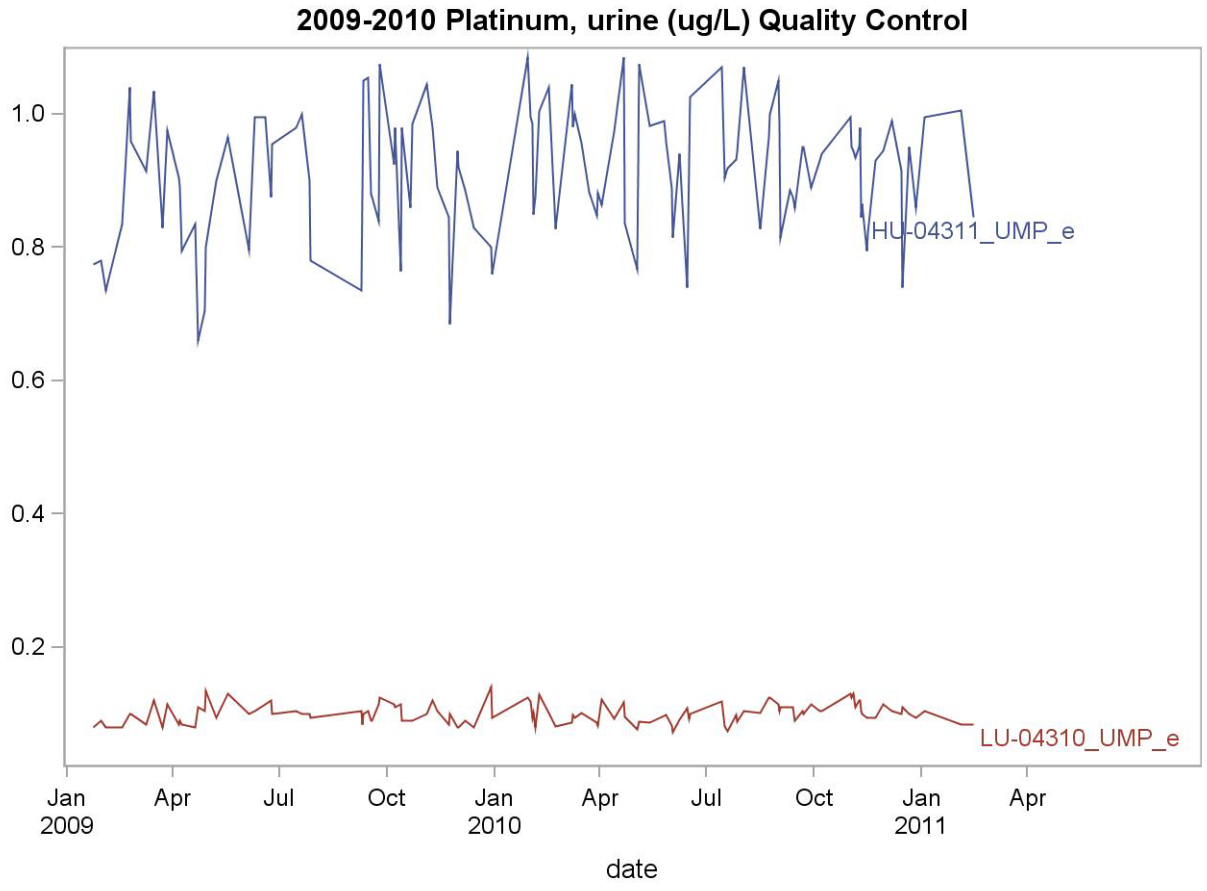


Urine Multi-Element ICP-DRC-MS

NHANES 2009-2010

I. Platinum

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	168	23JAN09	14FEB11	0.9012	0.0928	10.3
LU-04310_UMP_e	163	23JAN09	14FEB11	0.0985	0.0150	15.2

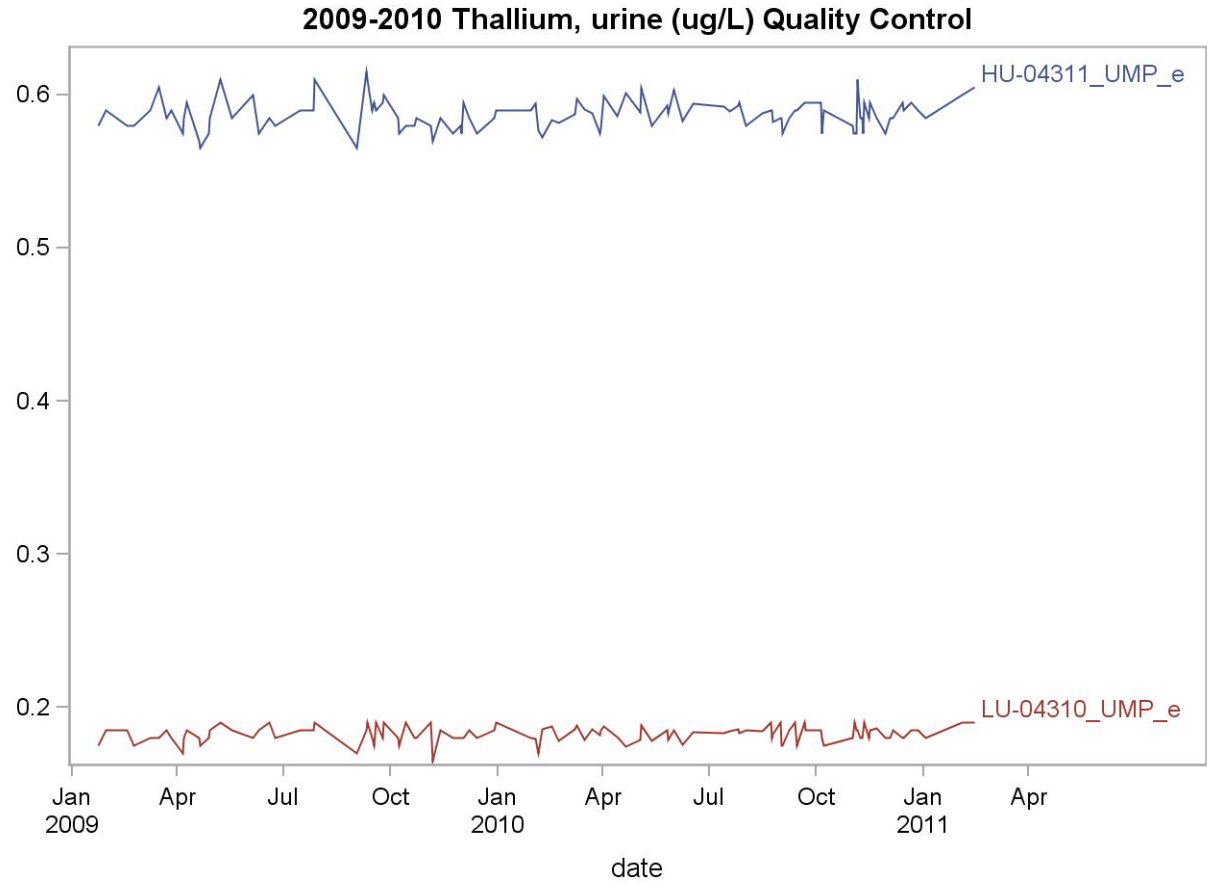


Urine Multi-Element ICP-DRC-MS

NHANES 2009-2010

J. Thallium

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	157	23JAN09	14FEB11	0.5855	0.0097	1.7
LU-04310_UMP_e	160	23JAN09	14FEB11	0.1808	0.0059	3.3

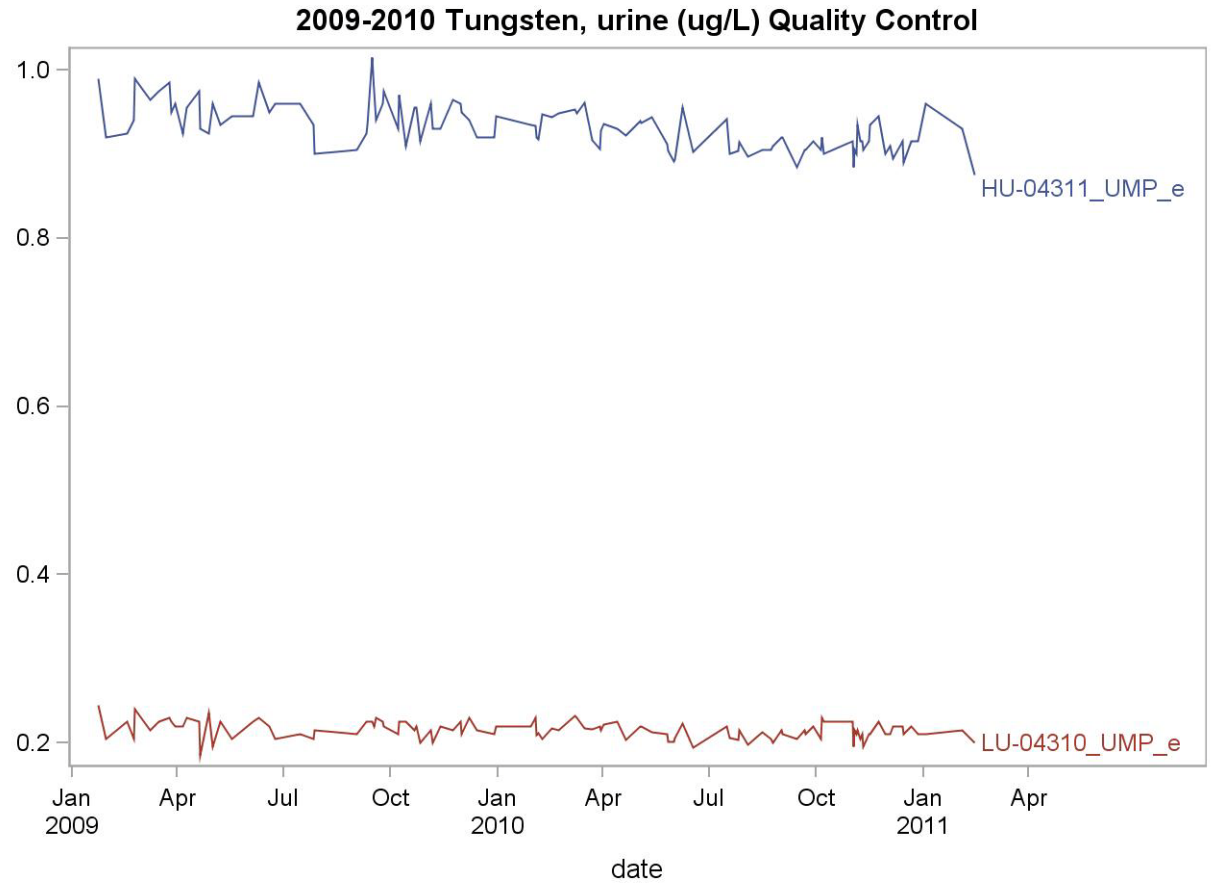


Urine Multi-Element ICP-DRC-MS

NHANES 2009-2010

K. Tungsten

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	164	23JAN09	14FEB11	0.9284	0.0264	2.8
LU-04310_UMP_e	163	23JAN09	14FEB11	0.2131	0.0107	5.0

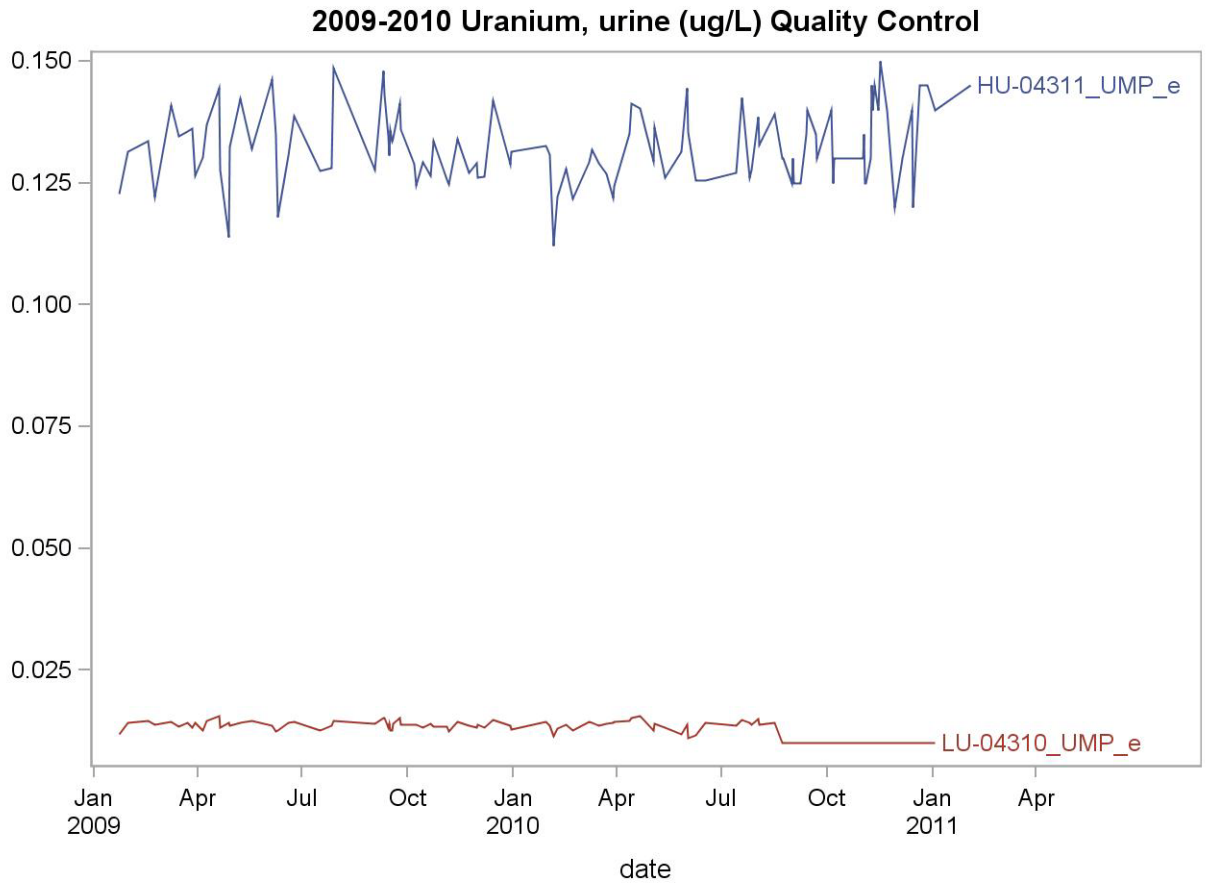


Urine Multi-Element ICP-DRC-MS

NHANES 2009-2010

L. Uranium

Lot	N	Start Date	End Date	Mean	Standard Deviation	Coefficient of Variation
HU-04311_UMP_e	158	23JAN09	03FEB11	0.13145	0.00742	5.6
LU-04310_UMP_e	151	23JAN09	03JAN11	0.01281	0.00163	12.7



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