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# Analytical method for total chromium and nickel in urine using an inductively coupled plasma-universal cell technology-mass spectrometer (ICP-UCT-MS) in kinetic energy discrimination (KED) mode

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## Abstract

Biomonitoring and emergency response measurements are an important aspect of the Division of Laboratory Sciences of the National Center for Environmental Health, Centers for Disease Control and Prevention (CDC). The continuing advancement in instrumentation allows for enhancements to existing analytical methods. Prior to this work, chromium and nickel were analyzed on a sector field inductively coupled plasma-mass spectrometer (SF-ICP-MS). This type of instrumentation provides the necessary sensitivity, selectivity, accuracy, and precision but due to the higher complexity of instrumentation and operation, it is not preferred for routine high throughput biomonitoring needs. Instead a quadrupole based method has been developed on a PerkinElmer NexION™ 300D ICP-MS. The instrument is operated using 6.0 mL $min^{-1}$ helium as the collision cell gas and in kinetic energy discrimination mode, interferences are successfully removed for the analysis of $^{52}Cr$ ($^{40}Ar^{12}C$ and $^{35}Cl^{16}O^{1}H$) and $^{60}Ni$ ($^{44}Ca^{16}O$). The limits of detection are 0.162 μg $L^{-1}$ Cr and 0.248 μg $L^{-1}$ Ni. Method accuracy using NIST SRM 2668 level 1 (1.08 μg $L^{-1}$ Cr and 2.31μg $L^{-1}$ Ni) and level 2 (27.7 μg $L^{-1}$ Cr and 115 μg $L^{-1}$ Ni) was within the 95% confidence intervals reported in the NIST certificate. Among-run precision is less than 10% RSDs (N = 20) for in house quality control and NIST SRM urine samples. While the limits of detection (LOD) for the new quadrupole ICP-UCT-MS with KED method are similar to the SF-ICP-MS method, better measurement precision is observed for the quadrupole method. The new method presented provides fast, accurate, and more precise results on a less complex and more robust ICP-MS platform.

### Keywords

inductively coupled plasma-mass spectrometry; chromium; nickel; urine samples; collision cell

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"The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of The Centers for Disease Control and Prevention"

## INTRODUCTION

Chromium, a naturally occurring element, is considered both essential (chromium(III)) and toxic (chromium(VI)), depending on its chemical form. Chromium(III) is an essential nutrient that has a significant role in carbohydrate metabolism and insulin signaling.[1] However, excess amounts can cause adverse health effects. Chromium(VI), which is easily transported across cell membranes, is considered toxic and has been associated with lung cancer and stomach ulcers.[2] Exposure to chromium can occur by drinking water, consuming vegetables, fruits, meat, and/or supplements. Industrial exposure can occur during alloy production, stainless steel welding, chrome plating, or leather tanning.[2] Additionally, metal prostheses used in hip and knee replacements contain chromium.[3-5] Absorbed chromium is mainly found in the kidneys and liver but can be distributed throughout the human body, especially bone, and it is excreted mostly in urine.[2]

Nickel, also a naturally occurring element, has been documented to be toxic to humans [6]; however, investigations are ongoing to determine if some levels or forms of nickel uptake are also essential.[7, 8] People are principally exposed to nickel through skin contact with nickel containing jewelry, consumption of foods (e.g., chocolate, nuts, and oatmeal), and industrial exposures such as battery production, alloy production, or stainless steel welding. [9, 10] As one of the main components in metal-on-metal hip and knee implants, nickel from erosion of implant materials can be a source of exposure in people with these implants.[3-5] Nickel is typically absorbed in the lungs or gastrointestinal tract, with the main excretion occurring in urine.[9, 10]

Inductively coupled plasma mass spectrometry (ICP-MS) is a very sensitive, multi-element, laboratory technique that allows for an efficient approach to measuring multiple elements per sample at low concentrations.[11] As a result, ICP-MS has found increasing application in biomonitoring, measuring chemicals in biological samples for assessing people's exposure to environmental chemicals.[12, 13] For biomonitoring of chromium and nickel the urine matrix is used because it is the major excretion pathway and because specimen collection is non-invasive. However, spectral and non-spectral interferences arising from the urine matrix complicate ICP-MS analysis. Polyatomic ions such as $^{35}Cl^{16}O^{1}H^{+}$ and $^{40}Ar^{12}C^{+}$ are problematic to analysis of chromium at isotope $^{52}Cr$. Isobaric interference from $^{58}Fe$ and polyatomic interferences such as $^{44}Ca^{16}O^{+}$ [3, 5, 11, 14] complicate analysis of nickel at $^{58}Ni$ and $^{60}Ni$. An evaluation of spectral interferences impacting chromium and nickel analysis by ICP-MS is presented in this work (see Table S1 and Table S2). These interferences can be distinguished from the actual analyte of interest using the resolution capabilities of sector field-inductively coupled plasma-mass spectrometry (SF-ICP-MS),[3, 15] but the resolution required comes at a cost of reduced sensitivity,[16] instrument cost, and instrument complexity. Quadrupole based ICP-MS (Q-ICP-MS) instruments are not as complex as SF-ICP-MS instruments, are lower in cost, and are typically available with either collision or reaction cell technology to reduce, eliminate, or avoid overlaps of interfering ions.[16, 17]

Collision and/or reaction cells are an option on most commercial Q-ICP-MS platforms. The use of either type of cell facilitates the reduction, elimination, or avoidance of polyatomic

interferences (matrix or plasma) by either collisions with an inert gas (e.g. He) or a reaction with a reactive gas (e.g. $NH_3$). The typical design places the collision/reaction cell in between the ion lens and the quadrupole mass filter. Use of a reaction cell can remove interferences through chemical reactions, but this also means that new polyatomic combinations can be created in the cell. This can be both helpful (shift analyte mass to a new mass, e.g. $^{75}As^{16}O^+$) and problematic (reactive gas creates new polyatomic interferences at the analyte of interest mass [18, 19]). Not all spectral interferences will have an exothermic reaction with the reactive gas of choice. If the reaction is endothermic (e.g. charge transfer reaction between $Ca^+$ and $NH_3$) then it is unfavorable and thus the interferences would not be removed in the reaction cell.[17, 20]

The collision cell is typically operated using a kinetic energy discrimination (KED) mode, which refers to having a potential barrier set between the cell and the quadrupole mass filter. [16] When polyatomic ions pass through a cell pressurized with an inert gas (e.g. He), collisions occur decreasing their potential energy below the KED bias voltage required to enter the quadrupole mass filter.[21] Atomic ions in the same cell pass through with fewer collisions, thus maintaining more of their energy and are permitted to enter the quadrupole mass filter. Unfortunately, this does not allow for discrimination of isobaric ions (e.g. $^{58}Fe^+$ and $^{58}Ni^+$ are both permitted to pass through). Isobaric ions are also difficult to chemically resolve in a reaction cell.

Method accuracy over time is important in biomonitoring and for evaluating exposures in other settings. Biomonitoring permits assessment of internal exposure to environmental chemicals without the uncertainty of using environmental sample analysis coupled with assumptions about exposure times and pathways within a framework of mathematical modeling. Accuracy of measurements within biological matrices, including correct avoidance of interferences, is critical to recognize the potential benefits of biomonitoring. Also, maintaining a constant degree of accuracy over time is important because a change could create an appearance of a trend in exposure of a population over time or an apparent difference between two populations studied at different times. Therefore, comparing old and new methods is critical to characterize any differences. Because the mean levels of exposure in a population to toxic chemicals are typically low, even small biases between methods or effects of interferences can be important.

A NexION™ 300D ICP-MS equipped with a universal cell capable of being operated in either dynamic reaction cell™ (DRC™) or KED mode (collision cell) is used to investigate and identify which gas that will best remove all interferences from urine matrix samples for the analysis of chromium and nickel. Ten percent hydrogen in argon, ammonia, oxygen, and methane gas were evaluated in DRC mode and only the use of helium gas is evaluated in KED mode. The final method conditions will be compared against a SF-ICP-MS previously implemented method in our laboratory for accuracy, precision, and limits of detection.

# EXPERIMENTAL

## Reagents

All reagents were prepared using 18 MΩ·cm water from a NANOpure® Diamond™ UV water purification system (Barnstead International, IA). Nitric acid (environmental grade, GFS Chemicals, Columbus, OH) was used in preparation of diluent and rinse solutions. Triton® X-100 (Sigma Aldrich, St. Louis, MO) was used in the rinse solution. Ethanol (Pharmco Products Inc., Brookfield, CT) and double distilled hydrochloric acid (30-35%, GFS Chemicals Inc.) were used to investigate potential interferences. Urine for matrix matching of calibration curve, "base urine", was obtained through anonymous human donations (CDC protocol 3994). Intermediate calibration standards were prepared in a 2% v/v $HNO_3$ and 1% v/v HCl matrix from custom mix multi-element stock standards (High-Purity Standards, Charleston, SC) and single-element stock standards (Inorganic Ventures, Christiansburg, VA). All calibration standards were traceable to National Institute for Standards and Technology (NIST, Gaithersburg, MD). Sample diluent and carrier solution for FAST autosampler operation consisted of 2% v/v $HNO_3$ and 10 μg $L^{-1}$ Rh. Sample introduction system rinse solution consisted of 5% v/v $HNO_3$ and 0.002% Triton® X-100.

## Sample Preparation

Working calibrators were prepared as 0.1 mL standard, 0.9 mL base urine, and 9.0 mL diluent. Unknown specimens were prepared as 0.25 mL urine and 2.25 mL diluent. When observed results were greater than the concentration range verified by calibrators, up to a 20× additional specimen dilution with water was performed to dilute the result within the calibration range (i.e. an extra 2× dilution was prepared as 0.125 mL water, 0.125 mL urine, and 2.25 mL diluent).

## Quality Control (QC) and Reference Materials

Two levels of urine-based bench QC materials, one at low concentrations and one at high concentrations, were analyzed at the beginning and again at the end of each run (see Table 7). Modified Westgard rules as detailed in the Division of Laboratory Sciences Policies and Procedures Manual, NCEH, CDC [22] were used to establish if runs were in control. Calibration verification above the calibration range of each run was accomplished using a higher concentration calibration verification standard. Method accuracy was assessed using NIST standard reference materials (SRM) 2668 Level 1 and 2 (see Table 6) as well as reference materials from the Trace Elements in Urine (TEU) proficiency testing program by the Wadsworth Center, New York State Department of Health and the Québec Multielement External Quality Assessment Scheme (QMEQAS) from the Institut National de Santé Publique Québec.

## Instrumentation

A NexION™ 300D ICP-Universal Cell Technology-MS (ICP-UCT-MS) (PerkinElmer, Shelton, CT) equipped with a DXi-FAST micro-peristaltic pump (Elemental Scientific Inc., Omaha, NE), a PolyPro-ST micro flow nebulizer, a quartz cyclonic spray chamber, a 2.0 mm quartz injector, nickel sampler cone, nickel skimmer cone, and aluminum

hyperskimmer cone was used for all experiments (instrument parameters are listed in Table 1). An SC-4 DX autosampler (Elemental Scientific Inc., Omaha, NE) was used to access diluted urine specimens for analysis and to control the FAST sample introduction timing (Table S3). The plasma and nebulizer gas use > 99.999% argon (Specialty Gases Southeast, Atlanta, GA). The UCT cell was operated during DRC mode evaluations using 90% argon/10% hydrogen (Airgas South, Atlanta, GA), ammonia (99.99% grade, Matheson Tri-gas), methane (99.999% grade, Airgas South), or oxygen (99.999% grade, Airgas South) gas. The UCT cell was operated in KED mode using helium (99.999% grade, Airgas South) gas. Spiked urine samples were analyzed for 1 hour prior to all experiments or samples to stabilize the UCT cell for analysis. Final dilutions for analysis were prepared using a Micromedic Digiflex™ automatic pipette (Titertek, Huntsville, AL).

## RESULTS AND DISCUSSION

### Selectivity

As expected, significant levels of interference were observed for Cr at m/z 52 (83.8 % abundance) in standard (vented) mode from $^{35}Cl^{16}O^{1}H^{+}$, $^{40}Ar^{12}C^{+}$, $^{40}Ca^{12}C^{+}$, and $^{39}K^{13}C^{+}$ when the component concentrations of the urine matrix were simulated, see Table 2. No interference was observed for Cr at m/z 52 from $^{36}S^{16}O^{+}$, $^{33}S^{19}F^{+}$, or $^{51}V^{1}H^{+}$ polyatomics when solutions were spiked with S (2% $H_2SO_4$), F (2% HF), or V (100 μg $L^{-1}$). Selecting another isotope of chromium does not provide an escape from these interferences. For example, the next most abundant chromium isotope, $^{53}Cr$ (9.5%), also suffers from interference from $^{37}Cl^{16}O^{+}$. Preliminary evaluation using DRC™ and KED modes provided information that the high background equivalent concentrations (BEC) values observed when spiking Ca and K were a direct result of trace amounts of Cr in the single element Ca and K standards. The main interferences ($^{40}Ar^{12}C^{+}$ and $^{35}Cl^{16}O^{1}H^{+}$) on $^{52}Cr^{+}$ analysis will be investigated further in subsequent sections using both collision and reaction cell modes.

The potential interferences for nickel at m/z 60 (26.1% abundance) are found in Table 3. No interference was observed at m/z 60 in standard (vented) mode from $^{41}K^{18}O^{1}H^{+}$, $^{41}K^{19}F^{+}$, $^{27}Al^{33}S^{+}$, $^{24}Mg^{36}Ar^{+}$, $^{26}Mg^{34}S^{+}$, $^{24}Mg^{36}S^{+}$, $^{25}Mg^{35}Cl^{+}$, $^{29}Si^{31}P^{+}$, or $^{28}Si^{32}S^{+}$ polyatomics when solutions were spiked with K (1,000,000 μg $L^{-1}$), F (2% v/v HF), Al (10 μg $L^{-1}$), S (2% v/v $H_2SO_4$), Mg (25,000 μg $L^{-1}$), Cl (1% v/v HCl), Si (5,000 μg $L^{-1}$), or P (2% v/v $H_3PO_4$). Isotope 58 (68.3% abundance) was not used for nickel analysis due to the presence of varying iron (0.3% abundance) concentrations (~ 55 – 40,000 μg $L^{-1}$ Fe) in urine. Preliminary evaluation using DRC™ and KED modes provided complete reduction of the potential interferences from Sn, Co, Sc, and Na. The main interference ($^{44}Ca^{16}O^{+}$) on $^{60}Ni^{+}$ analysis will be investigated further in subsequent sections using both collision and reaction modes.

### Interference Removal

Cell gas optimizations (Fig. S1 and S2) were performed using solutions containing the potential interferences and analyte of interest ($^{52}Cr$ or $^{60}Ni$) spiked into urine (1:10 dilution) or 2% v/v $HNO_3$ matrix. The signal-to-background (S/B) ratios from the cell gas optimizations are listed in Table 4 for each gas composition tested. Vented mode (no gas)

and DRC™ mode using methane or oxygen gas provided poor S/B ratios which is a direct result of not being effective at removing or suppressing the interference. Using DRC™ mode with ammonia or argon/hydrogen, or KED mode with helium gas provided the best S/B ratios for chromium and nickel. In DRC mode the background is ~ 100 times higher for $^{40}Ar^{12}C^{+}$ and $^{35}Cl^{16}O^{1}H^{+}$ using ammonia gas than argon/hydrogen or in KED mode helium gas. Cell gas optimization plots for ammonia and argon/hydrogen revealed that the interference of $^{44}Ca^{16}O^{+}$ was not completely reduced.

NIST SRMs were spiked with calcium and analyzed using one of three gases (ammonia, argon/hydrogen, or helium), the results are shown in Table 5. There is a distinct positive bias (9 – 18 %) for nickel in the presence of 5 or 20 mg $L^{-1}$ calcium when the spiked NIST SRM level 1 (representative of biomonitoring concentrations) samples are analyzed in DRC™ mode with either $NH_3$ or Ar/H. The NIST SRM level 2 (representative of toxic or emergency response concentrations) spiked samples show a positive bias of ~ 1-2 %, which equates to 1.1 – 2.0 μg $L^{-1}$ Ni. Louie and co-workers also reported a positive bias of 0.3 μg $L^{-1}$ for Ni when using ammonia as the reaction gas for sea-water samples.[25] Analyzing the same set of spiked NIST SRM samples using helium gas in KED mode shows a bias < 6.0 % for the level 1 spiked samples and < 1.0 % for level 2 spiked samples. The data in Table 5 supports the use of KED mode analysis for nickel since it will be more accurate for analyzing urine samples which can have a high degree of variance from matrix analytes.

There was no distinct advantage for using either the DRC™ reaction cell (ammonia or argon/hydrogen) or KED collision cell (helium) mode analysis for chromium. Since nickel analysis is best achieved using helium gas in KED mode, the chromium analysis will use the same conditions permitting the shortest analysis time. NIST SRMs were spiked with 50 mg $L^{-1}$ and 200 mg $L^{-1}$ EtOH ($^{40}Ar^{12}C^{+}$) or HCl ($^{35}Cl^{16}O^{1}H^{+}$), results can be found in Table 6. All results show a < 5% bias when the samples are spiked with the known interferences.

Final cell gas conditions for the reduction/removal of potential interferences will be set at 6.0 mL $min^{-1}$ He gas in KED mode. There was no change in signal when the RPq was varied from 0.1 to 0.9, therefore it was left at the default settings recommend by PerkinElmer, 0.25. The KED gas flow optimization for solutions in nitric acid only (no urine) can be found in Figures S3 and S4. Figure S3 shows that the $^{40}Ar^{12}C^{+}$ and $^{35}Cl^{16}O^{1}H^{+}$ interferences (at 1.0% EtOH or 1.0% v/v HCl) are removed at ≥ 6.0 mL $min^{-1}$ He gas at an RPq of 0.25. Figure S4 shows that the potential $^{44}Ca^{16}O^{+}$ interference (20 mg $L^{-1}$ Ca) is removed at ≥ 5.0 mL $min^{-1}$ He gas at an RPq of 0.25.

## Accuracy

Evaluation of the method accuracy was achieved by analyzing NIST SRM 2668 level 1 and 2 (Toxic Elements in Frozen Human Urine). The SRMs were analyzed over 20 analytical runs from two instruments that spanned roughly 20 days. Chromium and nickel results are listed in Table 7 for the SRMs and an additional high concentration spike recovery standard to ensure accuracy at the upper end of the linearity range. The average results are all within the 95% Confidence Interval (C.I.) for the target value certified by NIST. The high concentration spike recovery standard results were both found to have a −2.7 % bias to the target value of 150 μg $L^{-1}$ Cr or Ni with 2% RSDs showing that the accuracy is acceptable

throughout the range of LOD – 150 μg $L^{-1}$. Additionally, in house QC samples were spiked in order to determine % recovery of the method. Low QC samples spiked with 1, 3, and 10 μg $L^{-1}$ Cr and Ni had recoveries that range from 96 – 101 % for Cr and 98 – 103 % for Ni over 5 analytical runs (Table S4).

### Precision

The method uses a 1.0 mL sample loop that allows for ~ 110 s of stable signal (liquid flow rate listed in Table 1) with %RSDs in the range of 0.3 – 0.8 %. To ensure among run reproducibility, in house CDC quality control (QC) samples are prepared by spiking urine (large volume) with chromium and nickel at concentrations expected to correlate to low and high concentrations in a population. Table 8 lists the calculated precision and accuracy of these QC samples over 60 analytical runs. The mean target values were calculated across the initial 20 analytical runs. For chromium and nickel the among run precision for the low and high QC are < 10% over 60 analytical runs which spans a time period of ~ 2 months. To assess with-in run stability, 85 samples (10 μg $L^{-1}$ Cr and Ni) were analyzed sequentially (~ 150 min total analysis time) and resulted in %RSDs of 1.7 % for Cr and 1.3 % for Ni.

### Method Comparison

To compare the method described here with the previously used ICP-SF-MS method both were used to analyze the same set of 67 patient samples for chromium (0.23 – 36.8 μg $L^{-1}$ Cr). A correlation plot of the results from the two methods resulted in a linear regression of 0.9905, which represents good agreement in the sample results from both instruments. For nickel, 118 samples, with a concentration range of 0.75 – 35.9 μg $L^{-1}$, were analyzed using both methods. The correlation plot for Ni resulted in a linear regression of 0.9837. The precision of the two methods are compared in Table 9 using QC samples that had been analyzed on both platforms. The QC samples analyzed on the SF-ICP-MS method had a much larger run-to-run variation than was reported from the ICP-UCT-MS method.

Limits of detection (LOD) were calculated for the ICP-UCT-MS method using an adopted Taylor method.[26] A robust LOD is calculated using 60 analytical runs (includes standards, beginning and ending QC bracketing ~ 50 samples) over 60 days. The LOD was determined to be 0.162 μg $L^{-1}$ Cr and 0.248 μg $L^{-1}$ Ni. For chromium the LOD is higher than the SF-ICP-MS method (SF-ICP-MS 0.105 μg $L^{-1}$ Cr), but for nickel the LOD is lower than the SF-ICP-MS method (SF-ICP-MS 0.337 μg $L^{-1}$ Ni). The ICP-UCT-MS method LODs are below the concentration range of past study samples that have been tested over the last 5 years in this laboratory for Cr (0.23 – 36.8 μg $L^{-1}$) and Ni (0.75 – 35.9 μg $L^{-1}$). Published concentration ranges for various populations (0.06 – 40.0 μg $L^{-1}$ Cr and 0.06 – 32.1 μg $L^{-1}$ Ni)[5, 23] suggest that only a small percentage of results would be below the LOD.

## CONCLUSION

A method for analysis of chromium and nickel in urine has been developed on a PerkinElmer NexION™ 300D ICP-UCT-MS for replacement of a SF-ICP-MS method. Polyatomic interferences were removed by running the universal cell in collision cell / KED mode using helium gas at 6.0 mL $min^{-1}$. The use of ammonia and 10 % hydrogen in argon

were not effective in reducing the $^{44}Ca^{16}O^{+}$ interference for nickel analysis. The resulting limits of detection and accuracy were in good agreement with a previous SF-ICP-MS and with NIST SRMs, and the resulting run-to-run precision was an improvement over the previous SF-ICP-MS method. The quadrupole-based method provides an easier and more robust platform to operate with comparable or improved performance.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Table 1

Instrument parameters for the PerkinElmer NexION 300D ICP-UCT-MS.

| | |
|---|---|
| RF Power | 1.60 kW |
| Plasma Gas Flow (Ar) | 15 L $min^{-1}$ |
| Auxiliary Gas Flow (Ar) | 1.2 L $min^{-1}$ |
| Nebulizer Gas Flow (Ar) | ~ 0.94 - 1.06 L $min^{-1}$ |
| KED Mode | |
| Entrance Lens | −4 V |
| Exit Lens | −39 V |
| CRO | −16 V |
| QRO | −12 V |
| Detector | Single Channel Electron Multiplier, pulse mode |
| Method Parameters | |
| Sweeps/Reading | 70 |
| Readings/Replicate | 1 |
| Replicates | 3 |
| Dwell Times | 100 ms for $^{52}Cr$ & $^{60}Ni$, 50 ms for $^{103}Rh$ |
| Scan Mode | Peak Hopping |
| Gas Channel | Channel B, 6.0 mL $min^{-1}$ He |
| RPq | 0.25 |
| Liquid Flow Rate | 0.33 mL $min^{-1}$ |
| Sample Loop | 1.0 mL |
| Sample Flush Time | 4 s |
| Read Delay Time | 15 s |
| Wash Time | 30 s |
| Internal Standard | $^{103}Rh$ (10 μg $L^{-1}$) |
| Calibration Type | External Simple Linear<br>Matrix Matched |
| Calibration (μg/L) | 0.0, 0.1, 0.3, 1.0, 3.0, 10.0 |
| Sample Preparation | 1:10 dilution in 2% $HNO_3$ |

| **Mass Flow Controller** * | Conversion Factor | Actual Flow Rate @ 1.5 mL $min^{-1}$ |
|---|---|---|
| Helium | 1.45 | 2.18 mL $min^{-1}$ |
| Argon | 1.39 | 2.09 mL $min^{-1}$ |
| Oxygen | 0.99 | 1.49 mL $min^{-1}$ |
| Ammonia | 0.73 | 1.10 mL $min^{-1}$ |
| Methane | 0.72 | 1.08 mL $min^{-1}$ |

* NexION 300D is equipped with a nitrogen mass flow controller.

## Table 2

Background Equivalent Concentrations (BEC) for potential interferences on analysis of $^{52}Cr$.

| Potential Interference | Interference Concentration Tested (μg $L^{-1}$) | BEC (μg $L^{-1}$ Cr) Standard Mode |
|---|---|---|
| $^{35}Cl^{17}O^+$, $^{37}Cl^{15}N^+$, $^{37}Cl^{14}N^1H^+$, $^{35}Cl^{16}O^1H^+$ | 1,000,000 μg $L^{-1}$ Cl [23]<br>2.0 % v/v $HNO_3$ (N) | 6.84 |
| $^{40}Ar^{12}C^+$, $^{36}Ar^{16}O^+$, $^{38}Ar^{14}N^+$ | 2.0 % v/v $HNO_3$ (N)<br>0.5 % EtOH (C) | 298 |
| $^{40}Ca^{12}C^+$ | 100,000 μg $L^{-1}$ Ca [23]<br>0.5 % EtOH (C) | 140 |
| $^{39}K^{13}C^+$ | 1,000,000 μg $L^{-1}$ K [23]<br>0.5 % EtOH (C) | 137 |

## Table 3

Background Equivalent Concentrations (BEC) for potential interferences on analysis of $^{60}$Ni.

| Potential Interference | Interference Concentration Tested (μg $L^{-1}$) | BEC (μg $L^{-1}$ Ni) Standard Mode |
|---|---|---|
| $^{119}Sn^{++}$, $^{120}Sn^{++}$ | 5 μg $L^{-1}$ Sn [24] | 0.15 |
| $^{44}Ca^{16}O^{+}$, $^{48}Ca^{12}C^{+}$, $^{43}Ca^{16}O^{1}H^{+}$ | 20,000 μg $L^{-1}$ Ca [23] 0.5 % EtOH (C) | 3.64 |
| $^{59}Co^{1}H^{+}$ | 5 μg $L^{-1}$ Co [23] | 0.34 |
| $^{45}Sc^{15}N^{+}$, $^{45}Sc^{14}N^{1}H^{+}$ | 100 μg $L^{-1}$ Sc ¥ | 0.39 |
| $^{23}Na^{37}Cl^{+}$ | 1,000 μg $L^{-1}$ Na [23] | 0.70 |

¥No reference was found by author for Sc in urine.

**Table 4**

Signal-to-background ratios for 1 μg $L^{-1}$ Cr or Ni in matrix compared to matrix spiked interference solutions under vented, DRC™, or KED mode.

| Mode | Gas Composition | $^{52}Cr^{+}$/Matrix* | $^{60}Ni^{+}/^{44}Ca^{16}O^{+}$ |
|---|---|---|---|
| Standard (Vented) | No Gas | 0.3 | 1.3 |
| Reaction (DRC™) | 90% Ar/10% $H_2$ | 26.2 | 4.3 |
| | $O_2$ | 5.0 | 1.1 |
| | $NH_3$ | 24.0 | 3.8 |
| | $CH_4$ | 2.8 | 2.6 |
| Collision (KED) | He | 24.7 | 4.3 |

*Matrix = $^{40}Ar^{12}C^{+}$ and $^{35}Cl^{16}O^{1}H^{+}$

## Table 5

The effects of calcium ($^{44}Ca^{16}O^{+}$ interference) addition on $^{60}Ni^{+}$ analysis. Conditions tested include 1.8 mL $min^{-1}$ 90% Ar/10% H, RPq = 0.70 in DRC™ mode; 2.3 mL $min^{-1}$ $NH_3$, RPq = 0.70 in DRC™ mode; 6.0 mL $min^{-1}$ He, RPq = 0.25 in KED mode. Nist SRM 2668 Level 1 target value = 2.31 μg $L^{-1}$ Ni and Level 2 target value = 115.3 μg $L^{-1}$ Ni.

| DRC™/KED Conditions | NIST SRM | No Spike (μg $L^{-1}$) | + 5 mg $L^{-1}$ Ca (μg $L^{-1}$) | % Bias | + 20 mg $L^{-1}$ Ca (μg $L^{-1}$) | % Bias |
|---|---|---|---|---|---|---|
| **1.8 mL $min^{-1}$** | 2668 L1 | 2.47 | 2.69 | **8.9** | 2.81 | **13.8** |
| **Ar/H** | 2668 L2 | 120 | 122 | **1.7** | 121 | **1.2** |
| **2.3 mL $min^{-1}$** | 2668 L1 | 2.27 | 2.51 | **10.6** | 2.69 | **18.5** |
| **$NH_3$** | 2668 L2 | 118 | 120 | **0.9** | 120 | **1.6** |
| **6.0 mL $min^{-1}$** | 2668 L1 | 2.39 | 2.33 | **−2.5** | 2.25 | **−5.9** |
| **He** | 2668 L2 | 118 | 116 | **−0.9** | 117 | **−0.7** |

## Table 6

The effects of EtOH and HCl ($^{40}Ar^{12}C^{+}$ and $^{35}Cl^{16}O^{1}H^{+}$ interferences) addition on $^{52}Cr^{+}$ analysis using KED conditions of 6.0 mL $min^{-1}$ He, RPq = 0.25. Nist SRM 2668 Level 1 target value = 1.08 μg $L^{-1}$ Cr and Level 2 target value = 27.7 μg $L^{-1}$ Cr. CDC QC 709 (in house quality control sample) target value = 0.87 μg $L^{-1}$ Cr. NYDOH UE11-02 (proficiency testing (PT) program sample from NY Department of Health) target value = 13.02 μg $L^{-1}$ Cr.

| Sample ID | No Spike | + 50 mg $L^{-1}$ EtOH (μg $L^{-1}$) | % Bias | + 200 mg $L^{-1}$ EtOH (μg $L^{-1}$) | % Bias |
|---|---|---|---|---|---|
| **CDC QC 709** | 0.86 | 0.89 | **3.5** | 0.85 | **−1.2** |
| **NIST SRM 2668 Level 1** | 1.11 | 1.06 | **−4.5** | 1.16 | **4.5** |
| **NYDOH UE11-02** | 14 | 14.4 | **2.9** | 14.1 | **0.7** |
| **NIST SRM 2668 Level 2** | 29.4 | 29.4 | **0.0** | 29.3 | **−0.3** |

| Sample ID | No Spike | + 50 mg $L^{-1}$ $Cl^{-1}$ (μg $L^{-1}$) | % Bias | + 200 mg $L^{-1}$ $Cl^{-1}$ (μg $L^{-1}$) | % Bias |
|---|---|---|---|---|---|
| **CDC QC 709** | 0.88 | 0.84 | **−4.5** | 0.90 | **2.3** |
| **NIST SRM 2668 Level 1** | 1.11 | 1.05 | **−5.4** | 1.06 | **−4.5** |
| **NYDOH UE11-02** | 14 | 13.4 | **−4.3** | 14.1 | **0.7** |
| **NIST SRM 2668 Level 2** | 30.4 | 29.7 | **−2.3** | 29.9 | **−1.6** |

## Table 7

Validation of method accuracy using NIST SRM 2668 Level 1 and 2. N = 20.

| | | | Cr |
|---|---|---|---|
| | **Sample ID** | **Target, μg $L^{-1}$ (± 1 SD)** | **Average (μg $L^{-1}$)** |
| **NIST** | SRM 2668 L1 | **1.08** (0.77 – 1.39) | 1.19 ± 0.20 |
| | SRM 2668 L2 | **27.7** (25.6 – 29.8) | 29.3 ± 0.75 |
| **CDC*** | High Concentration Spike Recovery Standard | **150** (135 – 165) | 146 ± 3 |

| | | | Ni |
|---|---|---|---|
| | | **Target, μg $L^{-1}$ (± 1 SD)** | **Average (μg $L^{-1}$)** |
| **NIST** | SRM 2668 L1 | **2.31** (1.99 – 2.63) | 2.17 ± 0.14 |
| | SRM 2668 L2 | **115** (110 – 121) | 118 ± 2 |
| **CDC*** | High Concentration Spike Recovery Standard | **150** (135 – 165) | 146 ± 3 |

* High Concentration Spike Recovery Standard represents method linearity.

## Table 8

In house CDC quality control pools. Target Values characterized using N = 40 (20 beginning analytical results + 20 ending analytical results). Average values, N = 120 (60 beginning analytical results + 60 ending analytical results).

| | | Cr | | |
|---|---|---|---|---|
| **QC Sample** | | **Target, μg $L^{-1}$ (± 1 SD)** | **Average (μg $L^{-1}$)** | **% RSD** |
| **CDC** | Low | **0.867** (0.716 – 1.02) | 0.880 ± 0.080 | 9.7 |
| | High | **3.66** (3.46 – 3.86) | 3.61± 0.17 | 4.6 |

| | | Ni | | |
|---|---|---|---|---|
| | | **Target, μg $L^{-1}$ (± 1 SD)** | **Average (μg $L^{-1}$)** | **% RSD** |
| **CDC** | Low | **1.38** (0.928 – 1.83) | 1.55 ± 0.15 | 9.5 |
| | High | **6.34** (5.82 – 6.87) | 6.64 ± 0.27 | 4.0 |

**Table 9**

Comparison of precision from low and high QC samples for Cr and Ni for the previously implemented SF-ICP-MS method with new ICP-UCT-MS method. Results are representative of 1 standard deviation (SD) to the target value for each method.

| | | Target (μg $L^{-1}$) | SF-ICP-MS (± 1 SD μg $L^{-1}$) | ICP-UCT-MS (± 1 SD μg $L^{-1}$) |
|---|---|---|---|---|
| Cr | Low QC | 0.630 | ± 0.895 | ± 0.264 |
| | High QC | 2.36 | ± 0.417 | ± 0.204 |
| Ni | Low QC | 0.177 | ± 0.639 | ± 0.142 |
| | High QC | 0.300 | ± 1.79 | ± 0.127 |