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Is Urinary Cadmium a Biomarker of Long-term Exposure in Humans? A Review

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Abstract

Cadmium is a naturally-occurring element, and humans are exposed from cigarettes, food, and industrial sources. Following exposure, cadmium accumulates in the kidney and is slowly released into the urine, usually proportionally to the levels found in the kidneys. Cadmium levels in a single spot urine sample have been considered indicative of long-term exposure to cadmium; however, such a potentially exceptional biomarker requires careful scrutiny. In this review, we report good to excellent temporal stability of urinary cadmium (intraclass correlation coefficient 0.66–0.81) regardless of spot urine or first morning void sampling. Factors such as changes in smoking habits and diseases characterized by increased excretion of proteins may produce short-term changes in urinary cadmium levels. We recommend that epidemiologists use this powerful biomarker in prospective studies stratified by smoking status, along with thoughtful consideration of additional factors that can influence renal physiology and cadmium excretion.

Keywords

Cadmium; Urinary-cadmium; Creatinine; Biomonitoring; Heavy metal; Biomarker

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Introduction

Cadmium is a silver metal with a bluish tinge that occurs naturally in the earth's crust. It has been heavily used in industrial activities and is also often found in phosphate-based fertilizers [1]. Human exposure to cadmium has increased over the past several hundred years; for example, levels in human bones from the twentieth century have been reported at about ten times above pre-industrial levels [2]. Following exposure, much of the cadmium accumulates in the kidney, and levels in urine have been shown to be proportional to levels in the kidney. Therefore, urinary cadmium (U-Cd) levels are often considered to be an indicator of long-term exposure [3]. In the realm of environmental exposure biomarkers, an easy-to-collect biomarker that is indicative of long-term exposure is exceedingly rare and merits careful scrutiny. Questions remain about this biomarker, and we seek to address some of them in this review paper to help assess the merits of using U-Cd as a biomarker of long-term exposure for the general population: (1) Are levels of U-Cd temporally stable across samples? and (2) What factors are predictive of U-Cd levels and do any of those factors produce variation in U-Cd over short periods of time?

In this review of the urinary cadmium biomarker, we open with a brief summary of the public health relevance and toxicokinetics of cadmium. Then, we discuss recent research on the temporal stability of U-Cd, followed by factors predictive of the marker, and then conclude with a brief discussion of broader implications for exposure assessment and environmental epidemiology.

Public Health Relevance of Cadmium

Primary sources of Cd exposure in the general population include food and tobacco, with key contributions from industrial emissions and Cd-containing fertilizer. Among nonsmokers, the primary source of Cd exposure is through the diet. For example, the application of phosphate fertilizer for a period of 36 years resulted in a 14-fold increase in Cd content of surface soils [4]. In general, Cd in soil accumulates in crops which are then consumed or smoked. Measured Cd levels in Fall wheat doubled from 1920 to 1979 [5], which has been attributed to the application of fertilizer and sewage sludge. Cd is present in virtually all foods, with more than 80 % of food-Cd coming from cereals, vegetables, and potatoes [6]. Average Cd intake in food varies from 8 to 25 μg/day, with another 1–3 μg per day among cigarette smokers [7]. The US Food and Drug Administration's Total Diet Study update reported a 26 % increase in dietary Cd exposure from 1990 to 2003, from 8.8 to 11.1 μg/person/day [8]. Many European countries have national policies that limit Cd in phosphate fertilizers [9], but the USA has only recently implemented regulations and even then, only in a small number of states [1].

Other anthropogenic sources include human-made Cd emissions arising from the manufacture, use and disposal of products containing Cd such as batteries, or from the presence of Cd impurities in manufactured products [5, 10]. Cd emissions from over 12,500 facilities (e.g., solid waste incineration, iron and steel production, zinc mining, and metal finishing production) in the USA result in Cd deposition on agricultural soils and plant uptake [11], which then contributes to dietary exposure.

Toxicological and occupational studies confirm that Cd is a renal and bone toxicant and a lung carcinogen [1]. Renal effects have been observed in occupational studies from chronic inhalation of Cd in fumes and dust in excess of 10 μg/m^3 [12–14] or from cumulative dietary exposure greater than 1600 mg [15]. Lung cancer has been observed from occupational exposures >8 years mg/m^3, although concurrent arsenic exposure has been difficult to disentangle [16–19]; nonetheless, the International Agency for Research on Cancer has classified Cd as a human lung carcinogen (group 1) [20]. In the Jinzu river basin in Japan, Itai-Itai disease (literally translated as “ouch-ouch”), which is characterized by intense pain, fractures, and distortion of the long bones, was associated with cadmium in contaminated river water used to irrigate rice fields [21–24]. More recent studies of chronic human exposure to Cd at levels more common to the general population (<25 μg/day) suggest that Cd may be associated with renal effects, osteoporosis, cardiovascular outcomes, and several cancers, among other outcomes [25–35].

Toxicokinetics of Cadmium

Toxicological studies beginning in the 1950s demonstrated that following exposure via the digestive tract, Cd was initially highest in the liver and then highest in the kidneys [36, 37]. Conversely, studies in rodents showed that inhalation of cigarette smoke caused an increase of Cd in lung and kidney tissue, but not in the liver [38]. It was later shown that induction of metallothionein, a low molecular weight protein with a tertiary structure forming alpha and beta domains of metal clusters [3], explained the redistribution of Cd from the liver to the kidneys [39–41]. We now know that following exposure, Cd is absorbed more readily via inhalation than ingestion, and women tend to exhibit higher levels than men, most likely reflecting increased absorption due to lower iron levels [22, 42–45]. Once in systemic circulation, Cd is initially bound to albumin in blood plasma, then transferred to the liver where the Cd-albumin complex is taken up, degraded, and Cd is released [3] (Fig. 1, physiology of Cd excretion) (adapted from Nordberg [3] and Zalups [59], with permission from Elsevier.)

The released Cd induces synthesis of metallothionein [3]. Two major forms of metallothionein, MT-1 and MT-2, are inducible by Cd and can bind a range of metals, serving generally in the homeostasis of heavy metals (e.g., zinc) and thereby providing protection against many of their toxic effects [3, 46]. Both the constitutive cellular metallothioneins and those that are induced by chemicals are important in the detoxification of Cd [47]. After binding to metallothionein in liver cells, a small proportion of Cd-metallothionein is released into blood plasma and filtered through the glomerular membrane carrying Cd to the renal tubules [39, 48]. Like other small proteins, Cd-metallothionein is efficiently cleared from blood plasma by glomerular filtration and reabsorbed into the proximal tubules of the kidneys [3]. This pathway has been demonstrated using radiolabeling in animal experiments [49–51]. After uptake by the kidneys, Cd enters the lysosomes in the tubular cells where it is released from metallothionein [52] and may cause renal damage. Autopsy studies indicate that this process results in accumulation of Cd in the kidneys where it remains for many years, with an estimated half-life of 10–30 years [53–56]. A small portion of Cd is continuously but slowly excreted in urine [54]. Therefore, U-Cd is thought to reflect long-term exposure [57, 58], while blood Cd reflects a combination of

both long-term and more recent exposures [3]. In addition, some Cd remains in, or is released back to, the gastrointestinal tract and excreted in the feces.

Introduction to Urine Cadmium

In the absence of occupational exposure to Cd, binding sites (e.g., metallothionein) are not saturated, and U-Cd generally increases in proportion to the amount of Cd stored in the kidney [1]. The degree to which U-Cd can be considered a reliable biomarker of long-term exposure in the general population will be discussed in the following sections on temporal stability and predictors of U-Cd.

An important consideration for any urinary biomarker is urine density. Urinary concentrations of contaminants are highly influenced by the degree of dilution of the urine and adjusting values for dilution is critical [60]. Normalizing urine biomarker levels using either urinary creatinine levels, specific gravity, osmolality, or urinary flow rate are most commonly used and correlate reasonably strongly with one another, yet each approach offers distinct benefits and drawbacks [61–65]. Urinary creatinine concentrations are most typically reported and therefore will be the focus of much of the discussion here. Creatinine normalized cadmium values will be abbreviated as U-Cd_{cr} in this review. One important consideration of using U-Cd_{Cr}, however, is that individuals with renal disease may excrete cadmium, creatinine, or other markers differently from healthy individuals [66, 67]; therefore, U-Cd should be used as a biomarker of exposure with caution in patients with kidney disease or diabetes.

Temporal Stability of Urine Cadmium

We identified seven studies [68–70, 71•, 72–74] that examined the temporal stability of U-Cd_{cr} and reported intra class correlation (ICC) coefficients; ICCs ranged from 0.42 to 0.89. According to the criteria illustrated by Rosner [75], reproducibility is considered good when $0.40 \leq ICC < 0.75$ and excellent when $ICC \geq 0.75$. In those studies, ICCs were highest for first morning void samples or 24 h samples measured within a few days of each other (ICC = 0.89) [72]; for samples collected anywhere from 1 to 12 months apart the ICCs ranged from 0.42 to 0.81 regardless of the type of sample [68, 69, 76]. It is unclear why these studies generated different ICC values. One potential difference between studies was whether or not they corrected for prevalent interferences by molybdenum oxide or tin [77]. Analysis of U-Cd is generally performed by inductively-coupled plasma mass spectrometry (ICP-MS), and these analyses can often suffer from both isobaric and polyatomic interferences that must be accounted for in the experimental design and data interpretation. There is currently some discussion within the analytical community regarding the appropriate approach of interference correction in U-Cd analysis. When we only included those studies which specified an attempted correction of polyatomic interferences when it may have been a concern (Table 1), the range of ICC values narrows to 0.66–0.81, with no clear difference whether the samples were spot urine or first morning void or whether the time interval between samples was months or a few years [71•, 72–74]. Therefore, studies of temporal stability generally support the interpretation that the U-Cd biomarker reflects long-term Cd body burden. However, it is important to note that these studies did not include individuals

who experienced substantial variations in recent exposures (e.g., a new occupational Cd exposure or changes in smoking habits). Therefore, we do not know whether changes in recent exposures might impact the degree of temporal stability in the biomarker.

Predictors of Urine Cadmium

Another way to investigate the extent to which U-Cd is an indicator of long-term exposure is to assess which factors predict U-Cd and their short-term variation. The ideal study design to answer this question would be a longitudinal study which investigates the variation of U-Cd levels following changes in exposure. Unfortunately, in our review of the literature, we did not find any such longitudinal studies, with the exception of a small investigation on the decrease of secondhand smoke exposure in non-active smokers [71•]. However, a number of studies have measured U-Cd worldwide and investigated the correlation between exposure sources and those levels [78–84]. Significant correlations between estimated Cd exposure and U-Cd levels have been found in populations exposed to environmental contamination [23, 78, 79]. In the absence of unusually high environmental or occupational sources, the U-Cd_{cr} concentration is usually <2 μg Cd/g creatinine in Western populations and is most strongly correlated with smoking, age, and female sex [78–84].

Cigarette smoking contributes to most of the variability in U-Cd due to the lungs' high rate of absorption of Cd in tobacco. Current smokers have higher urinary concentrations than former and never smokers [54], and it has been widely reported that former smokers have significantly higher U-Cd than never smokers, which one would expect if U-Cd is a biomarker of long-term exposure [78–84]. Recently, however, at least two reports suggested there might be no such difference between former and never smokers [80, 85]. In order to further investigate the matter, we contacted study authors and were able to pool data from five study populations that reported U-Cd_{cr} at levels generally <2 μg Cd/g creatinine, and also had information on smoking status and age [68, 80, 86, 87, 88•, 89] (Fig. 2). In pooling the data, studies that used the same study population, e.g., [88•, 89, 90], were not double-counted. In a pooled analysis, the mean ± SD U-Cd_{cr} was 0.47 ± 0.50, 0.69 ± 0.88, and 0.91 ± 0.81 μg Cd/g creatinine, with n = 12630, 6309, and 7698 for never, former, and current smokers, respectively. The difference between these populations was highly significant, as evidenced by Student T test values for both never vs. former and never vs. current smokers of $p < 0.01$ (Fig. 2a). This overall difference between never and former smokers was driven by differences in U-Cd_{cr} levels among the older population (Fig. 2b). While U-Cd_{cr} levels appear to vary between never and former smokers, these data are unable to address whether levels of U-Cd_{cr} decrease after smoking cessation. Sanchez-Rodriguez et al. (2015) report that a year after a public smoking ban went into effect, non-smokers showed a median drop in U-Cd_{cr} of 0.07 μg/g, with 76 % of participants showing a drop in U-Cd_{cr} [71•]. Adams and Newcomb (2014) modeled cross-sectional NHANES data and reported that U-Cd drops 23 % in the first year after quitting smoking among 55-year-old males with 20 pack years of smoking history [88•]. In their model, U-Cd levels in former smokers remain elevated compared with never smokers even 30 years following smoking cessation, suggesting that U-Cd reflects both recent smoking exposure and long-term smoking history.

Age is also consistently associated with U-Cd_{cr} [78–84] (Fig. 2b), although the extent to which creatinine adjustment may inflate this association has not yet been established [80]. One possible explanation for this inflation is that urine creatinine levels tend to decrease with age as muscle mass diminishes [91]. In our analyses of the NHANES 1999–2012 data with at least 1500 people in each age group, the association of U-Cd with age is maintained regardless of creatinine adjustment (U-Cd: age 21–30; 0.24 μg/L, age 71–80; 0.55 μg/L and U-Cd_{cr}: age 21–30; 0.17 μg/g, age 71–80; 0.56 μg/g).

U-Cd is also higher among women, with iron status and number of pregnancies (during which body iron stores are often depleted) being important factors because low iron increases Cd absorption [42, 68, 81–83, 92, 93]. Cd uses the same intestinal absorption transport system as zinc, calcium, and iron [94], three essential divalent cations. Iron (Fe) body stores were shown to especially influence the absorption rate of Cd: the lower the Fe body stores, the more Cd is absorbed from food in the intestinal tract [95]. Cd can be transported across the intestinal epithelium by the concerted action of the apical divalent metal transporter (DMT1) as well as the metal transported protein (MTP1). The expression of these proteins changes in response to the status of the body's Fe stores, and Cd competes with Fe for absorption. This is particularly significant when cereals and green leafy vegetables, which can be relatively rich in Cd and poor in Fe, are consumed. This phenomenon is more prevalent in women, who tend to have lower body Fe stores, in particular during pregnancy [42, 43, 83, 93].

Linear models accounting for age, sex, number of pregnancies, and smoking habits typically contribute to less than 30 % of U-Cd variability, which drops to ~10 % when the population is stratified by smoking status [82]. Even acknowledging the possibility of measurement error or nonlinearity, this suggests that other factors contribute to U-Cd variability, in particular an individual's diet which can be a meaningful source of Cd. When dietary Cd intake is estimated using a food frequency questionnaire (FFQ), only a small portion of the observed variability in U-Cd is explained [81–84, 92, 96]. Other than organ meats like kidney and liver, which have very high levels of Cd but are seldom eaten regularly, low levels of Cd are found throughout the diet in diverse foods including meats, shellfish, vegetables, grains, soybeans/tofu, and dairy. This variety of dietary sources limits the likelihood of confounding in epidemiologic studies, but dietary sources have not been consistently associated with U-Cd_{cr} in FFQ studies [81–84, 92, 96]. It is possible that the FFQ does not reflect historic exposure and that is the reason it so poorly estimates U-Cd. However, duplicate diet studies in which urine is collected within 24 h of dietary samples, tends to show better correlation. In two of three studies in which Cd was measured in a duplicate diet sample, U-Cd_{cr} was positively associated with dietary Cd ($\rho = 0.4$ in both [79, 81], $\rho = -0.1$ in [97]). Julin et al. [81] argue that if the sampled dietary intake reflects historic patterns of dietary intake, then it may be more likely to be associated with U-Cd_{cr}, although we cannot verify this assertion. In all three studies, the correlation between dietary intake and both blood Cd and U-Cd was similar, which might suggest that U-Cd_{cr} is influenced to some degree by recent dietary exposures; however, the high degree of temporal stability of the marker (Table 1) suggests that the degree to which U-Cd_{cr} reflects current dietary exposure to Cd is likely small. Therefore, it is suggested, but not confirmed, that the

correlation between Cd dietary intake and U-Cd would be greater if duplicate diet samples were obtained many years before urine samples and not at the same time as in these studies.

A recent commentary [98•] also highlights two reports of co-excretion of Cd with plasma proteins in urine [80, 99]; factors responsible for excretion of these proteins might therefore also be predictive of U-Cd_{cr}. A possible mechanistic explanation for this observation involves the capacity of the kidneys to filter and reabsorb low molecular weight proteins [80]. As described in the section on toxicokinetics above, following exposure, Cd-metallothionein is generally reabsorbed by the proximal tubules. The amount of the protein complex not reabsorbed is excreted in the urine, and as the body's ability to reabsorb these proteins changes (e.g., due to disease), this can result in increased excretion of Cd along with other proteins. Therefore, because of co-excretion mechanisms, an increase in U-Cd might be observed in people with chronic diseases involving the kidneys and in those who experience an increase of plasma proteins in the urine (proteinuria or albuminuria), which may be a result of bone loss, cardiovascular diseases, or diabetic nephropathy [98•]. The greater risk predicted for certain diseases in cross-sectional epidemiology studies in the presence of elevated U-Cd may in fact be the result of reverse causality, in which higher U-Cd levels were caused by the disease and not vice versa. Therefore, prospective longitudinal studies are required to clarify the risks from relatively low levels of U-Cd that have been suggested through cross-sectional investigation.

Conclusions

In the universe of biomonitoring markers, U-Cd remains one of the best tools to assess long-term exposure to cadmium. The high degree of temporal stability in the biomarker, as evidenced by ICC values ranging from 0.66 to 0.81 regardless of spot samples or first morning voids, suggests that short-term variability in dietary exposures is likely only a small contributor to the U-Cd measure. Changes in U-Cd following smoking cessation, however, suggest that investigators should be careful to only investigate epidemiologic associations in separate strata of current, former, and never smokers. Researchers should also consider the physiology of cadmium exposure and excretion when designing epidemiologic studies to avoid being confounded by reverse causality and recent exposures. Prospective, longitudinal studies are recommended.

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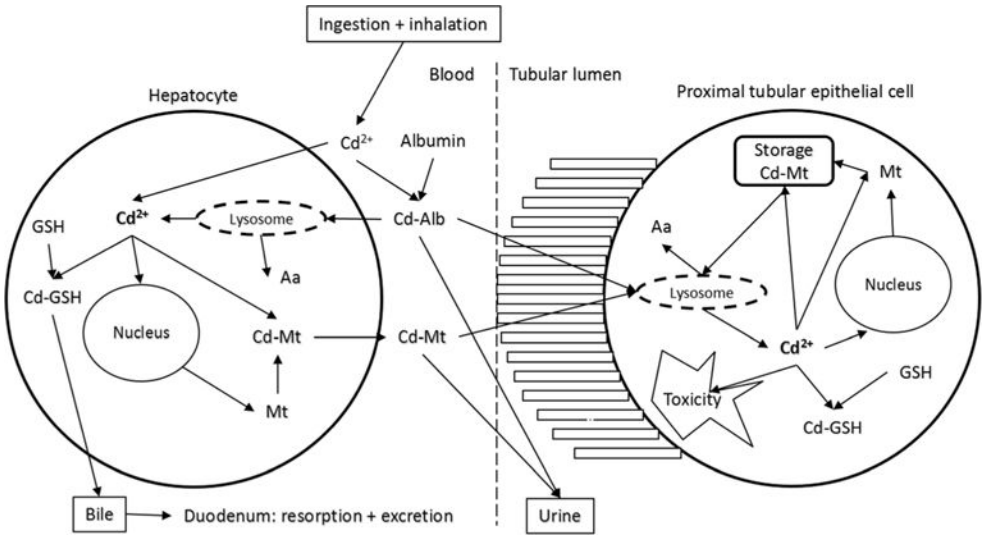

Fig. 1.

Physiology of Cd excretion (Adapted from Nordberg [3] and Zalups [59], with permission from Elsevier)

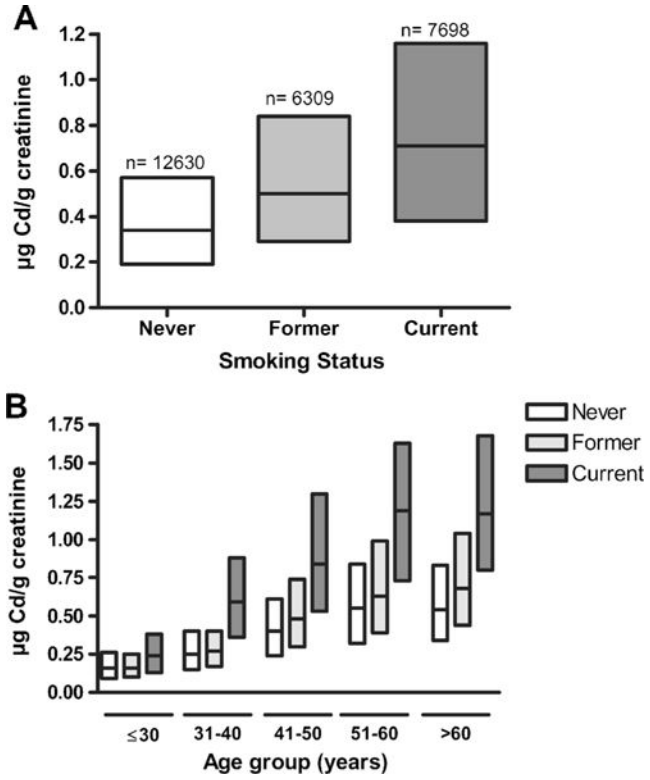

Fig. 2.

Creatinine-adjusted U-Cd median and IQR from six studies in never, former, and current smokers, overall (**a**) and stratified by age (**b**) [67, 79, 85–87, 88•]. The NHANES 1999–2010 data were included only once

Table 1

List of studies reporting ICC for repeated U-Cd measurements

Author	Population (n_{ind}, $n_{samples}$)	Time frame between repeat samples	Type of urine sample	Range average U-Cd_{cr} values (μg/g)	ICC U-Cd_{cr} (type of samples, $n_{samples}$)	Analytical method	Polyatomic interferences on Cd (ICP-MS only)
Gunier et al. (2013) [68]	Healthy Californian women (141, 282)	3–9 months	24 h	0.39–0.42	0.42 (24 h, 282)[a] 0.51 (3 months, NA) 0.59 (6 months, NA) 0.42 (9 months, NA)	ICP-MS	Unclear correction approach; Possible interferences
Smolders et al. (2014) [70]	Healthy men and women (8, 352)	Every sample over a 6 days period	Spot	0.08–0.66	0.75 (Spot, 352)	ICP-MS	Unclear correction approach; Possible interferences
Wang et al.(2015) [69]	Healthy men (11, 529)	3 months	24 h FMU Spot	0.42–0.49	0.70 (24 h, 88)[4] 0.68 (FMU, 88) 0.53 (Spot, 529)	ICP-MS	Unclear correction approach; Possible interferences
Akerstrom et al. (2014) [72]	Non-smoking healthy men and women (24, 288)	7 days	24 h FMU Spot	0.08–0.17	0.89 (24 h, 48)[a] 0.89 (FMU, 48) 0.70 (spot, 288)	ICP-MS	Addressed by analytical approach[1]
Sanchez-Rodriguez et al. (2015) [71•]	Healthy men and women (83, 166)	1 year	FMU	0.10–0.25	0.72 (FMU, 166)	(DRC)-ICP-MS	Addressed by analytical approach[2]
Vacchi-Suzzi et al. (2016) [74]	Healthy men and women (100, 244)	1 week, 1 month, 6 months	FMU Spot	0.19–0.21	0.76 (1 week FMU, 88) 0.66 (1 mo. FMU, 110) 0.78 (6 mo. spot, 156)	ICP-MS	Addressed by analytical approach[3]
Arisawa et al. (1997) [73]	Healthy Japanese men and womenina cadmium polluted area (48, 96)	3 years	FMU	6.70–8.40	0.81 (FMU, 96)	Zeeman effect electro thermal atomic absorption spectrometry	No concerns

ICP-MS inductively coupled plasma mass spectrometry, *DRC-ICP-MS* dynamic reaction cell-inductively coupled plasma mass spectrometry, *FMU* first morning urine, *NA* not available, n_{ind} number of individual participants in a study, $n_{samples}$ number of samples provided in a study (some studies had only two samples per participant; other studies had at least a dozen samples)

[a] Not creatinine normalized

[1] Potentially addressed by mathematical correction equations

[2] Addressed by reactive gas oxygen to remove polyatomic interferences

[3] Addressed by use of collision cell for polyatomic interferences and off-mass reporting for Sn isobaric interference

[4] The 24-h samples are not creatinine normalized because they combine multiple urine samples over the course of a day