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Multi-element analysis of urine using octopole collision cell ICP-Q-MS

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This study presents an octopole collision cell ICP-Q-MS methodology for interference-free multi-element analysis of urine. The attention was paid to the performance of the 4th generation octopole-based collision cell in the Agilent 7900 Series ICP-MS in He-mode with kinetic energy discrimination (KED) for the elimination of polyatomic ions that are the main source of spectral interferences during the analysis of numerous elements, such as V, Cr, Fe, Co, Ni, Cu, As, Se, etc. However, collision mode using helium gas had the additional benefit of reducing the response for major matrix elements, thereby effectively raising the upper linear calibration range for these elements. Afterwards, the major elements could be determined in the same analytical run as the trace elements in the range of analytes typically reported in urine samples. The analysis was carried out after the initial 10-fold dilution of the urine samples and Rh was used as an internal standard to diminish non-spectral interferences originating from the sample matrix. Due to the excellent detection capability and practically no interferences, the method could be finally employed for analysis of 26 elements. Accuracy of the method was checked by the regular use of certified reference materials Seronorm™ Trace Elements Urine Blank Lot OK4636 and Seronorm™ Trace Elements Urine L-1 Lot 1011644, as well as by accurate isotope ratios measurements if possible.

Keywords: ICP-Q-MS; Multi-element analysis of urine; Interferences in ICP-MS

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Introduction

Fast analyses of urine samples based on accurate analytical methods are necessary for routine clinical laboratories to perform quickly a screening of the elements potentially toxic or otherwise hazardous for health [1–3].

The inductively coupled plasma mass spectrometry (ICP-MS) is especially useful for this purpose due to its multi-elemental capability, low limits of detection, high dynamic concentration range, high sample throughput and the ability to deal with spectral and non-spectral interferences [4]. The usefulness of the ICP-MS in the analysis of biological samples, including urine, was already described in literature on several occasions [3,5,6]. The analysis of urine that contains high concentrations of salts (e.g. NaCl, KCl, $CaCO_3$, $MgCl_2$, or $NH_4H_2PO_4$) and urea [7] requires a more sophisticated approach to obtain accurate results by ICP-MS. In the ICP-MS analysis of urine, both spectral and non-spectral interferences are expected to be encountered [1,2]. While non-spectral effects can be overcome using a proper calibration strategy including the use of internal standards [8], standard additions [9] and/or the isotope dilution [10], more serious are the spectral effects due to the overlaps by different polyatomic ions formed from the combination of species derived from the matrix elements, plasma gas and sample solvents [11].

High-resolution mass spectrometers with the sector field mass analyser can overcome most of these problems [6,12,13]; however, owing to their high price, these instruments are not easily accessible for most laboratories. TOF-ICP-MS instruments with all the advantages, such as the fast multielemental simultaneous analysis and improved precision of measurements of the isotope ratios do not have the adequate resolution needed for elimination of spectral interferences typically occurring during the analysis of urine. Then, mathematical corrections must be employed, but this approach is less effective when performing trace analysis [14,15].

At the present time, the quadrupole (Q) based ICP-MS equipped with a collision/reaction cell (CRC) for the elimination of spectral interferences is the most spread ICP-MS instrumentation on the market [16]. In the reaction cell mode, a reaction gas (H_2, NH_3, O_2, N_2O or CH_4) converts the interfering and/or analyte ions into different species or un-charged atoms or molecules [16,17]. The reaction cell mode can be used for more efficient removal of known spectral interferences, which may however lead to a formation of new unwanted interfering polyatomic ions causing problems at multielemental analysis [10,16,17]. In general, the collision cell mode is more suitable for the multi-elemental analysis of unknown samples [10]. For this purpose, helium is used most frequently as the collision gas of choice. The collision cell works on the principle of kinetic energy discrimination (KED). Polyatomic ions are larger than analyte ions of the same m/z. Therefore, collisions between polyatomic ions and He atoms occurs much

more often than those between analyte ions and He atoms. The resulting loss of kinetic energy of collided polyatomic ions is used for their elimination from the ion beam using a voltage bias at the exit of the collision cell [10,17].

This work presents the effective operation of the 4th generation ORS^4 cell in He-mode with KED in the Agilent 7900 Series ICP-Q-MS for accurate multi-element analysis of urine.

Materials and methods

Instrumentation and analysis

The quadrupole based ICP-MS Agilent 7900 utilizing an octopole-based collision cell for interference removal based on KED in the "He" mode (Agilent Technologies, Palo Alto, CA, USA) was used in this study. The instrument was equipped with a concentric nebuliser MicroMist (400 μL min^{-1}), the Peltier-cooled (2 °C) Scott quartz spray chamber and a quartz torch with the injector tube internal diameter of 2.5 mm. For precise delivery of samples and internal standard (ISTD), the low-pulsation 10-roller peristaltic pump with three separate channels was employed. The internal standard kit consisting of the connection tubing, connectors and the "Y" piece was used for simultaneous internal standard aspiration and its mixing with a sample. The sampling and skimmer nickel cones with orifice diameters of 1, respectively 0.45 mm were used. The ICP-MS working conditions were optimised during every start-up sequence in order to obtain the highest possible sensitivity for the elements of low, middle and high *m*/*z* using the multi-elemental tuning solution "Tuning solution for ICP-MS" (Agilent) containing 1 μg L^{-1} of Ce, Co, Li, Mg, Tl and Y. Using typical operating conditions summarised in Table 1, the sensitivity of 6000 counts s^{-1} per μg L^{-1} and the resolution expressed as the peak width (in *m*/*z*) at 50 % of the peak height (W-50%) of 0.64 were achieved for $^7Li^+$. The same parameters were 50000 counts s^{-1} per μg L^{-1} and 0.62 for $^{89}Y^+$ and 30000 counts s^{-1} and 0.60 for $^{205}Tl^+$ respectively.

For the analysis of samples, the "general purpose" plasma mode included in the ICP-MS MassHunter software was used. The working parameters of the cell mode "no gas" were auto-tuned during the instrument start-up sequence. The working parameters of the collision cell for modes "He" and "HE He" were adjusted manually. The time required for a transition between the cell modes was 5 s. Parameters related to the sample introduction and plasma conditions were consistent for all modes (see Table 1).

To compensate possible instrumental drift and matrix effects, the internal standard (ISTD) Rh of concentration 200 μg L^{-1} was simultaneously aspired and mixed with the sample. Concentrations of the elements analysed were evaluated from calibration lines with coefficients of determination better than 0.999.

Table 1 The working conditions of the ICP-MS Agilent 7900

Parameter	**Setting**		
ICP			
Plasma mode	General purpose		
Rf power (27 MHz) (W)	1550		
Sampling depth (mm)	8		
Plasma gas flow (L min^{-1})	15		
Auxiliary gas flow (L min^{-1})	0.9		
Nebuliser gas flow (L min^{-1})	1.04		
Nebulizer pump (rps)	0.1		
Spray chamber temperature (°C)	2		
Mass spectrometer	**No gas mode**	**He mode**	**HE He mode [a]**
Extract 1 (V)		0	
Extract 2 (V)		−250	
Omega bias (V)	−100	−120	−120
Omega lens (V)	9.7	7.8	9.6
Cell entrance	−30	−40	−140
Cell exit	−50	−60	−150
Deflect (V)	11.6	1	−77
Plate bias	−35	−60	−150
Helium flow (mL min^{-1})	0	5	10
OctP bias	−8	−18	−100
OctP RF		200	
Energy discrimination (V)		5	
Number of isotopes	15 [b]	10 [c]	4 [d]
Acquisition			
Points per peak	1		
Replicates	3		
Sweeps/replicate	100		
Total acquisition time (s)	51		

[a] - HE He mode – high energy helium mode; Monitored isotopes (integration time):
[b] - ^{7}Li, ^{11}B, ^{24}Mg, ^{31}P, ^{43}Ca, ^{95}Mo, ^{103}Rh, ^{114}Cd, ^{133}Cs, ^{137}Ba, ^{139}La, ^{140}Ce, ^{187}Re, ^{206}Pb, ^{238}U (all 0.1 s);
[c] - ^{23}Na, ^{39}K (both 0.3 s), ^{51}V (1 s), ^{52}Cr, ^{59}Co, ^{63}Cu (all 0.3 s), ^{75}As (1 s), ^{85}Rb, ^{88}Sr (both 0.1 s), ^{103}Rh (0.3 s);
[d] - ^{56}Fe, ^{60}Ni (both 0.3 s), ^{77}Se (1 s), ^{103}Rh (0.3 s)

Chemicals and standard solutions

Ultrapure water obtained using the Milli-Q® system (Millipore, Billerica, MA, USA) of 0.055 μS cm^{-1} conductivity was used for the preparation of all the solutions in this work. Sub-boiled nitric acid was prepared from 65% HNO_3 (w/w) of Selectipur quality (Lach-Ner, Neratovice, Czech Republic) using the distillation unit (model BSB 939 IR; Berghof, Eningen, Germany). The multielemental stock solution Supelco "ICP multi-element standard IV" (Merck, Darmstadt, Germany), the multielement stock solution of the rare earth elments Astasol mix "M008" (Analytika, Prague, Czech

Republic) and single-element standard solutions with concentration 1 ± 0.002 g L^{-1} (Analytika or SCP Science, Baie-d'Urfé, Canada) were used for the preparation of the multielemental stock solution containing 10 mg L^{-1} of Li, B, V, Cr, Fe, Co, Ni, Cu, As, Se, Rb, Sr, Mo, Cd, Sn, Sb, Cs, Ba, Re, Tl, Pb and 1 mg L^{-1} of La, Ce, U. This stock solution was 20-times diluted to prepare the working solution containing 500 and 50 μg L^{-1} of the abovementioned elements. From this working solution, a six-point calibration in the range of 0–100 μg L^{-1} for Li, B, V, Cr, Fe, Co, Ni, Cu, As, Se, Rb, Sr, Mo, Cd, Sn, Sb, Cs, Ba, Re, Tl, Pb and 0–10 μg L^{-1} for La, Ce, U was prepared. A five-point calibration line in the range of 0–10 mg L^{-1} for matrix elements Na, Mg, P, K and Ca was prepared from 1 ± 0.002 g L^{-1} single-element stock solutions (SCP Science). Rhodium internal standard solution of the concentration of 200 μg L^{-1} was prepared from a stock solution 1 ± 0.002 g L^{-1} Rh obtained from SCP Science.

Samples

The certified reference materials of artificial urine Seronorm™ Trace Elements Urine Blank Lot OK4636 and Seronorm™ Trace Elements Urine L-1 Lot 1011644 (SERO AS, Billingstad, Norway) were used for validation of the method. These standards were purchased as a lyophilized powder in vials meant to be filled with 5 mL water to be ready for analysis. After this dilution, samples were thoroughly shaken and ten-times diluted with deionized water before analysis.

Results and discussion

Non-spectral and spectral interferences

High concentrations of major matrix elements in urine, such as, C, N, Na, P, S, Cl, K and Ca [7,18] impacts seriously the ICP-MS analyses of trace and ultra-trace elements due to the non-spectral and spectral interferences [2]. However, even ten-fold simple dilution of the urine samples with deionised water is sufficient to eliminate the matrix effects from the urine matrix, thus enabling the use of water calibration standards to calibrate the method. Nevertheless, the method requires the usage of an internal standard to correct different behaviour of the standard solution and sample during nebulisation and ionisation in the ICP. For this purpose, Rh was selected as a suitable internal standard as it has mid-range mass and ionization potential and is not found in urine samples [14].

The most significant interfering polyatomic ions encountered on Agilent 7900 that affect the analysis of majority of elements, are of the *m*/*z* below 100. Spectral interferences were treated using the octopole collision cell with He as a collision gas. For this purpose, two different helium modes were employed as can be seen from the data presented in Table 1, where detailed working parameters are specified. The “He”

mode was used to eliminate mild spectral interferences to analyse $^{51}V^{+}$ ($^{35}Cl^{16}O^{+}$, $^{37}C^{14}N^{+}$), $^{52}Cr^{+}$ ($^{35}Cl^{16}OH^{+}$, $^{35}Cl^{17}O^{+}$, $^{36}S^{16}O^{+}$, $^{40}Ar^{12}C^{+}$), $^{63}Cu^{+}$ ($^{31}P^{16}O^{16}OH^{+}$, $^{40}Ar^{23}Na^{+}$), $^{75}As^{+}$ ($^{40}Ar^{35}Cl^{+}$, $^{40}Ca^{35}Cl^{+}$, $^{43}C^{16}O^{16}O^{+}$), $^{85}Rb^{+}$ ($^{40}Ar^{45}Sc^{+}$, $^{69}Ga^{16}O^{+}$), and $^{88}Sr^{+}$ ($^{40}Ar^{48}Ti^{+}$, $^{72}Ge^{16}O^{+}$), while the high energy helium mode "HE He" had to be employed to mitigate spectral effects onto the analysis of $^{56}Fe^{+}$ ($^{40}Ca^{16}O^{+}$, $^{40}Ar^{16}O^{+}$), $^{60}Ni^{+}$ ($^{44}Ca^{16}O^{+}$, $^{43}Ca^{16}OH^{+}$, $^{12}C^{16}O^{16}O^{16}O^{+}$) and $^{77}Se^{+}$ ($^{40}Ar^{37}Cl^{+}$, $^{40}Ca^{37}Cl^{+}$) [11]. The elements that do not suffer from spectral interferences were acquired in "no-gas" mode. To decide, which cell mode (He or HE He) is required for the analysis of interfered elements, the comparison of isotopic ratios calculated for all the cell modes was performed by taking into account the presence of matrix-free standard solutions and Seronorm™ urine certified reference materials (see Table 2). The optimal cell mode for each isotope was chosen based on the best match of isotope ratios obtained for a standard solution and CRMs Seronorm™. A properly tuned collision cell allowed all the isotopes of interest to be measured accurately. However, the use of a milder cell mode was preferred, if possible, considering the negative impact of helium based cell modes on sensitivity.

Table 2 The comparison of results of different isotope ratios measured in multi-element standard solution and urine samples Seronorm™ Blank Lot OK4636 and L-1 Lot 1011644

Isotope ratio	Cell mode	SS [a] 10 µg L^{-1}	Seronorm™ Urine Blank Lot OK4636	Seronorm™ Urine L-1 Lot 1011644
$^{52}Cr/^{53}Cr$	No Gas	8.67 ± 0.26 [b]	14.8 ± 1.2	10.7 ± 0.9
	He	**8.15 ± 0.24**	**7.85 ± 0.98**	**8.01 ± 4.13**
	HE He	8.20 ± 0.17	8.12 ± 2.67	6.06 ± 1.16
$^{56}Fe/^{54}Fe$	He	10.2 ± 0.6	16.2 ± 2.0	18.0 ± 3.7
	HE He	**10.2 ± 0.2**	**6.48 ± 0.30**	**7.07 ± 0.33**
$^{58}Ni/^{60}Ni$	No Gas	2.50 ± 0.01	4.13 ± 0.23	5.01 ± 0.54
	He	2.30 ± 0.05	2.38 ± 0.05	2.45 ± 0.13
	HE He	**2.40 ± 0.01**	**2.40 ± 0.27**	**2.48 ± 0.21**
$^{63}Cu/^{65}Cu$	No Gas	2.09 ± 0.07	3.88 ± 0.08	3.50 ± 0.10
	He	**2.02 ± 0.01**	**2.04 ± 0.06**	**2.02 ± 0.01**
	HE He	2.12 ± 0.01	2.14 ± 0.04	2.14 ± 0.07
$^{78}Se/^{77}Se$	No Gas	7.84 ± 0.19	11.4 ± 0.6	12.7 ± 0.6
	He	3.46 ± 0.49	3.42 ± 1.03	4.07 ± 1.36
	HE He	**3.28 ± 0.14**	**3.15 ± 0.34**	**3.33 ± 0.46**
$^{85}Rb/^{87}Rb$	No Gas	2.00 ± 0.02	2.46 ± 0.09	2.43 ± 0.05
	He	**1.91 ± 0.07**	**2.53 ± 0.03**	**2.24 ± 0.01**
	HE He	1.72 ± 0.02	2.16 ± 0.01	2.33 ± 0.04
$^{88}Sr/^{86}Sr$	No Gas	8.83 ± 0.45	9.65 ± 0.30	9.71 ± 0.07
	He	**9.36 ± 0.01**	**9.37 ± 0.35**	**9.37 ± 0.37**
	HE He	9.49 ± 0.46	9.52 ± 0.10	9.50 ± 0.44

[a] SS - Standard solution; [b] Mean ± 2 S.D (n = 3); Selected cell modes are highlighted **bold**

Table 2 The comparison of results of different isotope ratios measured in multi-element standard solution and urine samples Seronorm™ Blank Lot OK4636 and L-1 Lot 1011644 (continued)

Isotope ratio	Cell mode	SS [a] 10 mg L^{-1}	Seronorm™ Urine Blank Lot OK4636	Seronorm™ Urine L-1 Lot 1011644
$^{44}Ca/^{43}Ca$	**No Gas**	**14.4 ± 0.1** [b]	**14.7 ± 0.4**	**14.8 ± 0.1**
	He	17.6 ± 0.2	17.7 ± 0.3	17.6 ± 0.2
	HE He	17.9 ± 0.5	15.7 ± 0.3	17.9 ± 0.4

[a] SS - Standard solution; [b] Mean ± 2 S.D (n = 3); Selected cell modes are highlighted **bold**

For mono-isotopic elements, such as Na, P, V, Co and As, the operating conditions were chosen based on the quality of results obtained for the analysis of Seronorm™ urine certified reference materials.

The influence of spectral interferences on the analysis of major matrix elements Na, Mg, P, and Ca was insignificant. The "He" mode was used to analyse Na and K because of attenuating a high signal intensity of the isotopes $^{23}Na^+$ and $^{39}K^+$ to fit it within the range of ICP-MS signal intensity. Utilising the "He" mode, the slopes of the calibration lines of $^{23}Na^+$ and $^{39}K^+$, had decreased in magnitude by one or two orders, respectively. This approach made the presented ICP-MS method capable of quantifying the concentrations of the elements analysed within the range of 11 orders of magnitude in the same run for ten-times diluted urine samples.

Analytical figures of merit and analytical applications

Evaluation of the method accuracy was accomplished by analysing Seronorm™ Trace Elements Urine Blank Lot OK4636 and Seronorm™ Trace Elements Urine L-1 Lot 1011644. The results for the Seronorm™ certified standards are shown in Table 3. The trueness of the method for analysis of 26 elements was considered if the certified value fell within the calculated confidence interval being evaluated for the method proposed. However, the mean estimate of the measured value was also compared with the confidence interval of the CRMs. The intra-day precision expressed as the RSD obtained from repetitive analysis (n = 3) of the same sample was mostly in the range of 1–15 %. The limits of detection (LOD, 3σ, n = 10; see Table 3) estimated were sufficiently low in order to provide reliable results for all the elements measured. The total time required for analysis of one sample, including the sample introduction and a stabilization delay, acquisition time, and time required for a transition between cell modes and for the sample exchange, was approximately 120 s. By considering the time needed for the instrument start-up sequence, for measurement of the calibration standards, and for checking the samples, 190 or even more samples can be analysed per one working day.

Table 3 Results [μg L^{-1}] of the analysis of the CRMs Seronorm™ including recoveries, intra-day precisions and limits of detection [μg L^{-1}]

Isotope	Cell mode	Seronorm™ Urine Blank Lot OK4636				Seronorm™ Urine L-1 Lot 1011644				
		Certified	Found [a]	*R* [%]	RSD [%]	Certified [b]	Found [a]	*R* [%]	RSD [%]	LOD_p [c]
^{7}Li	No gas	15.8 ± 1.2	14.5 ± 1.3	92	4.4	(7)	9.0 ± 0.7	129	3.7	0.051
^{11}B	No gas	1294 ± 121	1385 ± 205	107	7.4	(723)	867 ± 109	120	6.3	0.0012
^{23}Na	He	2487 ± 140 [d]	2755 ± 375 [d]	111	6.8	(2331) [d]	2373 ± 475 [d]	102	1.0	0.044 [d]
^{24}Mg	No gas	89 ± 4 [d]	93 ± 8 [d]	104	4.5	(64) [d]	83 ± 5.5 [d]	130	3.3	0.00024 [d]
^{31}P	No gas	872 ± 28 [d]	949 ± 63 [d]	109	3.3	(559) [d]	728 ± 74 [d]	130	5.1	0.0009 [d]
^{39}K	He	2349 ± 203 [d]	2454 ± 49 [d]	104	1.0	(1474) [d]	1567 ± 9 [d]	106	0.3	0.0076 [d]
^{43}Ca	No gas	116 ± 6 [d]	121 ± 7 [d]	104	2.7	(71) [d]	82 ± 7 [d]	115	4.4	0.037 [d]
^{51}V	He	0.53 ± 0.08	0.79 ± 0.20	149	13	0.66 ± 0.08	0.73 ± 0.07	111	4.8	0.0031
^{52}Cr	He	0.56 ± 0.15	0.68 ± 0.05	121	3.8	Not determined				0.032
^{56}Fe	HE He	8.3 ± 1.2	12.8 ± 3.8	154	14.8	(13.7)	13.7 ± 0.4	100	1.3	0.104
^{59}Co	He	0.28 ± 0.05	0.28 ± 0.02	100	3.8	0.72 ± 0.15	0.69 ± 0.07	96	4.9	0.0029
^{60}Ni	HE He	2.4 ± 0.6	2.4 ± 0.1	100	2.4	1.51 ± 0.6	1.93 ± 0.07	128	1.8	0.081
^{63}Cu	He	18.6 ± 2.1	23.5 ± 5.2	126	11	(31)	28.1 ± 0.5	91	0.9	0.013
^{75}As	He	Not determined				79 ± 16	82 ± 1	104	0.5	0.012
^{77}Se	HE He	21.7 ± 2.8	27.7 ± 4.2	128	7.5	13.9 ± 2.8	14.8 ± 2.0	106	6.7	0.104
^{85}Rb	He	1800 ± 90	1830 ± 40	102	1.1	(990)	989 ± 20	99	1.0	0.039
^{88}Sr	He	122 ± 6	131 ± 4	107	1.4	(98)	92 ± 2	94	1.3	0.057
^{95}Mo	No gas	61.4 ± 3.9	59.0 ± 5.8	96	4.9	(37)	38 ± 6	103	7.3	0.126
^{114}Cd	No gas	0.31 ± 0.5	0.30 ± 0.01	97	2.3	0.20 ± 0.04	0.20 ± 0.03	100	8.6	0.018
^{133}Cs	No gas	7.8 ± 0.4	7.8 ± 0.2	100	1.3	(5.8)	5.9 ± 0.5	102	4.6	0.0038
^{137}Ba	No gas	17.5 ± 6.9	16.2 ± 0.3	93	0.8	(28)	21 ± 2	75	4.6	0.050
^{139}La	No gas	14.5 ± 5.9	10.7 ± 2.5	74	12	(36)	24 ± 7	67	14	0.0021
^{140}Ce	No gas	28 ± 11	14 ± 3	50	11	(31)	20 ± 11	65	28	0.00093
^{187}Re	No gas	0.094 ± 0.004	0.092 ± 0.011	98	6.1	(0.020)	0.017 ± 0.010	85	29	0.0041
^{206}Pb	No gas	0.75 ± 0.05	0.63 ± 0.10	84	8.0	0.66 ± 0.13	0.33 ± 0.10 [e]	50	15	0.022
^{238}U	No gas	0.037 ± 0.006	0.056 ± 0.015	151	14	(0.051)	0.045 ± 0.005	88	6.0	0.00089

[a] Mean ± 2 S.D.; [b] Approximate values are given in brackets; [c] The procedural limits of detection were calculated considering the dilution factor (10×) associated with the sample preparation; [d] values are given in mg L^{-1}; [e] the acceptable range for Pb is 0.39–0.93 μg L^{-1}

Conclusions

A method for analysis of 26 elements in urine has been developed on an Agilent 7900 ICP-Q-MS. Polyatomic interferences were removed by running the octopole cell in two helium-based working modes "He" and "HE He". The resulting accuracy was in good agreement with Seronorm™ urine blank and Seronorm™ urine L-1 certified standards. The concentrations of the individual elements in a range from ng L^{-1} to hundreds of mg L^{-1} were determined in the same sample run in ten-times diluted urine samples. The limits of detection were more than sufficiently low for all the elements monitored in relation to their content in real samples. No systematic errors caused by the sample matrix were observed in the results obtained owing to the use of Rh as the internal standard. The quadrupole-based MS apparatus and the respective method provide an easy, fast, and robust platform for use in routine clinical practice in the assessment of both environmental pollution and occupational exposure by heavy metals.

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