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ORIGINAL PAPER

Microanalyzer for biomonitoring lead (Pb) in blood and urine

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Abstract Biomonitoring of lead (Pb) in blood and urine enables quantitative evaluation of human occupational and environmental exposures to Pb. State-of-the-art ICP–MS instruments can only analyze metals in laboratories, resulting in lengthy turnaround times, and they are expensive. In response to the growing need for a metal analyzer capable of on-site, real-time monitoring of trace toxic metals in individuals, we developed a portable microanalyzer based on flow-injection/stripping voltammetry (ASV), and validated the system using rat blood and urine spiked with known amounts of Pb. Fouling of electrodes by proteins often prevents the effective use of electrochemical sensors in biological matrices. Minimization of such fouling was accomplished with suitable sample pretreatment and by establishing turbulent flow of blood and urine containing Pb onto the electrode inside the microanalyzer, which resulted in no apparent electrode fouling even when the samples contained 50% urine or 10% blood by volume. No matrix effect was observed for the voltammetric Pb signals, even when the samples contained 10% blood or 10% urine. The microanalyzer offered linear concentration ranges relevant to Pb exposure levels in humans (0–20 ppb in 10% blood samples, 0–50 ppb in 50% urine samples). The device showed excellent sensitivity and reproducibility; Pb detection limits were 0.44 ppb and 0.46 ppb, and % R.S.D. was 4.9 and 2.4 in 50% urine and 10% blood samples, respectively. It gave similar Pb concentrations in blood and urine to those measured by ICP–MS. It offered high throughput (3 min per sample) and economical use of samples (60 μL per measurement) as well as low reagent consumption (1 μg of Hg per measurement), thus minimizing environmental concerns associated with mercury use. Since it is miniaturized, the microanalyzer is portable and field-deployable. Thus, it shows much promise as the next-generation analyzer for the biomonitoring of toxic metals.

Keywords Biomonitoring · Pb · Flow injection · Stripping voltammetry · Urine · Blood

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Introduction

The biomonitoring of lead (Pb) in blood and urine enables the quantitative evaluation of human exposure to both occupational and environmental Pb hazards [1, 2]. Despite the considerable efforts that have been made to identify and eliminate Pb sources, this metal still remains a significant health concern [3], particularly for young children [4]. Blood is the most common matrix used when biomonitoring for Pb, while urine is the matrix used to monitor for exposure to organic Pb compounds, mainly tetraethyl and tetramethyl Pb [5], and to assess body burden of inorganic Pb after the administration of chelating agents [6]. The state-of-the-art method for the analysis of Pb in urine and blood is inductively coupled plasma mass spectrometry (ICP–MS). ICP–MS analyses are performed in laboratories, resulting in lengthy turnaround times. Other methods that are used to determine Pb, according to the NIOSH Manual of Analytical Methods (NMAM), are "atomic spectrophotometric methods following hot plate acid digestion, including NIOSH methods 7082 (flame atomic absorption spectrophotometry), 7105 (graphite furnace atomic absorption spectrophotometry), and 7300 (inductively coupled plasma atomic emission spectrophotometry, ICP–AES)." All of these methods are laboratory-based. They are also

expensive and require significant labor and analytical resources [7]. Thus, there is a growing need to develop reliable, portable, and cost-effective analytical instruments for on-site, real-time monitoring of trace metals, like Pb, in individuals.

Established field-portable methods for Pb include NIOSH Methods 7702 (field-portable XRF for air samples on filters), 7701 (field-portable analytical method for lead air filter samples using ultrasound/ASV), and 7700 (field-portable screening method by spot test kit). According to NMAM, none of these are established field-portable methods for Pb detection in biological matrices. In addition, the accuracy of Pb was determined to be about ±17–19% in nitric acid for the ultrasound/ASV technique, and ±16% on air filters for portable XRF; the accuracy is likely to be worse in biological matrices due to the high complexity of the matrices, and so the accuracy must be improved for clinical use. Electrochemical sensing based on stripping voltammetry appears to be a promising technique for portable metal analyzers, since it is sensitive, compact, low-cost, easily integrated into field-deployable units, and can be automated [8–10].

The major obstacles that prevent the wide application of electrochemical sensors for analyzing metal ions in biological samples are (1) the binding of target metals to proteins [7], leading to low voltammetric response to known metal concentrations [11, 12], and (2) the electrode fouling caused by proteins in the biological samples, leading to significant reductions in signal and electrode lifetime. Adsorption of proteins at the solid–liquid interface is widely known to occur [13–18], even in samples containing extremely low protein contents (e.g., samples containing less than 1% saliva [15]). For voltammetric detection of Cu in blood, the Compton group [16] has used solvent extraction coupled with ultrasound to free Cu from blood glycoproteins, followed by sonicated squarewave stripping voltammetric measurements, termed "sonoelectroanalysis," of the Cu at a glassy electrode. They have used sonoelectroanalysis at a nafion-coated mercury thin-film glassy carbon for the detection of Pb in saliva [15]. The sonication and nafion coating significantly improved the detection of trace Cu and Pb in the two fluids; however, the detections required large dilution factors of blood (e.g., 2000-fold) and artificial saliva (e.g., 40-fold). Alternative approaches that other researchers have explored involve using an internal standard to compensate for any biological matrix effect during metal analysis at Hg-film sensors. Indium [19] and thallium(III) [20] have been used as the internal standards for blood Pb analysis, which relies on using the signal ratio of Pb to the internal standard as the quantitative tool. However, this technique increases measurement complexity, is difficult to perform when the signal ratio is not linear or when there is poor resolution of Pb and the internal standard peaks (e.g., at low Pb concentration [19]), and may have potential health concerns (e.g., from the highly toxic thallium).

In response to the need for on-site biomonitoring of Pb, a microanalyzer employing ASV has been developed in this work, since it is compact and portable, requires small sample volumes (microliters), and offers rapid analysis of metal ions. Since getting biological samples into a form that can take full advantage of the instrument's capability is the most challenging task of the analysis [12], this manuscript also focused on pretreatment methods for the biological samples prior to the voltammetic analysis. The electrochemical parameters were optimized and the figures of merit (detection limits, reproducibility, and linear calibration range) were determined. Validation of the microanalyzer was performed by comparing the results from the analysis obtained using Pb spiked samples with those from ICP–MS.

Experimental

Microanalytical system

A diagram of the microanalyzer is presented in Fig. 1a. It consisted of a computer-controlled micropump (MilliGAT pump, Global FIA, Fox Island, WA, USA), an injection valve with a 60 μL sample loop (13.2 cm in length and 0.076 cm inside diameter), interconnecting PTFE tubing, and a microelectrochemical cell. The cell was based on a wall-jet (flow-onto) design [13, 21]. The working electrode was embedded in PEEK block 1 (Fig. 1b), while the reference (Ag/AgCl wire) and auxiliary electrodes (Pt wire) were embedded in either the same block or PEEK block 2 (Fig. 1b); all three electrodes were in contact with fluid at all times during the measurement. A circular groove was made 0.324″ from the center in PEEK block 2; the groove was 0.035″ wide and 0.035″ deep. A laser-cut Teflon gasket was sandwiched between two PEEK blocks to form a radial flow cell. A solution was injected onto the working electrode through a 0.019″ i.d. inlet located in the center of block 2. The liquid then flowed in the radial direction to the circular groove and flowed out through the 0.031″ i.d. outlet. A computer-controlled micropump delivered samples and reagents to the cell through the cell inlet. The solution then flowed into the groove and onto the glassy carbon working electrode and exited the cell through the outlet positioned directly across the Pt auxiliary electrode. The three electrodes were connected to a potentionstat (model μAutolab III, Eco Chemie, Utrecht, Netherlands), which can be replaced with a hand-held bipotentiostat (model 1232, CH Instruments Inc., Austin, TX, USA) for portability. The potentiostat was connected to the same computer for instrumental control and data recording.

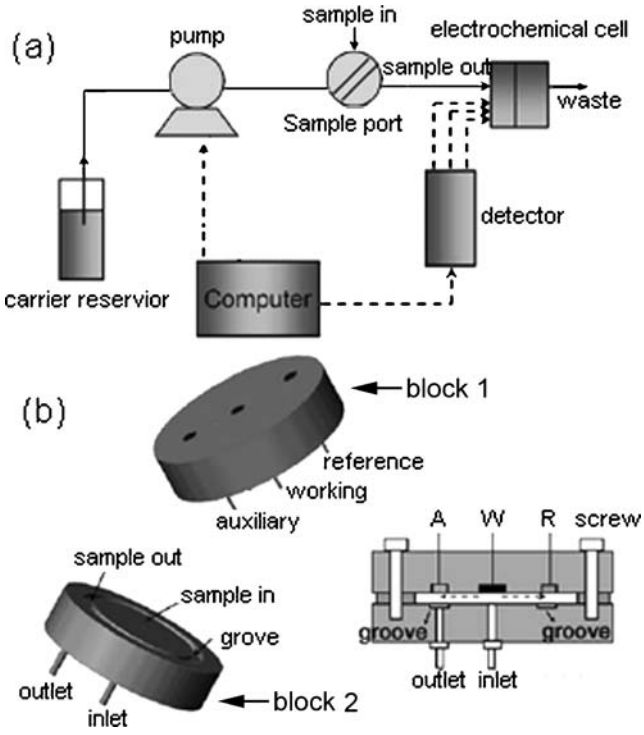

Fig. 1a, b Schematics of the metal analyzer (**a**) and the electrochemical cell (1.8 cm×2.4 cm in size ; **b**); *solid lines* represent liquid lines and *dashed lines* represent electronic cable lines

Collection of rat blood and urine

Blood and urine specimens were collected from naïve male Sprague Dawley rats, 0.33–0.37 kg in weight, as follows. Urine was collected from four rats that were placed in glass metabolism cages designed for the separation of excreta. Urine was collected at 24-hour intervals for a 72-hour collection period (three samples/animal) on dry ice. Once collected, the urine samples were aliquoted into smaller volumes (~1 mL) and stored frozen. For blood collection, each animal was anesthetized with isoflurane, the animal was exsanguinated by cardiac puncture, and 5–10 mL of blood was collected from each animal. Once the blood was collected, it was likewise aliquoted into smaller volumes (~1 mL), and the animals were euthanized by CO_2 inhalation. All specimens were stored frozen (−80 °C) until the Pb analysis was conducted.

Sample preparation for Pb voltammetric analysis

Table 1 summarizes the pretreatment approaches for urine and blood specimens prior to the voltammetric analysis of Pb. Unless specified otherwise, all percentages reported for liquid compositions throughout this paper are given in percent by volume (vol.%). The goal of **Pretreatment I** was to release Pb from proteins and then to remove the proteins from the samples by ultrafiltration. This was followed by **Pretreatment II**, which was intended to prepare the resulting ultrafiltrate for the electroanalysis of Pb.

Urine Two milliliters of rat urine were spiked with a given volume (0–250 μL) of 1000 ppb Pb(II) solution, which was prepared by diluting standard Pb solution from Aldrich Co. (comprising 1000 mg/L Pb in a 1–2 wt.% HNO_3 solution) with ultrapure Millipore water. The mixture was then incubated for 10 min, which was sufficient for Pb equilibration, as suggested by previous kinetic binding of Pb in saliva [22]. Next, the mixture was spiked with a given volume (~200 μL) of concentrated HCl (12.18 M) (trace element grade, Aldrich Co., St. Louis, MO, USA). At this point, the urine volume fraction was over 95% of the total solution, the concentration of Pb was between 0 and 50 ppb (μg/L), and the acid concentration was 1.0 M. The mixture was incubated for ten minutes, followed by protein removal via ultrafiltration using Amicon® Ultra-4 centrifugal filter units (Amicon Corp., Denver, MA, USA) that had cellulose membranes that allowed 5000 kDa NMWL cut-offs. The centrifugation was performed at a relative centrifugal force (RCF) of 8520*g* for 5–10 min per mL of filtrate. The filtrate was removed and stored at 4 °C awaiting the Pb voltammetric analysis. If desired, blood and urine samples can be pretreated in a reduced volume by employing a smaller ultrafiltration device (e.g., the 500-μL Microcon from Millipore).

Blood Blood samples for voltammetric Pb analysis were prepared in the same fashion as the urine samples, except that 20% of each sample was blood. The rest (80 vol.%) was a Pb stock solution, HCl (1.0 M), and deionized water , which yielded samples containing between 0 and 200 ppb Pb. To assess the effects of the proteins and the acid treatment efficiency on the voltammetric Pb signal, the blood sample was also subjected to protein removal by ultrafiltration prior to spiking the ultrafiltrate with a known concentration of Pb.

Prior to the analysis, both of the blood and urine samples prepared as mentioned above were diluted with ultrapure water, and spiked with Hg stock solution (containing 1015 ppm in 1−2 wt.% HNO_3, Sigma-Aldrich, St. Louis, MO, USA), and concentrated 12.2 M HCl (if necessary). This was done to obtain feed samples containing 10% and 50% of urine (U1 and U2, Table 1) or 10% of blood (B1 and B2, Table 1), all containing 5 ppm Hg and 0.5 M HCl. The chloride ions from HCl enabled the proper functioning of the electrochemical cell.

Sample preparation for ICP–MS

The Pb samples for the ICP–MS analysis were prepared in a similar fashion to those for the voltammetric analysis: Pb

Table 1 Pretreatment of blood and urine samples for voltammetric Pb analysis

Sample	Pretreatment I	Pretreatment II
B1	20% blood in DI+1.0 M acid − proteins + Pb	2× dilution to Pb in 10% blood/5 ppm Hg/0.5 M HCI
B2	20% blood in DI + Pb+1.0 M acid − proteins	2× dilution to Pb in 10% blood/5 ppm Hg/0.5 M HCI
U1	100% urine + Pb+1.0 M acid − proteins	10× dilution to Pb in 10% urine/5 ppm Hg/0.5 M HCI
U2	100% urine + Pb+1.0 M acid − proteins	2× dilution to Pb in 50% urine/5 ppm Hg/0.5 M HCI

was spiked into urine or blood samples, and then the samples were acidified and ultrafiltrated. The filtrates from of the ultrafiltration unit were diluted 20- to 100-fold with 2% of HNO_3 prior to the ICP–MS analysis.

Voltammetric Pb analysis

Squarewave stripping voltammetry (SWV) was used for the voltammetric measurement of Pb. Typical operating parameters used for SWV and flow injection are summarized in Table 2. The working electrode was pretreated with 50% of HNO_3, followed by DI water, acetone, and DI water, respectively, prior to its use. Before each measurement, the electrode was preconditioned (cleaned) by applying 0.6 V for 90 s while the carrier (5 ppm Hg in 0.5 M HCl solution) was flowing at 1 μL/s. Next, blood or urine spiked with Pb and with the same Hg and HCl concentrations as in the carrier was let in through the injection valve and delivered along with the carrier at 1 μL/s over the electrode surface, while −1.0 V was applied to the working electrode for 110 s to simultaneously deposit Pb and Hg onto the electrode surface. After the deposition period, the flow was stopped, and the potential at −0.75 V was applied for a 10 s quiet period, before the potential of the working electrode was scanned from −0.75 V to −0.45 V also under no-flow conditions. On each new day of analysis, the two PEEK blocks were taken apart, and the working electrode was regenerated as previously described. All water was ultrapure (18.2 MΩ-cm resistivity). All reagents were of the highest purity possible, and all glassware was cleaned in 0.5 M HNO_3 and then ultrapure water prior to use.

Table 2 Typical operating conditions for voltammetric Pb analysis

SWV parameters	
Initial potential	−0.75 V
Final potential	−0.45 V
Amplitude	50 mV
Frequency	50 Hz
Step potential	2.5 mV
Quiet time	10 s
Flow injection sensor parameters	
Flow rate	1 μL/s
Carrier	5 ppm Hg/0.5 M HCI
Precondition	0.6 V, 90 s in carrier
Deposition	−1.0 V, 110 s

Pb analysis by ICP–MS

A model PQ2 VG Plasma Quad ICP–MS (VG Instruments Inc., Cherry Hill Drive, MA, USA) was used for Pb analysis with scanning mode acquisition: the parameters were set at 10.24 ms dwelltime, 19 channels/amu, PC detector mode, 0.5 s/sweep, and a selected mass range of 99.6–210.4. Mass 208 was selected for Pb analysis. To minimize any matrix effect, the samples were diluted up to 100-fold with 2% HNO_3, which was also used as the rinse and background solution. All sample and standard solutions contained 2.5 ppb of gallium (Ga-71) and thallium (Tl-205) as internal standards. Five Pb standard solutions, 0, 0.1, 0.5, 1, and 5 ppb in 2% HNO_3, were analyzed along with the samples to establish a calibration curve (R^2=1.00) that covered the concentration range of Pb(II) used in the samples. The analysis time per mass was 3 s, and a total of three replicates were run per sample.

Results and discussion

Sample pretreatment

Figure 2 shows similar Pb signals obtained from the samples B1 (which was spiked with Pb after the sample had been acidified and the proteins had been removed from the sample) and B2 (which was spiked with Pb before the sample was acidified and the proteins were removed from the sample). While the proteins (of NMWL >5000 kDa) were removed from the samples by ultrafiltration, the free Pb remained in the ultrafiltrate, which was analyzed by the microanalyzer. The fact that the same signals were obtained from both B1 and B2 suggests that pretreatment of the samples with 1.0 M acid completely released the Pb from the blood proteins.

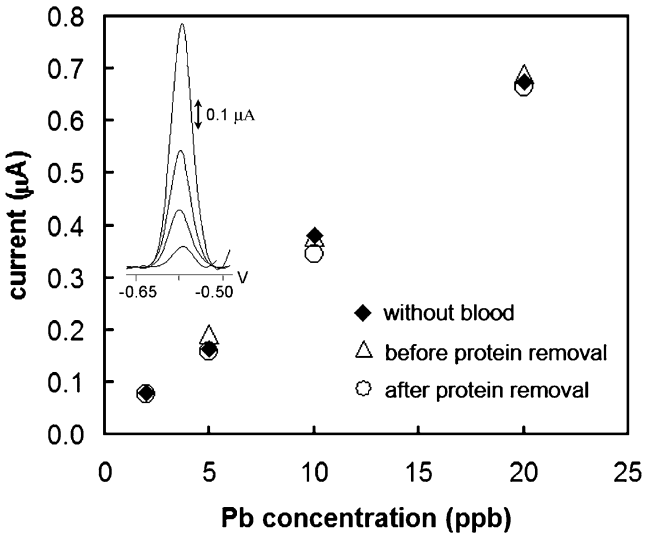

Fig. 2 Pb signals as a function of Pb concentrations in (*diamonds*) solution without blood; (*circles*) B1 blood sample (see Table 1), which was spiked with Pb after the proteins had been removed, and (*triangles*) B2 blood sample (see Table 1), in which the sample was spiked with Pb before the proteins were removed; the *inset* shows the corresponding voltammograms of Pb in B2 solution

Matrix effect

Figure 2 also shows that no matrix effect was observed from the blood in Pb signals measured for samples containing 10% blood or no blood. Likewise, a matrix effect was not apparent in the Pb signals measured for samples containing 10% urine, as shown in Fig. 3. Thus, for samples containing 10% blood or urine, the calibration curve can be established in pure medium (i.e., that containing no blood or urine). However, there was an apparent matrix effect when the samples contained 50% urine, so further dilution is recommended in this case; otherwise the calibration curve must be established from Pb standard solutions that have the same or a similar matrix to the samples.

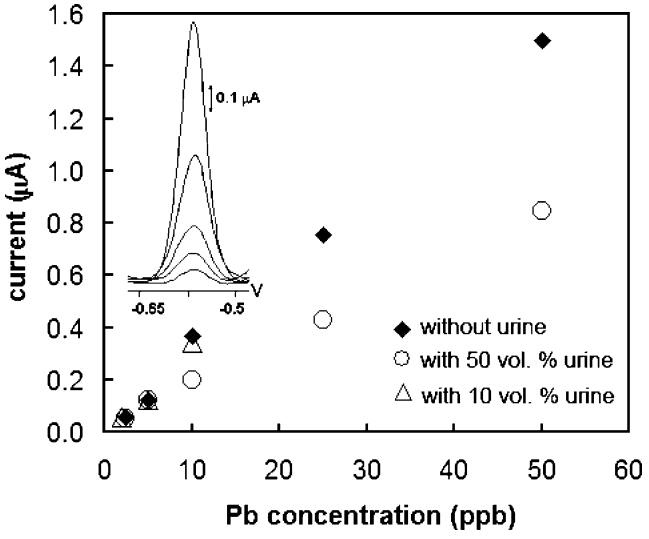

Fig. 3 Pb signals as a function of Pb concentration in solutions with 0, 10%, and 50% by volume of urine; *inset* shows the corresponding voltammograms of Pb in solutions with 50% urine

Calibration curve

Table 3 summarizes the linear parameters for all of the Pb calibration curves. In blood samples, the linear calibration curves were obtained from 0–20 ppb Pb in 10% blood samples (equivalent to 0–200 ppb Pb in whole blood). This range is highly relevant for assessments of environmental and occupational Pb exposures. For example, CDC's normal blood Pb concentration is less than 10 μg/dL (or 100 ppb) for adults [23], while Pb poisoning levels are equal to or above 10 μg/dL for children under six years old [24]. For higher Pb exposures, such as 60 μg/dL (or 600 ppb) of blood, the OSHA standard, at which workers must be removed from high-exposure jobs, the sample can be diluted to higher dilution factors (e.g., >10-fold), which will entirely eliminate any matrix effect.

In urine samples, linear calibration curves were obtained from 0 to 10 ppb Pb in samples containing 10% urine and 0 to 50 ppb Pb in samples containing 50% urine; both are equivalent to 0–100 ppb Pb in whole urine. This range is also relevant when biomonitoring Pb in urine; for example, after EDTA infusion, a Pb excretion rate of over 50 μg/24-hour urine suggests an increased body burden as a result of past exposure to Pb [25].

Reproducibility and reliability

Electrode fouling by proteins is a major obstacle to electroanalysis of metal ions in biological samples. Compton's group has suggested that "sonoelectroanalysis," where ultrasound is applied during the analyte deposition period, could minimize electrode fouling in biological samples [15, 16, 18, 26]. The momentum from the applied sound wave promotes highly turbulent flow and causes cavitation activity (e.g., collapse of cavities) at the solid–liquid interface. This cavitation at the surface and the shear forces obtained when the electrode is flushed are believed to remove organic species from the electrode surface, allowing the deposition of the target analyte to proceed.

Under the right conditions, and with appropriate sample pretreatment (e.g., removing most of the proteins and acidifying the samples), constant and turbulent flow-through of the samples inside the microanalytical cell during the deposition period can also remove the organic species, thereby minimizing electrode fouling. In addition, after stripping (measurement) and electrode cleaning at a positive potential (0.6 V for 90 s) in the carrier solution, the Hg film was removed along with Pb and proteins, which

Table 3 Linear parameters for voltammetric Pb analysis

Conditions	Linear slope (μA/ppb Pb)	R^2	Data range
Without urine	0.030	0.996	0–50 ppb Pb
With 10 vol.% urine	0.032	0.953	0–10 ppb Pb
With 50 vol.% urine	0.017	0995	0–50 ppb Pb
%R.S.D.=4.9, (N=7, 10 ppb Pb in 50 vol.% urine sample)			
Without blood	0.035	0.993	0–20 ppb Pb
With 10 vol.% blood,			
Pb spiked before protein removal	0.033	0.999	0–20 ppb Pb
Pb spiked after protein removal	0.035	0.991	0–20 ppb Pb
%R.S.D.=2.4, (N=10, 10 Pb in 10 vol.% blood sample)			

further minimizing the fouling effects of proteins. As a result, the microanalyzer yielded excellent reproducibility for Pb measurements in both blood and urine samples. In samples containing 10% of blood, the percent relative standard deviation (%R.S.D.) for ten consecutive measurements of 10 ppb Pb was 2.4. Although a matrix effect was apparent in samples containing 50% urine, the %R.S.D. for seven consecutive measurements of 10 ppb Pb was 4.9, suggesting that there was no electrode fouling at this high urine content. The %R.S.D. was similar to the value of 5% reported when ICP–MS was used for blood Pb analysis [27].

The analyzer was normally reliable for a whole day of analysis (over 50 runs). At the start of each new day of analysis, the sensor was easily cleaned by rubbing the working electrode with acid and acetone as previously mentioned. When used to measure 10 ppb Pb on three separate days (after being regenerated), the analyzer yielded Pb peak areas that were 1, 1.03, and 1.10 times the peak areas obtained on day 1, suggesting that the analyzer shows good interelectrode reproducibility. Since all of the calibration curves passed the zero point, these factors were used to scale all peak signals obtained on a given day to those obtained on the day that the calibration curve was measured.

Detection limits

The detection limit was determined as the concentration of Pb that would give a signal three times of the background noise (3×S/N). The detection limits for Pb were 0.29 ppb in samples that contained no urine or blood, 0.44 ppb in samples containing 50% urine, and 0.46 ppb in samples containing 10% blood. These values compared well with those reported for ICP–MS, which gave Pb detection limits (3S/N) of 0.06 ppb in samples prepared by diluting blood 10-fold with Triton X-100 and nitric acid [28], and were much better than those obtained using graphite furnace atomic absorption spectrophotometry, which gave reported detection limits for Pb in blood of between 3–10 ppb [24].

Validation by ICP–MS

ICP–MS was used to validate the analytical values for the Pb concentrations obtained by the Pb microanalyzer. Table 4 summarizes the Pb concentrations measured by ICP–MS and the microanalyzer in blood and urine specimens spiked with Pb at levels relevant for Pb biomonitoring. Prior to Pb detection with the microanalyzer, the Pb-spiked urine and blood samples were diluted to 50% and 10%, respectively, but the Pb contents reported in Table 4 were those for whole blood and urine specimens (after adjusting for dilution factors). The average values and errors were highly comparable between both methods, suggesting that the microanalyzer can be applied to the on-site biomonitoring of Pb in lieu of lab-based ICP–MS.

Conclusions

In this work, a microanalyzer was developed that is capable of measuring Pb in blood and urine at concentration levels relevant to environmental and occupational exposures. The microanalyzer was based upon the flow-injection/voltammetric analysis of Pb after it had been preconcentrated an Hg film electrode deposited in situ and embedded in a miniaturized microanalytical cell. A new and simple method for sample pretreatment was also utilized in order

Table 4 Pb levels in urine and blood measured by ICP–MS and the microanalyzer

Biological samples	Pb concentration (ppb)	
	By ICP–MS	By microanalyzer
Urine	13.45±0.13 (n=2)	14.14±2.01 (n=2)
	25.91±NA (n=1)	23.41±1.17 (n=2)
Blood	64.54±7.98 (n=2)	58.03±1.07 (n=2)
	110.86±2.33 (n=2)	114.55±0.43 (n=2)

to completely release the protein-bound Pb as well as to minimize electrode fouling without the need for tricky acid digestions. Like acoustic streaming, the flow-through of the samples increases the mass transport, thereby reducing the deposition time (to only 110 s at −1.0 V) and increasing the sensitivity [29, 30]. The microanalyzer has excellent sensitivity and reproducibility: they are of the same order of magnitude as the state-of-the-art method, ICP–MS. It also offered a very high throughput (e.g., less than three minutes per sample). Being a microanalyzer, it uses samples economically (e.g., ~60 μL per measurement), making the collection of blood less invasive (i.e., only a finger prick instead of a blood draw), which is particularly important when sampling children. It also reduces the amount of reagent required (e.g., ~200 μL of 5 ppm Hg, or ~1 μg of Hg per measurement), thus minimizing the health concerns associated with mercury. The microanalyzer allowed solution streams to be easily interchanged without operational interruption. Liquid deliveries and voltammetric measurements can be easily automated using the technique. Unlike the ICP–MS, the microanalyzer is highly portable and field-deployable since it has been miniaturized. Overall, the microanalyzer developed in this work represents the next generation of metal ion analyzer for the biomonitoring of toxic metals.

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