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Determination of lead in blood by laser ablation ICP-TOF-MS analysis of blood spotted and dried on filter paper: a feasibility study

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Abstract Screening programs for pediatric lead (Pb) poisoning routinely collect blood by finger stick onto specially designed filter paper (FP) for subsequent laboratory testing. Here, laser ablation inductively coupled plasma time-of-flight mass spectrometry is evaluated as a novel method for the determination of Pb in blood spotted onto FP cards. The method requires no sample pretreatment and may be particularly suitable for rapidly screening a large number of samples. Signal intensity from the ICP-MS strongly correlated ($r^2=0.996$) with Pb target values for five blood cards from a laboratory proficiency testing program. Better precision was obtained by replicate ablation line scans (<15% rsd) compared to a grid of 25 individual ablation spots (>30% rsd). Because <2% of the sample is consumed in the laser ablation analysis, selected samples can also be analyzed by traditional techniques or archived. Lead isotope ratios determined during the same total-Pb analysis appear to be effective for discerning contamination extraneous to the blood sample. Determining that an elevated result was due to contamination may negate the need for retesting with invasive pediatric venipuncture. Some elements monitored along with Pb exhibited signal profiles conducive to potential quantitation (Ca, V, Fe, Cu Zn), whereas others did not (Cr, Mn, Co, Ni, Cd, Hg, Tl, U). Copper, Ca, and V were inversely correlated with Pb ($r=-0.89$, -0.90, and -0.92, respectively). Scanning electron microscope images revealed surface modality differences between FP spotted with fresh whole blood and reconstituted freeze-dried blood reference material.

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Introduction

Lead (Pb) is a toxic metal that has been widely distributed in the environment as a result of natural processes, including soil erosion, forest fires, and decay of radon gas, and from human activities, such as combustion of leaded gasoline, the manufacture, use, and degradation of Pb-based paints, batteries, pipes, and ammunition, and waste from ore mining [1]. It is well known that exposure to Pb can adversely affect the nervous system and children are particularly susceptible to Pb poisoning [2]. Children with blood lead levels (BLLs) >10 µg dL^{-1} (1 µg dL^{-1}= 0.0483 µmol L^{-1}) are at an increased risk for learning and behavioral problems [1]. With the use of leaded gasoline phased out beginning in the early 1970s and the sale of paint with Pb pigments banned in 1978, BLLs for children in the USA have decreased dramatically, by approximately 80% (to <3 µg dL^{-1}) since the late 1970s [3, 4]. Nevertheless, BLLs above the current acceptable threshold of 10 µg dL^{-1} remain prevalent in one particular subset of the population: low-income, urban children living in older housing [5].

State blood Pb surveillance programs, designed to target prevention efforts and monitor progress toward reducing BLLs, continue to provide the US Center for Disease Control and Prevention (CDC) with BLL data [3]. These biomonitoring programs typically collect large numbers of blood samples by venipuncture or by finger or heel stick. Although collecting blood from a vein minimizes the potential for contamination, the stick methods are generally

considered easier and less traumatic to the child. Different approaches to sampling and analysis have been investigated to speed analysis and reduce costs. One successful approach uses blood spots on filter paper (FP) as an alternative to liquid blood for Pb measurements. Blood obtained by finger or heel stick is spotted onto a labeled FP card and allowed to air dry. This collection methodology, which is easy to administer and stabilizes the sample for long periods, was evaluated through a proficiency testing program and found to provide accurate BLL concentrations when properly utilized FP testing methods were used [6]. In a separate study, FP papers from one manufacturer were evaluated for background contamination and variability and determined suitable for whole blood Pb screening in large pediatric populations [7].

Analysis of dried FP blood spots for Pb typically involves some type of sample pretreatment, such as extraction or ashing of blood spot punches (cut outs), followed by analysis using atomic absorption spectrometry (either flame or electrothermal) or inductively coupled plasma mass spectrometry (ICP-MS) [8–10]. In this study, laser ablation ICP-time-of-flight (TOF)-MS was evaluated as a novel method for elemental and isotopic analysis of dried blood spots on FP. In this paper, the methodology is described, figures of merit are presented, and advantages and limitations of the method are discussed.

Experimental

Instrumentation

An LSX-213 laser ablation system (Cetac Technologies, Inc., Omaha, NE, USA) was coupled to an Optimass 8000 ICP-TOF-MS (GBC Scientific Equipment Ltd, Australia). As the laser sweeps across the FP surface, the sample and filter matrix are rapidly heated and resultant vapors and ejected particles are swept into the ICP-MS with argon carrier gas. Ablation products are converted into ions in the plasma which are subsequently orthogonally accelerated (oa) into the TOF-MS for multi-element mass spectral analysis. Performance characteristics for the ICP-oa-TOF-MS have been reported elsewhere [11]. Typical instrumental conditions for the current study are provided in Table 1. Signal was collected using a discrete dynode electron multiplier in analog data processing mode. Others have shown that analog detection with the Optimass instrument obeys Poisson statistics and permits isotope ratio measurements to be achieved on higher analyte concentrations using shorter integrations times [12], which was applicable in this study. Signal from the detector was compiled in Microsoft Access and reduced in Microsoft Excel.

Table 1 Typical laser and ICP-MS conditions

Parameter	Value
Laser ablation	
Wavelength	213 nm
Pulse rate	20 Hz
Spot size	200 μm
Scan rate	100 μm s^{-1}
Energy setting	100%
Defocus setting	2,500
Plasma	
RF power	1.2 kW
Plasma gas flow	12 L min^{-1}
Auxiliary gas flow	1.2 L min^{-1}
Nebulizer gas flow	1.2 L min^{-1}
Data acquisition	
Acquisition time	350 s
# of spectra (data points)	350
Measurement mode	Analog
Multiplier gain	2,200
Mass spectrometer settings (V)	
Skimmer	−1,500
Extraction	−1,500
Z1	−900
Y mean	−250
Z lens mean	−1,250
Reflector	660
Pushout plate	420
Lens body	−190

The laser was operated using the largest spot size (200 μm) and a defocused beam to maximize the width of the laser beam and produce a relatively large stable signal. Helium is often added to the argon sweep gas to improve sample transport characteristics. In this study initial tests found it did not significantly improve signal response or stability. Because ablation of the sample without helium was yielding sufficient signal, additional tuning for the mixed gas stream was not carried out. Cutouts of blood-spotted cards (see samples and standards below) were analyzed in a standard ablation cell. However, an ablation cell specifically designed for samples that feature large flat surfaces is commercially available and would allow the blood card to be analyzed intact. Additional aspects of the analytical methodology are described along with the results (below).

Samples and standards

Blank FP sheets and five spotted blood Pb specimen cards were provided by the Wisconsin State Laboratory of Hygiene (WSLH). The materials were part of a prior FP proficiency testing program (year 2004). The Pb target values for these samples were established by the mean result of 11 referee laboratories testing liquid blood aliquots

of the samples. The values encompassed the range commonly found in childhood screening programs, with three exceeding the 10 μg dL^{-1} standard threshold for increased health concern. Specifically, samples 04FP18, 04FP24, 04FP42, 04FP03, and 04FP17 were determined to correspond to BLL values (μg dL^{-1}±1σ) of 1±0.79, 7± 0.53, 15±1.26, 20±1.43, and 30±1.94, respectively. The specimens were spotted in a trace metals clean room at WSLH.

Seronorm whole blood reference material (Sero AS, Billingstad, Norway) was prepared and spotted on a blank FP (same FP lot #) at UNLV. It should be noted that both Seronorm and NIST blood reference materials (SRM 955 and 966) may not be suitable as valid standards for human blood-Pb analyses using spotted FP blood cards. This is because Seronorm blood is reconstituted from freeze-dried blood and NIST reference materials are frozen (hemolyzed) and stem from animal (cow) blood, all of which results in differing spreading characteristics compared with fresh human blood. Moreover, results of a test event that examined FP spotted with animal blood instead of human blood found a bias among a group of proficiency testing program participants (N. Stanton, personal communication). Micron-scale images of FP spotted with Seronorm and fresh whole blood were taken with a scanning electron microscope (SEM) (JEOL, model JSM-5610; Peabody, MA, USA) at the Electron Microscopy and Imaging Laboratory at UNLV after coating the samples with gold by vapor deposition.

Results and discussion

Ablation mode and sample representativeness

A blood specimen card spotted multiple times from the same blood source was used to evaluate reproducibility. Two of the blood spots were analyzed by ablating a grid of 25 focused 200-μm laser spots (using a burst of 100 laser firings), spread uniformly across the blood spots. This resulted in relative standard deviations (rsd) of 32% and 48% based on peak areas. In contrast, three separate line scans for three of the blood spots ($n=9$) produced an overall precision of 13% rsd, a within (intra) spot precision of 12–16% rsd, and a between (inter) spot precision of 7% rsd. Moreover, the quasi-steady-state signal generated from the line scans is generally thought to be advantageous from an isotope ratio determination perspective compared with the transient signal from spot to spot analyses; although ICP-TOF-MS has been shown be effective at isotope ratio determinations on transient signals with precision as good as 0.04% rsd [12]. There are also practical advantages, including more straightforward data handling, when col-

lecting signal of longer duration. For these reasons, laser spots were abandoned as a mode of analysis in favor of line scans early in the investigation. Additional information on reproducibility is discussed below (see Figures of merit).

Laser ablation of dried FP blood spots is essentially non-destructive because so little of the sample is used in the analysis. Figure 1 shows three ablation line scans running across the FP into the blood spot region from left to right. Less than approximately 2% of the sample is consumed in this ablation scheme. Data is collected for the blank FP so that it can be appropriately subtracted from the blood spot to yield the true signal for the blood sample. Replicate scans are conducted to provide a measure of precision. Total scanning time is less than 5 min per sample. Figure 2 shows typical features of the data plotted as a function of ablation scan time. The gas blanks represent the signal collected prior to the ablation events and after the three scans are completed. At about 30 s into the run, laser ablation is initiated on the blank FP and the laser begins scanning toward the blood spot for approximately 30 s (filter blank). The laser continues to scan into the dried blood spot for 30 s more until a shutter blocks the beam. As the signal decays the laser is quickly repositioned for the second scan as above. This process is repeated a third time so that three peaks are generated. Another occasional feature observed in the signal intensity scans is what appear to be anomalously high signal spikes (Fig. 2, first blood spot scan). These spikes likely reflect Pb contamination from the filter matrix or from particles extraneous to the sample and are discussed in more detail in Pb isotope ratios as a diagnostic tool.

Figures of merit

Data for three ablation scans were collected and plotted for each of the FP blood spot samples. Using the proficiency
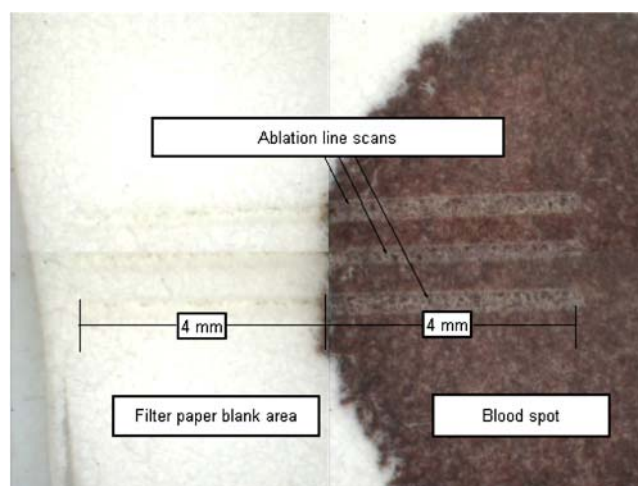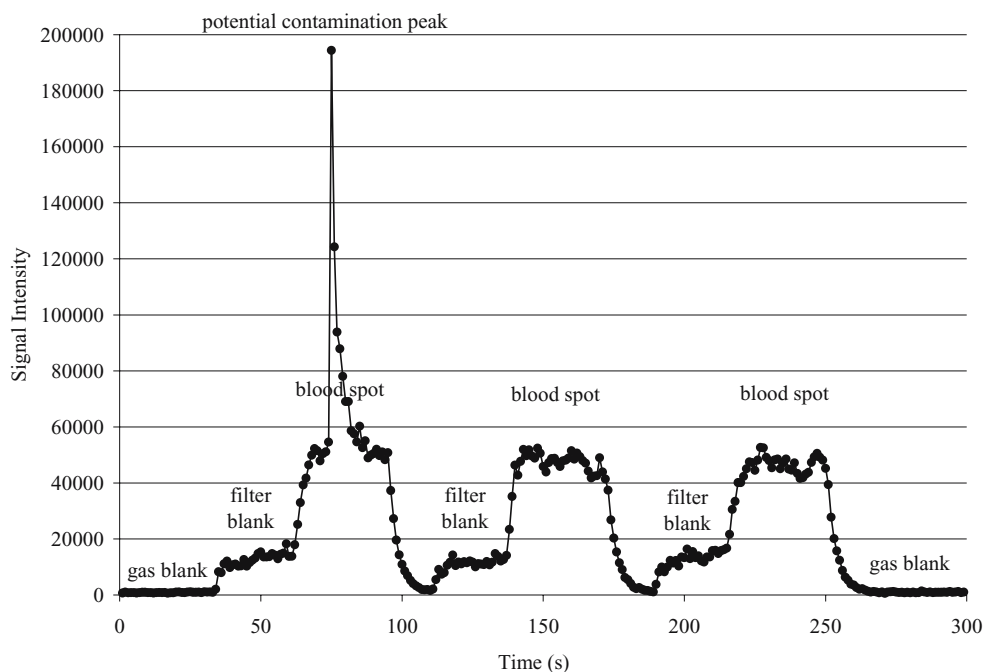

Fig. 1 Image of spotted filter paper blood specimen showing replicate ablation line scans

Fig. 2 ICP-MS Pb signal for three ablation scans of filter paper spotted with Seronorm whole blood reference material


sample target values and the average blank-subtracted Pb signal intensity for each blood spot scans, a plot was generated that could potentially be used as a calibration curve for quantitation of unknown samples (Fig. 3). Although these blood cards were spotted at least two years earlier, they still produced a calibration line with an R^2 value of 0.996. Given this high correlation value for these aged blood cards, there appears to be a potential application of the methodology to epidemiological studies and trend analysis using archived blood cards. However, because archival protocols and environmental conditions may differ

between institutions, fundamental studies are needed to validate use of the specimens because of potential sample degradation and contamination.

Seronorm whole blood reference material was prepared, spotted on a blank FP, and analyzed the same day as the other samples. Using the linear regression equation in Fig. 3, the reference material gave a value of 5.6± 0.3 µg dL^{-1} above the 3.3µg dL^{-1} reference value; no range was provided with the certificate. The freeze-dried nature of the Seronorm product results in spreading characteristics on the FP that differ from fresh whole blood

Fig. 3 Potential calibration curve generated by laser ablation ICP-MS analysis of spotted blood Pb specimens from a laboratory proficiency testing program
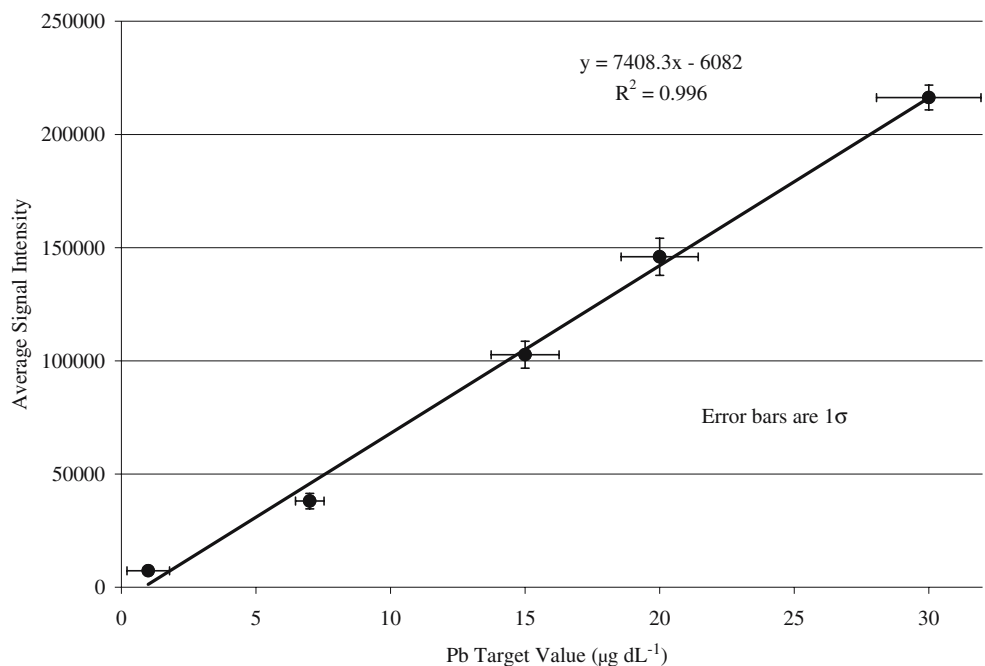
which has intact erythrocytes [13]. This was confirmed by SEM images which are discussed in a separate section below. Thus it is possible the Seronorm sample had different ablation properties making this reference material unsuitable for quality control purposes in this capacity.

Based on repeated measurements (n=18) of FP blank areas (adjacent to the blood spots), the detection limit (using the background equivalent concentration) was estimated at 0.9 µg dL^{-1}. The rsd for the blank readings was 12% overall, but typically less than 10% for individual filters (n=3). The filter background was equivalent to 2.7± 0.2 µg dL^{-1}, based on the slope of the calibration line. This appears to be relatively high compared with results for blanks using other methods [6]; however, laser ablation may liberate non-extractable Pb in the FP that other methods do not. In any case, as noted earlier the background for individual FP can be subtracted from the blood spot data. Reproducibility for individual blood spot scan data averaged 7% RSD and ranged from 3 to 13%. Differences between multiple blood spots on the same specimen card were in this same precision range (≈7% rsd).

Challenges to high-throughput quantitation

Quantitative measurements collected over several hours benefit from the use of an internal standard (IS) to compensate for instrumental drift. This is usually done by adding an element not normally found in the sample, but with a mass and ionization properties similar to the analyte. Whereas addition of an IS, such as indium or lutetium, to the sample upon collection or to the FP prior to analysis is possible, this adds the potential for contamination and generally complicates the analytical scheme. Two possible alternatives exist but need to be further investigated in the context of blood spot analysis. One would be to use an isotope of an element found in the filter matrix but not in the blood sample. The other, perhaps more plausible and intriguing method, would be to introduce a constant flow of dry aerosol containing the IS into the carrier gas stream either before or after the ablation cell. Others have successfully combined the effluent of a desolvating nebulizer to introduce standards for calibration purposes in laser ablation studies where solid standards are unavailable [11].

Another challenge to quantitation is data reduction. In the current study, data was plotted on Excel spreadsheets using macros provided by the ICP-MS manufacturer. This data reduction process can be time-consuming and in its current form would slow output. (It should be noted, however, that if contamination (e.g., signal spikes) are not present or determined to be a sufficiently minor contribution, then the existing instrument software can be used in a routine fashion (as in solution mode) for high-throughput quantitative measurements.) Given the above challenges to BLL quantitation by

laser ablation ICP-MS, the technique may, at present, be more suitable as a means for semi-quantitative analysis and/or rapidly assessing a large number of samples for signal intensities above a threshold standard.

Laser ablation ICP-MS as a rapid BLL screening tool

Due to the constraints discussed above, determining BLL by laser ablation ICP-MS of dried FP blood spots, although certainly possible, may not be amenable for laboratories analyzing large number of samples. On the other hand, the technique may be useful as a screening tool, designed to quickly identify samples yielding Pb signals above a set threshold. For example, a FP blood spot "standard" with a known BLL below the 10 µg dL^{-1} criteria (e.g., 7.5 µg dL^{-1}) could be used to determine the signal intensity above which samples can be flagged for further scrutiny and quantitation. Using the time scan feature on the ICP-TOF-MS to observe the Pb signal in real time, instead of collecting and storing mass scans requiring off-line data manipulation, would greatly speed the screening process. The standard could be analyzed at set intervals to monitor for instrumental drift. Another way to automate the analytical process is to use a commercially available spring-loaded ablation cell specifically designed for samples with large flat surfaces. The FP card would be positioned such that a blood spot is centered and the apparatus is lowered, pressing a rubber ring at its perimeter against the card and creating a seal for the cell. Using such an apparatus has the added advantage of keeping the blood spotted card intact for further study or archiving. Further investigation using a larger sample set is recommended to study the efficacy of this proposed screening method and to determine the incidences of false negative and false positive results.

Pb isotope ratios as a diagnostic tool

The TOF-MS used in this study is particularly well suited for elemental and isotope ratio measurements on fluctuating or transient signals, such as those that can be generated by laser ablation. The design of the mass spectrometer allows measurement of the complete mass spectrum from packets of ions pushed orthogonally from the ion beam, minimizing spectral skew and background noise [14]. In this study, data was collected simultaneously for ^{206}Pb, ^{207}Pb, and ^{208}Pb. Figure 4 shows the combined signal for the three isotopes and the associated ^{207}Pb/^{208}Pb ratio for specimen 04FP17. Despite fluctuations in the signal during the ablation scan of the blood spot, the ^{207}Pb/^{208}Pb ratio was remarkably stable within and between scans, averaging 0.41±0.02 (1σ). Table 2 presents data for the other five blood spotted samples. Whereas the precision degrades slightly with

Fig. 4 $^{206}Pb+^{207}Pb+^{208}Pb$ signal and $^{207}Pb/^{208}Pb$ isotope ratio for laser ablation scans of spotted blood Pb specimen 04FP17
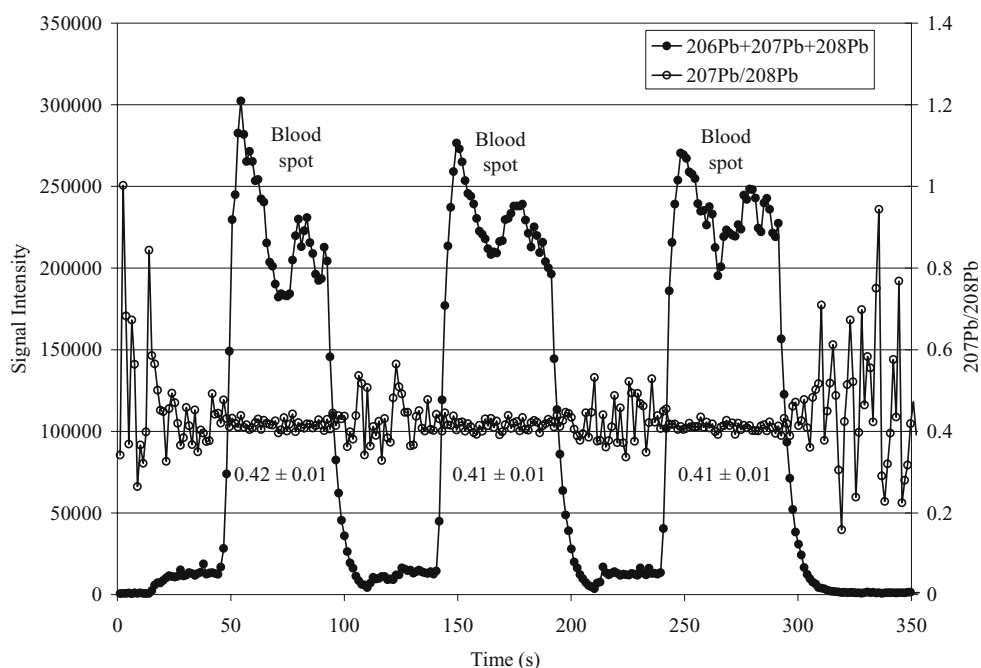
decreasing BLL, the overall ratio remains similar, averaging 0.42±0.02 and ranging from 0.40±0.01 to 0.44±0.03. Although the samples analyzed in this study are indistinguishable based on their $^{207}Pb/^{208}Pb$ ratio, other investigators have shown that it is possible to use Pb isotope ratios in pinpointing the source of Pb contamination in high blood-Pb case studies [15]. The isotope ratios reported here were not corrected for instrumental mass bias, which is typically <1% per amu at this mass range [14], well within one standard deviation of the measurement error.

Interestingly, the $^{207}Pb/^{208}Pb$ ratio may also be useful as a diagnostic tool to identify contamination extraneous to the blood sample. For example, several anomalously high signal spikes were observed during ablation scans of the FP blank area and blood spot regions, similar to that shown in Fig. 2 but of smaller magnitude and duration (typically <2 s corresponding to 1 or 2 data points). Examining the $^{207}Pb/^{208}Pb$ ratio of these sharp signal spikes for gross

deviations from the bulk sample revealed that the ratio is routinely different (usually higher) than the normal blood ratio (Table 2). In nearly all cases (13 of 15), the ratio in the signal spike clearly exceeded that of the blood. These anomalous ratios averaged 44% (range 9 to 93%) above the mean ratio. The signal spike artifacts are presumably due to ablation of a particle or cluster of particles foreign to the blood. The contaminating particles may be imbedded in the filter matrix during manufacture or deposited subsequently from airborne particulate matter. In any case, 5% or less of the data points were affected by these artifacts.

Although the contamination peaks may be viewed as a factor complicating the analysis, identifying their presence offers an advantage of being able to remove the suspect data, whereas other methods would include this contamination in their result. However, the impact of this level of contamination on the results obtained from other methods appears to be diluted by the larger sample size used

Table 2 Pb isotope ratios in for individual ablation scans and anomalous spikes of blood spotted onto filter paper

Sample	Target value (µg dL^{-1}) ±SD	$^{207}Pb/^{208}Pb$±SD[a]			Signal spikes	
		Scan 1	Scan 2	Scan 3	Data points affected during ablation scans (%)	$^{207}Pb/^{208}Pb$ ratio of the anomalous spikes
FP18	1±0.79	0.41±0.05	0.40±0.04	0.40±0.05	5.0	0.53, 0.65, 0.55, 0.60, 0.39
Seronorm	3.3	0.44±0.03	0.43±0.03	0.42±0.03	2.9	0.44
FP24	7±0.53	0.43±0.02	0.43±0.02	0.42±0.02	4.7	0.47, 0.52, 0.62
FP42	15±1.26	0.42±0.01	0.42±0.02	0.41±0.02	3.5	0.81, 0.62, 0.63, 0.51
FP03	20±1.43	0.42±0.02	0.42±0.01	0.43±0.01	2.6	0.59, 0.74
FP17	30±1.94	0.42±0.01	0.41±0.02	0.41±0.01	0.0	

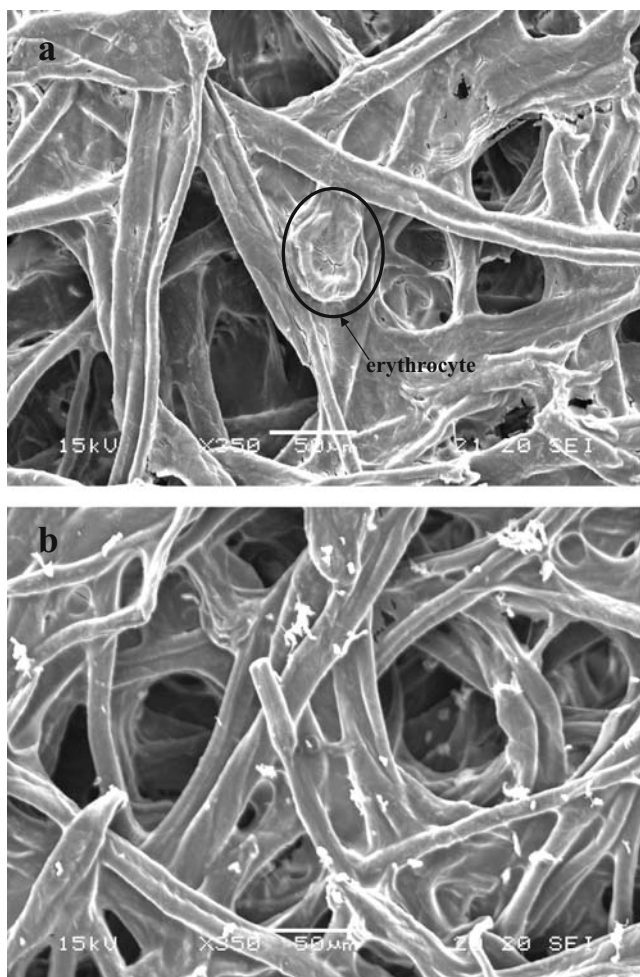[a] Not including data points affected by signal spikes

Fig. 5 Scanning electron microscope images of filter paper cards spotted with fresh human whole blood (**a**) and reconstituted freeze-dried Seronorm blood reference material (**b**)

(typically cutouts of the whole blood spot) because studies have shown that the methods are effective as a Pb biomonitoring and screening tool [6, 7]. Even the results from the current method (in quantitative mode) are not substantially influenced by the occasional signal spike. It is worth noting that the largest signal spike observed in this study was for the Seronorm reference sample (Fig. 2) and its $^{207}Pb/^{208}Pb$ ratio was near normal (0.44). One likely explanation for that specific anomalous signal spike is that the freeze-dried blood reference material was not fully dissolved in the reconstitution step and that the spike is associated with a crystal caught in the FP.

SEM images of blood spotted filter paper

Scanning electron microscope (SEM) images were taken of FP cards spotted with fresh human whole blood and with reconstituted Seronorm blood, a freeze-dried certified reference material (CRM) (Fig. 5). In the fresh whole blood spotted sample, red blood cells were observed on the filter paper's fibers (Fig. 5a). The erythrocytes appeared distorted from dehydration but were intact. In contrast, there were no cells visible in the reference material, not surprising because they are destroyed during preparation of the product. There was a film connecting much of the fibers for round-robin blood sample, no doubt related to the viscosity of the whole blood fluid. The FP for the reference sample did not contain these film sheets but rather the fibers themselves seemed to be thinly coated. Another difference between the two samples was that the CRM showed the presence of numerous fine particles or flakes (white spots in Fig. 5b). Energy dispersive X-ray spectroscopy scans of

Fig. 6 Plot showing the normalized signal for elements whose blood spot signal was enhanced relative to the blank filter paper
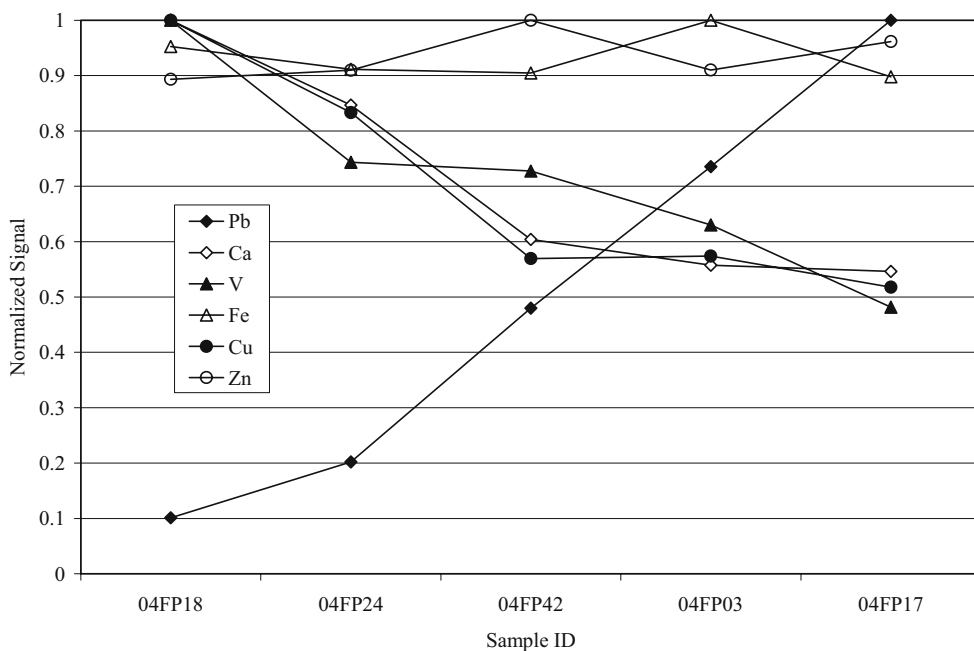
these particles did not produce sufficient signal above background to identify their composition. Based on these morphological differences, it is easy to see why the spreading characteristics differ between these materials. Although no obvious crystals were seen for the Seronorm FP, their presence could have been missed. In summary, the SEM images revealed gross surface modality differences between FPs spotted with a lypholized blood CRM and a round-robin blood sample, confirming that freeze-dried CRMs should not be used for validation purposes for testing blood-Pb when employing FP spotting.

Determination of other elements in FP blood spots

Multi-element capability is one of the primary advantages of ICP-MS and is often not fully utilized. Although specimen quality and possible contamination can be issues when collecting blood FP samples in the field, if adequately addressed other elements of environmental or nutritional importance may be screened on the same spotted sample during the same analytical run. In the current study, masses associated with other elements (^{48}Ca, ^{51}V, ^{57}Fe, ^{52}Cr, ^{55}Mn, ^{59}Co, ^{60}Ni, ^{65}Cu, ^{66}Zn, ^{114}Cd, ^{202}Hg, ^{205}Tl, and ^{238}U) were monitored along with Pb. Several elements (Ca, V, Fe, Cu, Zn) exhibited signal profiles similar to Pb in that their blood spot signals were enhanced relative to the FP background. The others (Cr, Mn, Co, Ni, Cd, Hg, Tl, and U) either had too little signal or showed no difference between the FP background and the blood spot, making them unsuitable for quantitation. No attempt was made to correct for possible isobaric interferences. Unfortunately, Hg is one of the elements that could not be distinguished from background. Mercury is a critical measurement issue for epidemiological studies, and routine determination in cord blood is of interest. Finally, because elements bound to proteins may interact with the FP matrix differently from those that have different speciation, future work should address homogeneity and sample representativeness for each element.

A plot showing the normalized signal for the five elements with signal profiles conducive to potential quantitation is shown in Fig. 6. Interestingly, none of the elements positively correlated with the Pb signal (concentration). However, inverse correlations were observed between Pb and Ca ($r^2=0.81$), Pb and V ($r^2=0.84$), and Pb and Cu ($r^2=0.80$). The other two elements (Fe and Zn) were essentially unchanged between blood specimens. Although beyond the scope of this work, there is a large body of literature on the correlations of Pb with other trace elements in blood, and the impact of nutritional deficiencies and medical conditions exacerbating the uptake of Pb into blood [16–18]. Assuming no contamination or losses during the collection, blood spotting, and subsequent storage, and similar distribution characteristics in the blood

spot, the laser ablation ICP-MS of blood cards shows promise for the rapid determination of select elemental profiles (patterns) in human blood. For the purposes of this feasibility study, the data presented here further serves to show the utility of this multi-element method.

Conclusion

Laser ablation ICP-MS of dried FP blood spots has potential as a rapid screening technique for BLLs. Because the analysis uses less than approximately 2% of the sample, more traditional techniques can be used on those samples producing signals above a selected threshold. More exact quantitation by laser ablation ICP-MS is possible but requires additional study to determine the most appropriate method for internal standardization. Laser spots are not recommended as a mode of analysis because greater variability was found for spot to spot analysis compared to line scan to line scan. Detection by time-of-flight mass spectrometry offers the advantage of Pb isotope ratio determinations with varying signal intensities, which has proved useful distinguishing data points likely associated with contamination. This is advantageous because it can be used to provide a blank subtraction without a separate distinct analysis. SEM images suggest reconstituted freeze-dried blood reference materials are inappropriate for quality control purposes for FP testing. Because the ICP-MS technique is highly sensitive and has multi-element capability, other elements or isotopes of nutritional value or health concern (e.g., As, Cd, Cu, Sb, Se) can potentially be monitored with Pb, provided the sample is not contaminated during collection and method validation specific for those elements is achieved. In this study, inverse correlations were found for Pb with Ca, V, and Cu for human whole blood spotted onto FP cards. Overall, the method shows considerable potential for the rapid determination of Pb, and possibly other elements, in blood which has been spotted onto FP cards.

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