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Wegner et al.

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[54] **COLLOIDAL-GOLD ELECTROSENSOR MEASURING DEVICE**

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[21] Appl. No.: **316,433**

[22] Filed: **Sep. 30, 1994**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 73,806, Jun. 7, 1993, Pat. No. 5,368,707, which is a continuation-in-part of Ser. No. 821,732, Jan. 15, 1992, Pat. No. 5,217,594.

[51] **Int. Cl.**[6] **G01N 27/26**

[52] **U.S. Cl.** **204/403**; 204/153.12; 204/153.1; 204/412; 204/415; 204/435; 435/817; 435/287.1; 436/74; 436/77

[58] **Field of Search** 204/403, 412, 204/415, 435, 153.12, 153.1; 435/817, 288; 436/74, 77

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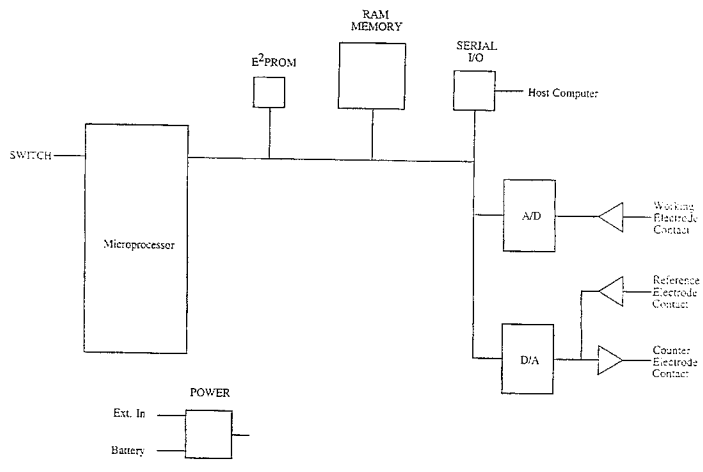
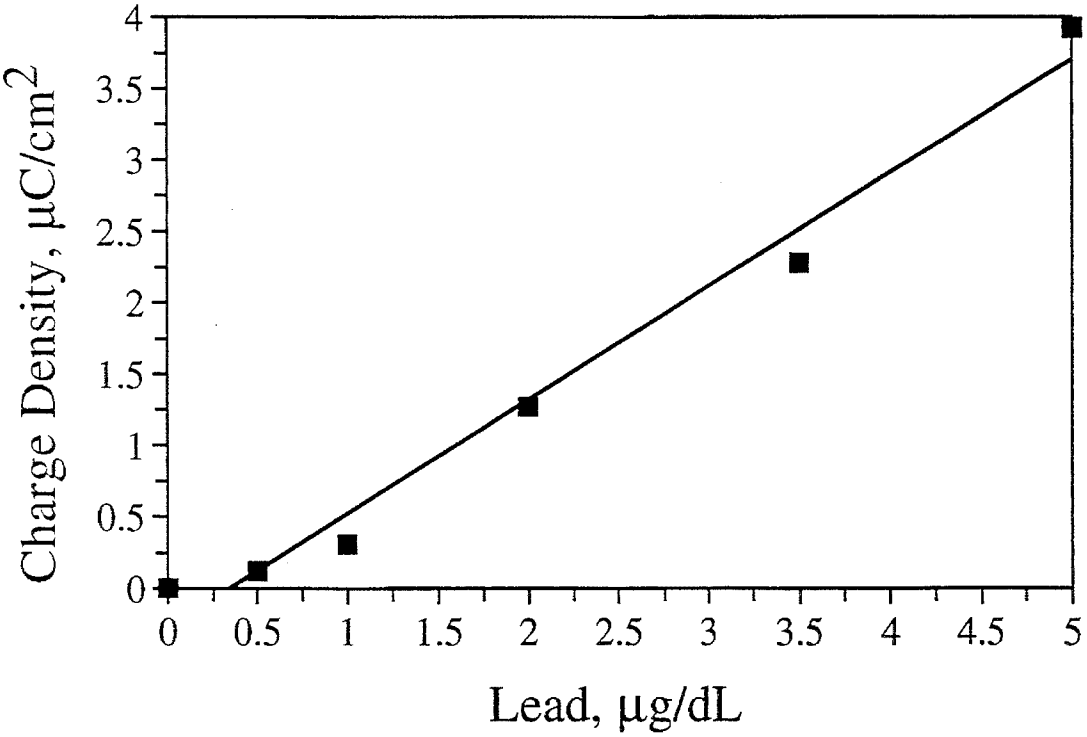
Assistant Examiner—Bruce F. Bell
Attorney, Agent, or Firm—Arnold, White & Durkee

[57] **ABSTRACT**

The present invention provides a new device for use in measuring lead levels in biological and environmental samples. Using square wave coulometry and colloidal gold particles impregnated on carbon electrodes, the present invention provides a rapid, reliable, portable and inexpensive means of detecting low lead levels. The colloidal gold modified electrodes have microelectrode array characteristics and produce significantly higher stripping detection signals for lead than are produced at bulk gold electrode surfaces. The method is effective in determining levels of lead down to at least 5 μg/dL in blood samples as small as 10 μL.

22 Claims, 9 Drawing Sheets

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3
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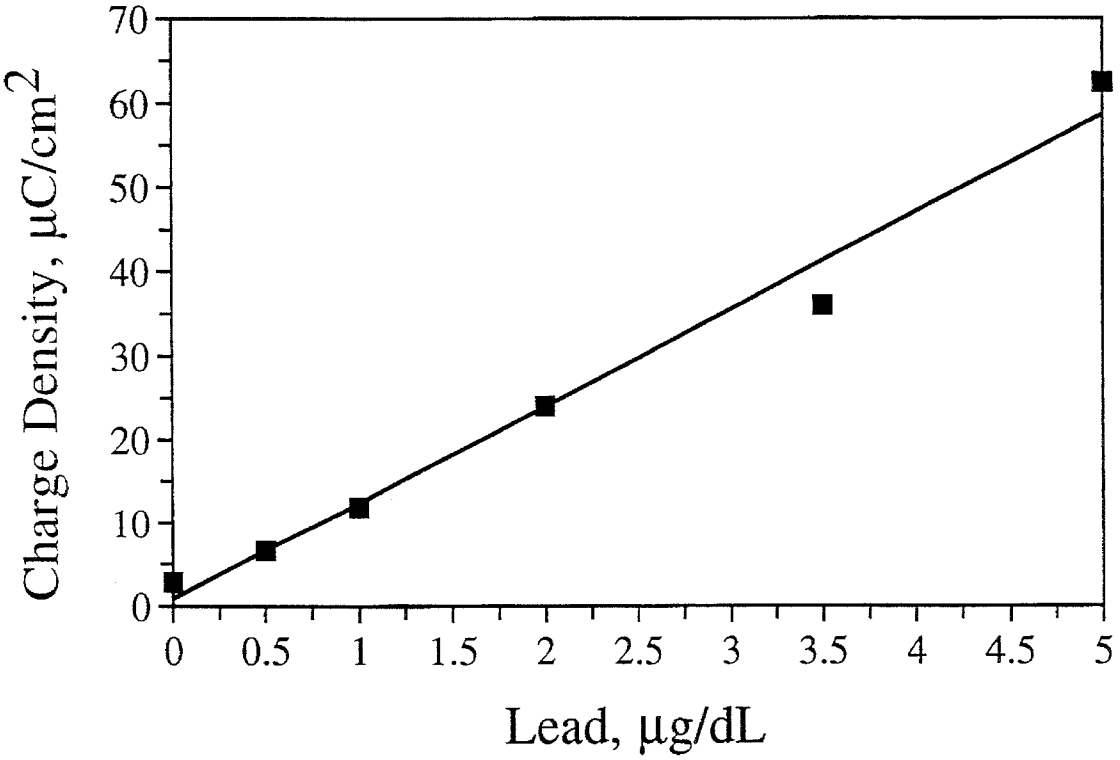
4
4.5
5
Lead, μg/dL

Fig. 1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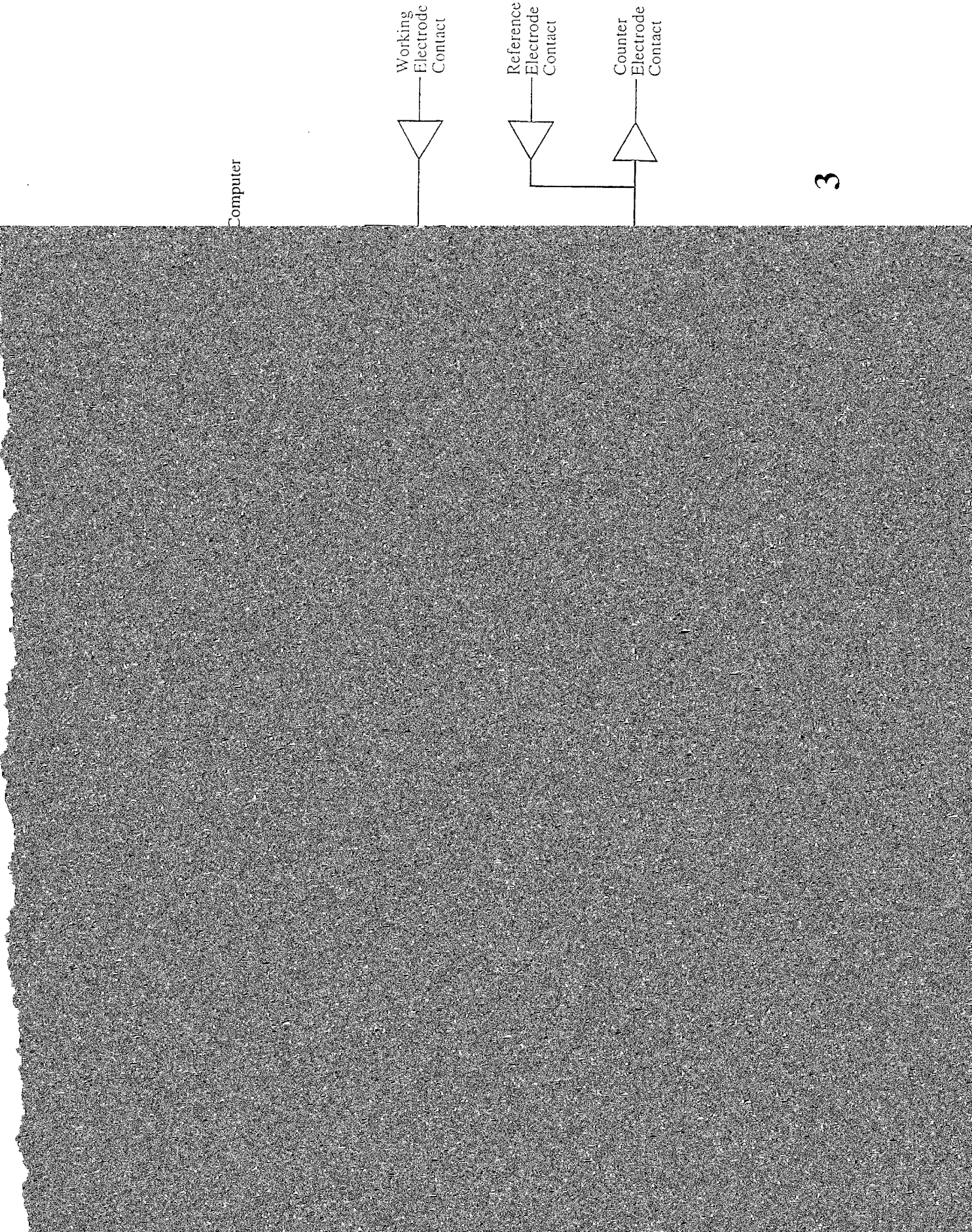
4
4.5
5
Lead, μg/dL

Fig. 2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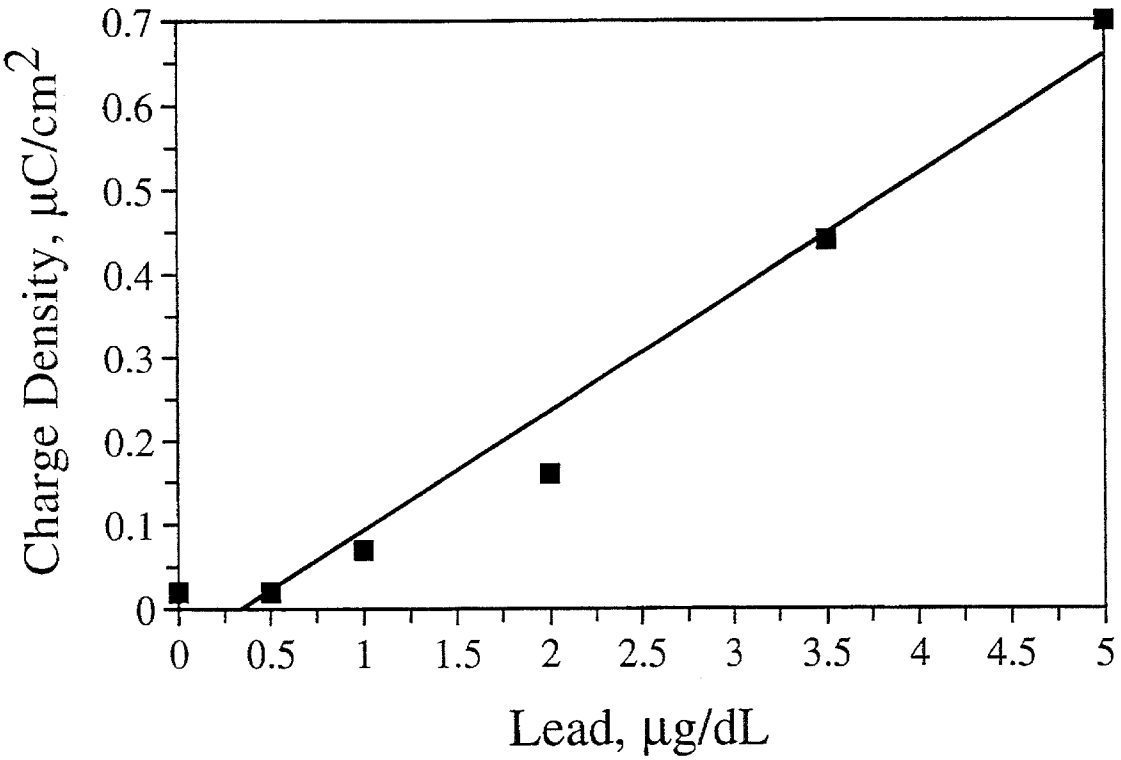
Reference Electrode Contact
Counter Electrode Contact
Computer

3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0.1
0
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1
1.5
2
2.5
3
3.5
4
4.5
5
Lead, μg/dL

Fig. 4

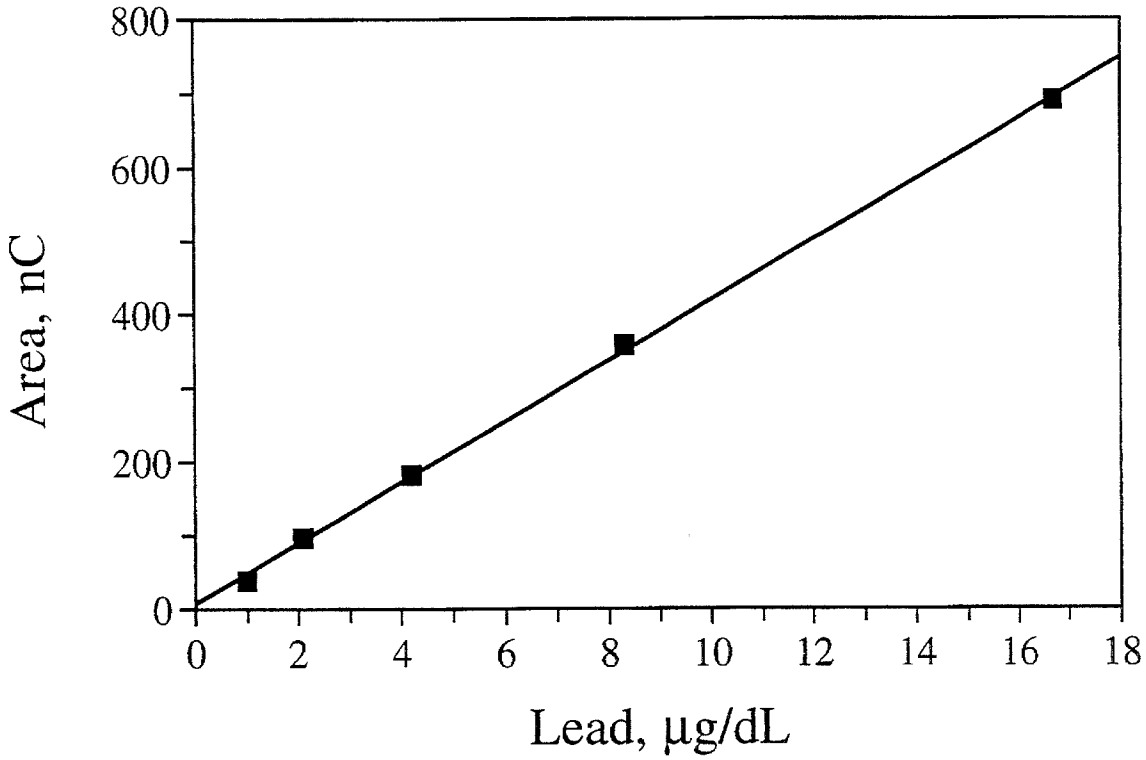
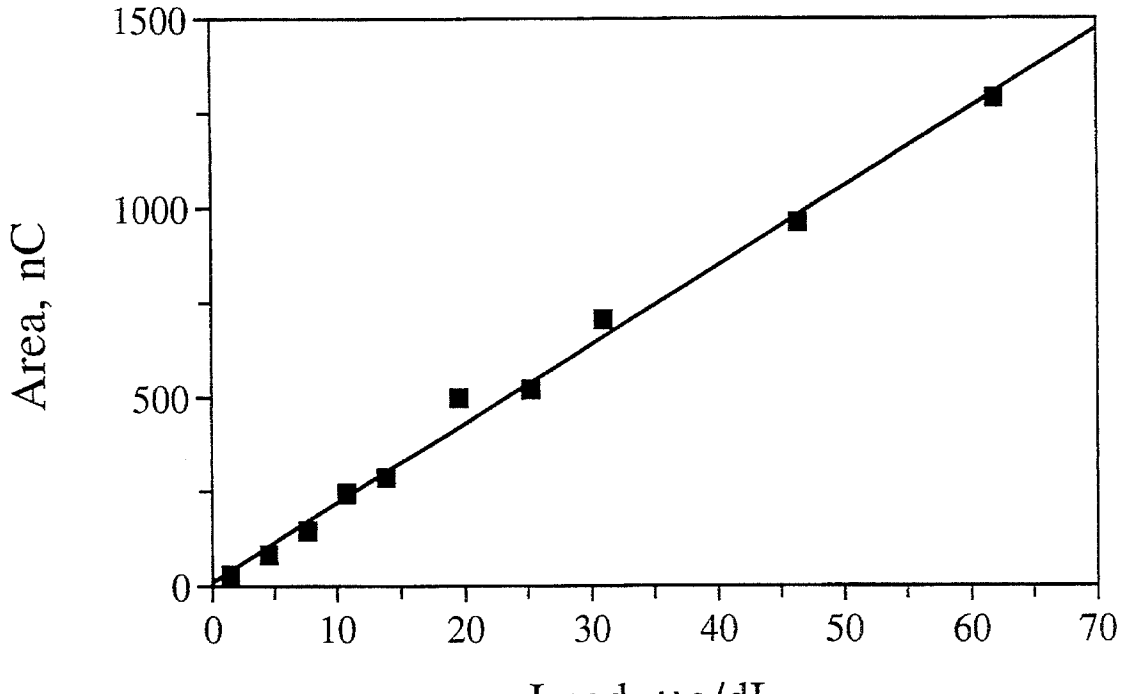


Fig. 5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20
30
40
50
60
70
Lead, µg/dL

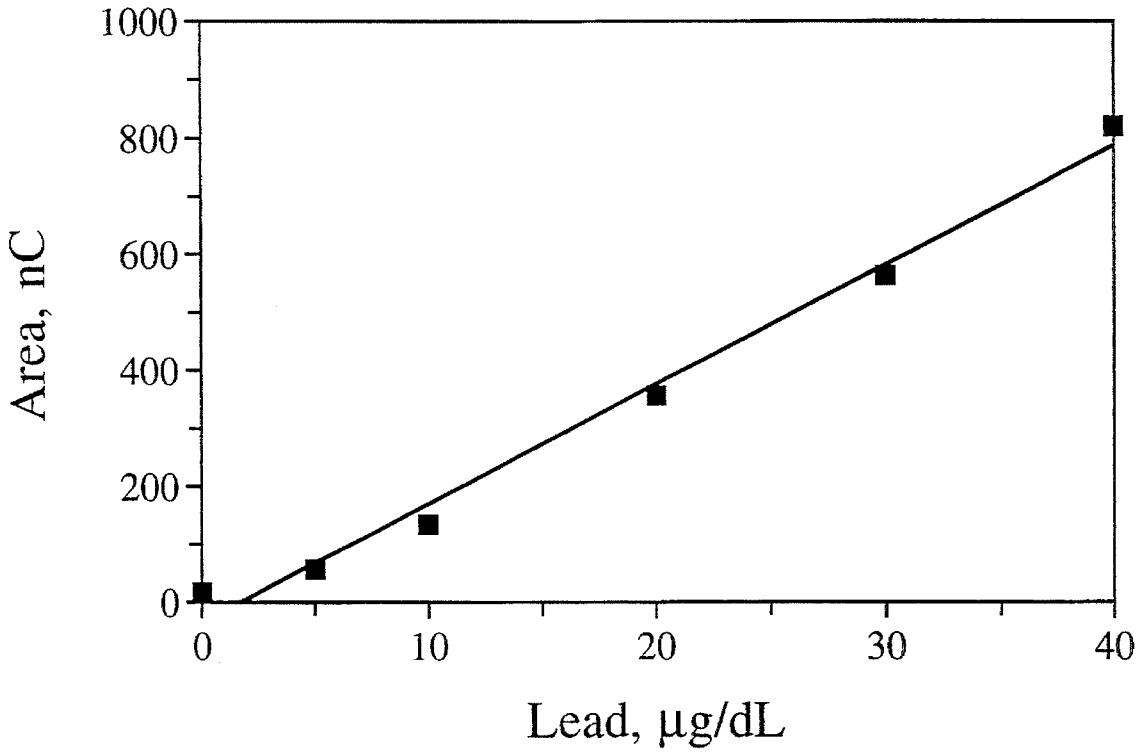
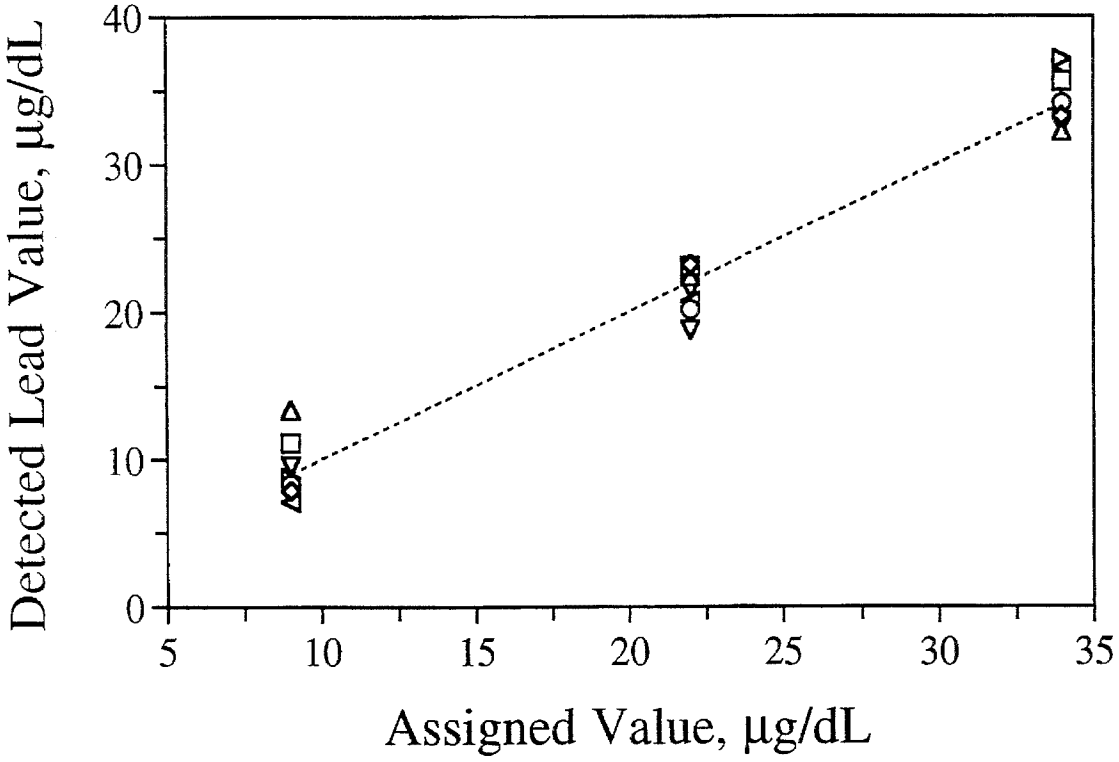


Fig. 7


Detected Lead Value, µg/dL
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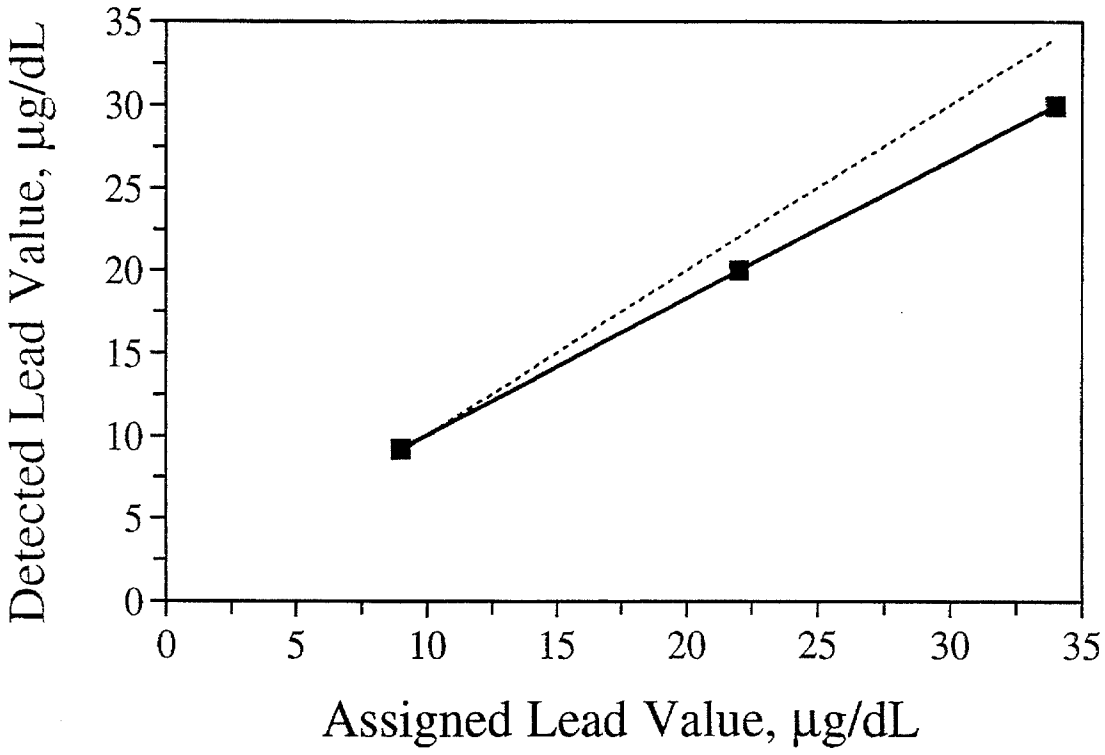
30
20
10
0
5
10
15
20
25
30
35
Assigned Value, µg/dL

Fig. 8


Detected Lead Value, µg/dL
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30
25
20
15
10
5
0
0
5
10
15
20
25
30
35
Assigned Lead Value, µg/dL

Fig. 9

dal gold solution onto a suitable substrate, such as glassy carbon or printed carbon ink. In certain modifications, the inventors have achieved excellent reproducibility by stabilizing colloidal gold sol solutions with a cationic polymer. The polymer apparently acts a dispersant as well as a stabilizer of the gold sol. An unexpected advantage of adding a polymer stabilizer is the elimination of background interference, possibly by selective membrane retention of interfering electrochemical species by the polymer. Without the polymer, problems with interfering electrochemical species were frequently encountered. Polymer addition may also lower the background current by blocking some of the conducting surface sites. Typical preparations of a colloidal gold sensor electrode are described in this example.

The disposable sensor strip is comprised of a three-electrode system. Each electrode has a different function. The silver electrode provides an electrochemical reference during the measurement. The carbon electrode provides a counter pole for the working electrode. The colloidal gold modified carbon electrode is the working electrode and provides the lead deposition and stripping surfaces. These electrodes are prepared by screen printing three electrodes with conductive silver ink and then screen printing carbon ink over the counter and working electrode. The carbon working electrode is completed by the controlled volumetric deposition and evaporation of a known volume of colloidal gold sol/poly(ester-sulfonic acid) polymer mixture on the electrode surface.

Colloidal Gold Solutions

Gold trichloride (Fisher Chemical Company, St. Louis, Mo.) was used to prepare a colloidal gold sol with a particle diameter of approximately 300 Å by the method of Moremans, et al, (1985). A solution of 1% aqueous sodium citrate was added to a rapidly boiling, stirred solution of gold trichloride, and the solution was refluxed for 30 minutes. The final concentrations (weight percent) were 0.01% $HAuCl_4$ and 0.03% sodium citrate.

Gold trichloride (Fisher Chemical Company, St. Louis, Mo.) was reduced with ascorbic acid to prepare a colloidal gold sol with a particle diameter of approximately 500 Å. The reaction was carried out at 0° C. and accomplished by the addition of ascorbic acid to a dilute solution of $HAuCl_4$ (ratio 5 moles ascorbic acid per mole of $HAuCl_4$). The reaction solution is stirred for 90 minutes at 0° C. During the course of the reaction there was a gradual color shift from deep purple to red wine color indicating a maturation in particle size distribution. Final size distribution of the colloidal gold did not occur for a least another 4 hours at room temperature. This method produced a colloidal gold suspension substantially equivalent to the citric acid reduction without using elevated temperatures.

Colloidal gold sols with particle diameters ranging from 100 Å to 1000 Å were purchased from BBI International, UK.

Gold electrode preparation

Dilute colloidal gold (0.05 mg/ml) was concentrated 20 times by centrifugation for 30 minutes at 4000 rpm. Poly-(ester-sulfonic acid) polymer (Eastman Chemical, Kingsport, Tenn.) was added to a final concentration of 0.9% (v/v). Three microliters of the (1 /mL) colloidal gold sol/poly(ester-sulfonic acid) polymer solution was volumetrically deposited on the working electrode surface and spread to cover the entire exposed surface of the working electrode. The electrode was then dried at 30°–40° C. under a heat gun for 5 minutes. In this example, the working electrode surface was modified with 3 μg of gold.

As an alternate to the above preparation, three microliters concentrated colloidal gold sol (1 mg/mL) was volumetrically deposited on the working electrode surface and spread to cover the entire exposed surface of the working electrode. The electrode was then dried at 30°–40° C. under a heat gun for 5 minutes. Two microliters of 2% (v/v) poly(ester-sulfonic acid) polymer was volumetrically deposited onto the colloidal gold modified working electrode surface and dried for another 5 minutes.

EXAMPLE 2

SWC Stripping Determination of lead in Water

Six water samples were tested. The samples were doped with lead to concentrations of 0 μg/dL, 0.5 μg/dL, 1.0 μg/dL, 2.0 μg/dL, 3.5 μg/dL, and 5.0 μg/dL respectively. The doped lead values were confirmed by anodic stripping voltammetry.

Carbon working electrodes were modified with 3 μL of 1 mg/mL 500 Å colloidal particles or with 3 μL of 1 mg/mL 500 Å colloidal particles with 1% poly(ester-sulfonic acid) polymer as described in Example 1. Water samples were pretreated with 100 mM HCl solutions. Water (30–50 μL) was placed on the disposable 3-electrode sensor strip, described in Example 1, so as to cover all three electrodes within the circle of the insulating layer. A square wave coulometry (SWC) program was initiated within 10 seconds of application of the sample on the disposable sensor strip. Execution of the measurement sequence was confirmed by the monitor reading "Test in Progress". Within approximately 2 min. the display showed a lead concentration value. Results for colloidal gold modified carbon electrodes are shown graphically in FIG. **1**. Results for colloidal gold particles with 1% poly(ester-sulfonic acid) polymer modified carbon electrodes are shown graphically in FIG. **2**.

The colloidal gold modified carbon electrodes were coupled to a reusable electronic meter that provided the potentiostatic and SWC analytical capabilities for the disclosed lead detection system. The meter can vary in size from hand-held to lap-top to table top dimensions. A block diagram of the reusable electronic meter's components is shown in FIG. **3**.

The reusable electronic meter's microprocessor automatically executes the following sequence:

Conditioning 1: A potential of –500 mV (vs. the silver reference electrode on the disposable sensor strip) is applied to the strip's working electrode (colloidal gold modified carbon) for 10 seconds.

Conditioning 2: The potential is changed to –50 mV and held at this value for 10 seconds.

Deposition: The potential is changed back to –500 mV and held for 90 seconds.

Stripping and data acquisition: A square wave voltammetry scan is run from –500 mV to +50 mV, during which currents are measured (twice during each square wave cycle) and saved in the memory of the meter (552 measurements per scan). The parameters of this square wave voltammetry are: frequency 50 Hz, amplitude 25 mV, potential step 2 mV.

Data treatment: Stored current values are numerically filtered (forward and reverse and net currents are filtered individually). A baseline subtraction algorithm is then executed and the lead stripping signal is measured by another algorithm that integrates the area under the stripping peak. The peak area value is then correlated with standard calibration data to determine the concentration of lead in the analyzed blood sample.

EXAMPLE 3

The advantages of colloidal gold modified carbon electrodes compared with thin film (bulk) gold electrodes are not

necessarily predicted or expected. The inventors have tested both types of electrodes in order to compare properties. The following describes direct comparisons of stripping voltammetry determinations of lead ion between colloidal gold modified carbon electrodes and bulk gold electrodes in the same samples and under the same experimental and instrumental conditions.

In order to compare the sensitivity of a conventional, reusable, solid gold ("bulk gold") disk electrode with the disclosed colloidal gold modified carbon electrode (prepared with 1.0 mg/mL 500 Å colloidal gold sol and 1.0 mg/mL 500 Å colloidal gold sol mixed with 1% poly(ester-sulfonic acid) polymer), a series of parallel SWC measurements of lead stripping response was conducted in 100 mM HCl solutions containing 0–5 mg/dL (equivalent to 0–50 ppb) of lead standard. Such comparison can be meaningful only if the sensitivity is related to the active surface area of the compared electrodes. This can be done by either considering the geometric surface areas of the electrodes or considering the active surface areas of the electrodes. The former introduces an uncertainty related to the roughness of the electrode surface and the fact that the colloidal gold particles not in contact with the carbon support do not participate in the stripping process. The comparison of the sensitivity per active surface area is free of these uncertainties and therefore more meaningful.

The bulk gold electrode had a diameter of 1.8 mm and a geometric surface area of 1.5 mm^2. The screen printed carbon ink electrode had a geometric surface area of 14.6 mm^2. The geometric surface area of the colloidal gold particles deposited on this carbon electrode was 18.7 mm^2. The colloidal gold geometric surface area calculation was based on the number of colloidal gold particles (determined from the measured average particle size), colloidal gold concentration, assuming ideal sphericity of gold particles, and ignoring the roughness of the gold particle surface.

The active electrode surface area was determined by measuring the charge required to reduce anodically oxidized gold from the electrode surface. This is a commonly accepted method of surface area determination for platinum and gold electrodes. A series of cyclic voltammetry (CV) experiments was conducted using each gold electrode and the same reference (silver ink on the sensor strip) and counter (carbon ink on the sensor strip) electrodes. Solutions (with ambient dissolved oxygen) of 100 mM HCl were used. The charge was measured by integration of a noise-filtered and background- and baseline-subtracted reduction peak for Au^{+1} species generated during the 100 mV/s CV scan from 0.0 V to 1.2 V to –0.5 V (vs. Ag reference electrode). The measurements were repeated to assure reproducibility. The measured charge was then divided by 3.86 mC/mm^2, which is the literature value of the standard charge per unit surface area for electrooxidation of gold. The surface area values obtained were 52.6 mm^2 for the bulk gold electrode and 2.6 mm^2 for the colloidal gold modified carbon electrodes.

FIG. 4, FIG. 1, and FIG. 2 show results of the SWC lead measurement for, respectively, a bulk gold electrode, a colloidal gold modified carbon electrode, and a colloidal gold mixed with poly(ester-sulfonic acid) polymer modified carbon electrode. In these graphs the stripping signals are expressed in units of charge density, i.e. $\mu C/cm^2$. These values were obtained by dividing the measured charge during the stripping scan by the active surface areas of the tested gold electrodes. The lead sensitivity of the colloidal gold modified carbon electrode (slope of FIG. 1) is approximately 5.6 times greater than the sensitivity of the bulk gold electrode (slope of FIG. 4). The lead sensitivity of the colloidal gold mixed with poly(ester-sulfonic acid) polymer modified carbon electrode (slope of FIG. 2) is approximately 14.5 times greater than the sensitivity of the colloidal gold modified carbon electrode (slope of FIG. 1) and 81 times greater than the sensitivity of the bulk gold electrode (slope of FIG. 4).

EXAMPLE 4

SWC Stripping Determination of lead in Urine

Synthetic urine is an aqueous solution of salts and organic compounds that mimics the chemical and physical properties of human urine. This product was purchased from CST Technologies, Inc. of Great Neck, N.Y. Five urine samples were tested. The samples were doped with lead to concentrations of 1.0 µg/dL, 2.0 µg/dL, 4.0 µg/dL, 8.0 µg/dL, and 16 µg/dL respectively. The doped lead values were confirmed by anodic stripping voltammetry.

Carbon working electrodes were modified with 3 µL of 1 mg/mL 500 Å colloidal particles with 1% poly(ester-sulfonic acid) polymer as described in Example 1. Samples were pretreated with 100 mM HCl solutions. Sample (30–50 µL) was placed on the disposable 3-electrode sensor strip, described in Example 1, so as to cover all three electrodes within the circle of the insulating layer. The square wave coulometry (SWC) program was initiated within 10 seconds of application of the sample on the disposable sensor strip. Execution of the measurement sequence was confirmed by the monitor reading "Test in Progress". Within approximately 2 min. the display showed a lead concentration. Results are shown graphically in FIG. 5.

The reusable electronic meter's microprocessor automatically executes the sequence described in Example 2.

EXAMPLE 5

This example illustrates the rapid and accurate determination of lead in blood samples. The inventors have discovered that pretreatment of blood samples to bring the pH below 1 without significant dilution is important in preventing polymerization and coagulation of blood components. A suitable pretreatment was achieved using 400 mM hydrochloric acid.

Preparation of blood:

Blood samples were analyzed shortly after being drawn; alternatively, they were refrigerated for several days before analysis. For longer storage (e.g., longer than a week) blood samples were frozen. Frozen blood samples including those used as blood lead reference materials (e.g., Centers for Disease Control standards), should be thawed and allowed to stand at least 30 minutes at room temperature before analysis.

Three volumes of 400 mM HCl solution was added to 1 volume of blood in a disposable 1.5 mL microcentrifuge tube. The tube was capped and immediately stirred vigorously by turning the tube upside-down at least 5 times with tapping between turns. After 5 minutes the amount of lead in the sample was determined using square wave coulometry as described in Example 2.

EXAMPLE 6

Anodic Stripping Determination of lead in Blood

Three different blood samples were tested with disclosed lead sensor system, bovine blood lead control samples prepared by the CDC, freshly drawn human blood, and three commercially available whole human blood lead control samples obtained from UTAK Labs, Inc. (Valencia, Calif.).

The CDC bovine samples contain ingested lead and were sent with target values. The freshly drawn human blood was spiked with lead after taking the blood sample. The UTAK human control samples were doped with lead and had assigned lead concentrations of 9 μg/dL, 22 μg/dL and 34 μg/dL respectively, The CDC and UTAK assigned values were confirmed by graphite furnace atomic absorption spectrometry and anodic stripping voltammetry. The freshly drawn human blood values were confirmed by anodic stripping voltammetry.

The carbon working electrode was modified with 3 μL of 1 mg/mL 200 Å colloidal gold particles with 0.5% poly(ester-sulfonic acid) polymer as described in Example 1. Blood samples were pretreated with HCl solution as described in Example 5. Blood (30–50 μL) was placed on the disposable 3-electrode sensor strip, described in Example 1, so as to cover all three electrodes within the circle of the insulating layer. The square wave coulometry (SWC) program was initiated within 10 seconds of application of the sample on the disposable sensor strip. Execution of the measurement sequence was confirmed by the Monitor reading "Test in Progress". Within approximately 2 min. the display showed a lead reading. Results for the bovine blood samples are shown graphically in FIG. **6**. Results for the freshly drawn human blood samples are shown graphically in FIG. **7**. Results for the UTAK human control blood samples are shown graphically in FIG. **8**.

The reusable electronic meter's microprocessor automatically executes the sequence described in Example 2.

EXAMPLE 7

This example illustrates the rapid and accurate determination of lead in blood samples with 500 Å colloidal gold particles deposited on screen printed carbon electrodes covered with a woven screen mesh. The inventors have found that a hydrophilic material covering the three electrode sensor, such as described in Example 1 facilitates the rapid and uniform distribution of a blood sample over the desired area. A suitable hydrophilic material is a polyester monofilament fabric purchased from Tetko, Inc. (Briarcliff Manor, N.Y.).

A colloidal gold modified carbon electrode was fabricated as described in Example 1 with 500 Å colloidal gold particles. A woven screen mesh of polyester monofilament fabric was affixed over the sample placement area of the working electrode, reference electrode, and counter electrode. Mesh covered colloidal gold modified electrodes were used to test three different blood lead control materials purchased from UTAK Labs, Inc. (Valencia, Calif.) that were acid treated as described in Example 5. These electrodes measured lead values for these control samples that were on average within 7.8% of their assigned lead values. Representative data are shown in FIG. **9**.

A reusable electronic meter's microprocessor automatically executed the sequence described in Example 2.

EXAMPLE 8

This example illustrates certain electrochemical properties of the colloidal gold modified electrodes developed by the inventors. The colloidal gold modified electrodes act as a microelectrode array. For the same geometric area, the stripping detection signal of a microelectrode array is greater than the stripping detection signal for a planar electrode.

The response of microelectrode arrays has three regimes of scanning frequency dependence. The divisions between the regimes depends on the analyte diffusion distance relative to the radius of the individual microelectrodes and the separation between the individual microelectrodes. In high frequency scans, analyte diffusion distance is small compared to microelectrode radius. Signal is limited by the aggregate area of the microelectrodes and is proportional to the square root of frequency. In low frequency scans, analyte diffusion distances to the individual microelectrodes overlap. Signal is limited by the macroscopic geometric area of the array and is proportional to the square root of frequency. In between frequency scan extremes analyte diffusion distances are not small compared to microelectrode radius but do not overlap the individual microelectrodes. Signal response is in a steady-state and essentially is independent of frequency.

Signal response exhibits mixed behavior at the boundaries of these regions. The frequency positions of the boundaries give information about the average microelectrode radius and the average distance of separation of the microelectrodes. At a frequency of 1 Hz the disclosed colloidal gold modified electrode exhibited a steady-state response to 1 ppm lead that extends at least from 0.5 to 2 Hz. Exploration of the steady state frequency boundaries of the disclosed colloidal gold modified electrodes provided an to estimate of microelectrode size (radius=1.5×10^{-3} cm), microelectrode number (9×10^{4}), and distance of separation of the microelectrodes (1.2×10^{-3}). The sensitivity of the electrode under the instrumental conditions used in this example is represented by:

Signal response=(104[concentration of sample lead])+1 where R^2=0.994.

After correction for geometric areas, the relative signal response of colloidal gold modified carbon electrodes in unstirred samples was ≧2 the relative signal response of bulk gold electrodes in unstirred samples.

Additional evidence to support the microelectrode array behavior of the disclosed colloidal gold modified carbon electrode was obtained by examining the dependence between the SWC signal and the deposition time in the absence of forced convection, e.g. stirring. The SWC signal for blood lead, or the stripping peak current, increased in proportion to the increase of the deposition time. This linear dependence proved the nonlinear diffusion pattern of the transport of lead ions to the electrode surface during the deposition step, which is characteristic of the microelectrode array behavior. A square root dependence between the signal and the deposition time would be expected for a macroelectrode in a quiescent solution. Furthermore, it was observed that under the conditions of relatively fast SWV the disclosed colloidal gold modified carbon electrodes generated sigmoidal shaped forward and reverse current curves with a diffusion plateau well above that expected for a macroelectrode.

Forward and reverse current curves obtained in SWV stripping experiments involving lead and the disclosed colloidal gold modified electrodes, exhibit a sigmoidal-like shape with a diffusion plateau well above. This shows that under the conditions of relatively fast SWV the disclosed electrodes acted as a microelectrode array.

All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the composition, methods and in the steps or in the

sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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What is claimed is:

1. An electrode comprising a conducting substrate onto which is deposited 10–30 μg/cm^2 of colloidal gold admixed with a cationic polymer.

2. The electrode of claim **1** wherein the cationic polymer is a poly(ester-sulfonic acid).

3. The electrode of claim **1** wherein the conducting substrate is glassy carbon.

4. The electrode of claim **1** wherein the conducting substrate is carbon ink.

5. The electrode of claim **4**, wherein the electrode is screen printed.

6. An electrode comprising colloidal gold dispersed in a cationic polymer matrix that is deposited onto an electrode surface to form a microelectrode array.

7. The microelectrode array of claim **6** wherein the cationic polymer is poly(ester-sulfonic acid).

8. The microelectrode array of claim **6** wherein the electrode surface is screen printed carbon ink or glassy carbon.

9. The microelectrode array of claim **6** wherein size of the colloidal gold is between about 200 and 500 angstroms in diameter.

10. A lead monitoring device comprising the electrode of claim **1** or claim **6**, a reference electrode, a counter electrode coupled, means of measuring current, and means for performing square wave coulometric analysis.

11. A method of determining lead ion levels, comprising the steps:

contacting a sample suspected of containing lead ion with the electrode of claim **1** or the microelectrode array of claim **6**;

reductively plating metallic lead onto the electrode surface;

stripping the plated lead from the electrode surface to form lead ion to produce a current; and

relating amount of current generated to the lead ion level in the sample.

12. The method of claim **11** wherein the sample is a water sample or a urine sample.

13. The method of claim **11** wherein the sample is a blood sample.

14. The method of claim **13** wherein the blood sample is admixed with an acid prior to the contacting step.

15. The method of claim **11** wherein current is determined by square wave coulometry.

16. The method of claim **11** wherein the sample volume is between 10 and 100 μL.

17. The method of claim **11** wherein the reductive plating is accomplished at about –0.5 volts.

18. The method of claim **11** wherein the stripping is by square wave voltammetry in a potential range between –0.5 and +0.5 volts.

19. A system for coulometric determination of heavy metal ions that have a stripping potential between –0.5 and +1.0 volts, comprising the electrode of claim **6**, a coupled working electrode and means for adjusting deposition potential between about –0.5 and +0.5 volts.

20. A method of determining blood lead ion levels in the range of about 1 to about 60 μg/dL comprising:

admixing acid with a blood sample suspected of containing lead;

reductively depositing the lead onto the coupled electrode of claim **6** at a potential of about –0.5 volts; and

coulometrically determining the amount of deposited lead.

21. An electrode comprising a carbon ink substrate onto which is deposited a film consisting essentially of colloidal gold particles having a size of about 200–500 Å admixed with a poly(ester-sulfonic acid) polymer.

22. The electrode of claim **21**, wherein the electrode is screen printed.

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