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Continuing issues with Lead: Recent Advances in Detection

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Abstract

In the past Pb^{2+} has been used in many industries, including gasoline, piping, toys, paints, and more. The use of lead has led to a natural increase of lead concentration in the environment especially in air and water. According to the U.S. CDC “no level of lead in blood is considered safe.” Exposure to very low amounts of lead can cause several health complications including developmental and neurological disorders. Over the past several years an emphasis has been placed in developing systems that can detect lead at a very low concentration. A great deal of work has been accomplished in the development of Pb^{2+} sensors that can not only detect but also quantify the amount and in some cases in the presence of other metal ions. Herein, we describe current regulations, mode of exposure and recent development of sensing techniques.

Keywords

Lead Poisoning; Heavy Metal; Metal Ion Detection; Heavy Metal Contamination; Fluorescent Sensors

Introduction

Lead has no known natural biological role in humans. It is a persistent environmental contaminant and has been viewed as a common environmental health concern. Lead is a strong chalcophile, found naturally in the environment mainly in ores of zinc, silver, and copper. The major sources of lead are in galena (PbS), cerrussite ($PbCO_3$), and anglesite ($PbSO_4$) deposits.[1] The primary cause of lead contaminated soils, air, and water systems are due to anthropogenic activities such as burning leaded gasoline, use of lead solder, lead piping, and lead based paints.[1,2] The natural levels of lead in surface and ground waters is very low (< 5 ppb) but in some areas higher than 1000 ppb lead have been found in both water and soil.[2]

There has been reports of mass lead intoxication in Senegal and Nigeria, which caused significant lose in life and developmental issues with children.[3,4] This lead-cycle initiated by anthropogenic activities is more extensive than the natural lead-cycle, causing lead pollution a worldwide issue. The median BLLs in children under age 6 fell from about 15–18 μg/dL in 1970 to 2–3 μg/dL in 1994. However, more than 250,000 children of the age 1–5 years have

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BLLs above the Center for Disease Control (CDC's) recommend action limit of 5 μg/dL.[5,6] Even at extremely low levels, lead has been linked with a range of health effects including behavioral problems and learning disabilities.[7–13] Lead enters the body through a multitude of pathways and understanding these pathways, the process of storage and transport, and localization in cells can help better evaluate the biological effects of lead.

The environmental concerns and associated health effects at a very low levels of lead means tools to detect and quantify lead must be operable at low concentrations. Sensitive, selective, and simple methods of detection are crucial in not only preventing contamination but for better understanding of biological pathways of lead. Several reviews have focused on the sensing techniques of different groups of metals (e.g., heavy metal, alkali metal) or focus on a specific type of sensing (e.g. DNAzymes, nanoparticles, fluorescent molecules, etc).[14–17]

Lead Exposure

In general, exposure to toxic metals may occur through food, medications, the environment i.e., water and air, or during occupational and/or recreational activities. In terms of environmental contamination, levels of pollutants are usually small in waters but they can be higher in certain zones due to industrial and domestic waste discharge.[18] Aquatic plants and animals, in particular some mollusks, can accumulate high levels of toxic elements such as arsenic and cadmium providing a vehicle to introduce toxic metals into the food chain.[18] In Europe, it has been reported that 17 species of birds of prey have had lead poisoning.[19] Some of these birds include the White-tailed Eagle and the endangered Spanish Imperial Eagle.[19] Heavy metals, including lead, are absorbed through the roots and leaves of plants.[20] This can then interfere with the levels of antioxidants in plants, and reduce the nutritive value of the produce.[20] Individuals are exposed to lead and its harmful effects through two main routes: from air and water. Lead containing particles or aerosols generated from lead-based paints, gasoline and industrial manufacturing serve as the primary route to aerial lead exposure. The second route is from water, dispensed from lead based pipes.[21–26] In adults, the deleterious effects of lead may be reversed through chelation therapy, but the effect on children is more permanent.

Young children are particularly sensitive to exposure to lead due to their developmental properties and hand-to-mouth behavior.[27] Young children are more susceptible to the hazardous health effects of lead exposure because they absorb more of the ingested lead.[28] Lead has been found in high concentrations in children's products, especially toys and candy.[29] Indeed, a widespread problem has been reported with high metal contamination in toys and certain jewelry as children ingest Pb-contaminated products. One of the main sources of Pb^{2+} in jewelry items is thought to be the use of recycled electronic wastes and lead battery.[30,31] In the past few years millions of toys have been recalled because of chemical safety hazards, for violating lead paint standard.[32,33] It has been reported that metal leaching from several plastics, including children's toys, has toxic effects on fish.[34] In addition to Pb, Ba Cd, and Cr have been found in baby toys.[35] Weidenhamer and Clement examined 39 jewelry items and found they contain 90% or more lead by weight.[36] Children living in urban areas typically exhibit elevated blood lead levels (BLLs) along with many

major cities having recent spikes in the lead concentration of their water system due to disinfectant switches.[26, 37–39]

Another current issue with lead exposure accompanies changes in the water systems disinfectants utilized. Figure 1 shows two different common approaches for disinfecting waters from microbial species. Traditionally, chlorine has been used in the drinking water system as a disinfectant, but recent concerns of toxic disinfectant by-products has lead to the use of a substitute, chloramine.[38] In addition to forming carcinogenic nitrosamines, the switch from chlorine to chloramine has also been connected to elevated levels of lead in drinking water.[40] Higher levels of Pb^{2+} in drinking water has lead to an elevated level of lead in human blood samples in Washington DC, Portland OR, Providence RI, and other cities.[41,42] Edwards and colleagues reported a significant increase in BLLs in Washington D.C.[42] The use of chlorine typically inhibits the leaching of lead from pipes as it oxidizes Pb^{2+} to Pb^{4+} and creates a coating of slightly insoluble lead oxide (PbO_2). Chloramine is a weaker oxidant than chlorine, which does not produce such protective coatings, and this in turn releases more Pb^{2+} into the drinking water.[6]

Maximum Contamination Level and Lead Toxicity

Lead is a toxic metal that has been in use for many decades as discussed above, and different regulatory agencies have set a limit of maximum contamination level (MCL) for lead. However, the limits vary from agency to agency as well as the material they regulate (Table 1). According to the U.S. CDC a 100–190 ppb BLL poses a potential threat and that diagnostic testing is strongly encouraged.[5] In 2010 the EPA set the maximum contaminant level goal (MCLG) for lead to zero ppb and the action level at 15 ppb, in drinking waters.[43] The U.S. Food and Drug Administration (FDA) has set maximum level of 0.1 ppm for lead in candy.[44] Additionally, the Consumer Product Safety Commission (CPSC) has recently lowered the limit of lead in children's product to 100 ppm.[45] This trend of lowering the maximum limit of lead in many consumer products is in response to the increasing recognition of the threat that lead poses. A low level exposure to lead can cause neurological, reproductive, cardiovascular, and developmental disorders.[7–13]

Lead is known to bioaccumulate in bones for up to 20 years and is not hazardous to human health unless it is released, this can occur when the bones experience turnover and remodeling by osteon activity.[46,47] Lead is a likely target of calcium- and zinc-binding proteins (C2A domain of synaptotagmin I and cysteine-rich zinc finger proteins) that control cell signaling and gene expression, respectively, but the molecular and cellular mechanisms of lead toxicity remain an open question.[48–52] Lead can also be taken up by the cell by copper and zinc transporters and have been observed to cause both oxidative stress and DNA damage.[53,54] Lead is also known to interfere with the biosynthesis of heme.[55] Bradman *et. al.* reported that iron deficiency increases BLLs perhaps due to an increase in absorption and retention of lead.[56] In addition, Pb^{2+} may bind in vacant Fe^{2+} sites in the hematopoietic system, resulting in reduced lead excretion.[56] Hopkins *et. al.* have demonstrated a close association between iron metabolism genes with lead exposure in children. As mentioned, iron deficiency has been implicated with an increased absorption and deposition of lead. However, iron supplement given to a control group did not change

the BLL, and children with genetic variants may be more prone to the lead poisoning.[57] Interest in explaining these pathways, as well as public concerns over toxic lead exposure, provides a need for devising new ways to track Pb^{2+} in natural samples.

Current Method of Detection

Metal ions enters into the cells through several ways and understanding these pathways of metal incorporation, the process of their storage and transport, and localization in cells can help for the better understand normal functioning as well as the diseased states. These methods with their detection limits are listed in table 2.

Techniques Approved by Regulatory Agencies

The United States EPA approved methods for lead detection are inductively coupled plasma mass spectrometry (ICP-MS)[58] with a detection limit of 0.6 ppb, inductively coupled plasma atomic emission spectrometry (ICP-AES)[59] with a detection limit of 42 ppb, and graphite furnace atomic absorption spectroscopy (GFAAS)[60] with a detection limit of 0.7 ppb. The detection limits and linear working ranges are dependent on the sample matrix, instrumentation, and selected operating conditions. These methods provide means to determine dissolved lead in ground waters, surface waters, drinking water, wastewaters, sludges, and soil samples.[58–60] There are four natural isotopes of lead and in ICP-MS three isotopes (^{206}Pb, ^{207}Pb, and ^{208}Pb) are typically monitored, however the method suffers from interferences including isobaric elemental interferences, abundance sensitivity, isobaric polyatomic ion interferences, and physical interferences. Another EPA approved method, ICP-AES, experiences interferences from Co, Al, Ce, Cu, Ni, Ti, and Fe at 100 mg/L (100 ppm) at the recommended wavelength of 220.353 nm.[59] Similar to ICP-MS, one can perform direct analysis of samples with GFAAS. Although GFAAS is a reliable and sensitive method, the necessity of additives and modifiers is considered to be a disadvantage. If the sample preparation involves digestion with HCl, for example, it can influence the sensitivity for lead detection. This effect can be corrected up to 10% with the addition of $Pd/Mg/H_2$ as a modifier.[60] Though the FDA and CPSC have significantly higher lead limits, they employ the analysis similar to the EPA.[61,62]

These methods usually require small sample size and sensitive, they are instrument intensive, non-portable, and require trained technicians. Also, the sample preparation of specific metal ions may require a long digestion process. First, the composite sample must be blended with water and/or nitric acid, and predigestion is often required for suspended samples. Generally, the microwave digestion is followed by analysis with GFAAS, ICP-AES, and ICP-MS. Overall, the most favorable EPA approved method of analysis for lead in an environmental water sample is ICP-MS.[58] ICP-MS analysis often serves as the simplest sample preparation, with least interference, and lowest detection limit. For these reasons, ICP-MS has been viewed as a gold standard for other methods, including those described herein. These methods that have been approved by the regulatory agencies have a major limitation as they cannot be easily used to monitor the distribution of metal ions in real time. Thus, a simple, rapid, inexpensive, minimal sample handling, selective, and sensitive method that permits real time detection of metal ions is of interest.

Electrochemical Techniques

A traditional method of metal ion detection is the application of electrochemical properties including anodic stripping voltammetry (ASV), cathodic stripping voltammetry (CSV), and adsorptive stripping voltammetry (AdSV).[63–65] These methods can be used determine metal ion concentrations in water to sub–parts-per-billion levels. They usually incorporate three electrodes, a working, auxiliary, and reference electrodes. The analytical species is reduced onto the working electrode and is then oxidized, “stripped”, back into the electrolyte solution.[66] The stripping current due to oxidation of each analyte is proportional to the concentration of that analyte on or in the electrode and thus, in the solution in question.[66] Mercury film electrodes (MFE) and the hanging mercury drop electrode (HMDE) have been traditionally used for ASV because of the negative potential range of mercury but due to the potential health hazards of mercury alternative electrodes have been sought.[67] A bismuth-film electrode (BFE) has been successfully used to determine Zn, Cd, and Pb at low concentrations. It has mostly been used for the determination of Pb and Zn in tap water and in human hair.[63] ASV has also been frequently used to determine BLLs.[57,63,68]

A recent development in electrochemical detection of Pb^{2+} utilizes the traditional bismuth electrode but also carbon composite, G-quadruplex, phenanthroline, and DNA combined with TiO_2 (Table 2). Quintana *et. al.* reported a sensitive bismuth-modified screen-printed electrodes (Bi-SPE) for lead detection that avoids the use of toxic mercury containing films.[69] Stripping voltammetry using SPEs allows the formation of an amalgam that enables the analyte to accumulate on the bismuth film, providing with a higher sensitivity and reproducibility. They carried out *in situ* or *ex situ* in the same frame as the European Union project. *Ex situ* involves putting SPE into the solution containing Bi^{3+} ions and then a potential to reduce bismuth to Bi^0 prior to the addition of the analyte. *In situ* experiment uses the sample solution containing Bi^{3+} and thus both analyte and the bismuth are electrochemically deposited on the working electrode. *In situ* produced a linear working range for lead ion concentration from 0.5 to 100 ppb and a detection limit of 0.15 ppb, which proved to be more selective than *ex situ* measurements.[69]

Additionally, Li *et. al.* used differential pulse voltammetry (DPV) to monitor the G-rich DNA conformational switch, induced by Pb^{2+}, from a random-coil to G-quadruplex (G4) with crystal violet as the G4-binding indicator.[70] G-quadruplexes are four-stranded DNA structures stabilized by coordination cations and some K^+-stabilized G-quadruplexes exhibit superior peroxidase-like activity. This effectively catalyzes a H_2O_2-mediated oxidation of 2,2′-azino-bis(3-ethlybenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), which causes a colorimetric and oxidative change. The technique has a detection limit of 82.2 ppt, well below the EPA limit. Another electrochemical DNA-based lead sensor has been developed, that involves vertically aligned conductive carbon hybridized TiO_2 nanotube (NT) arrays (DNA/C-TiO_2 NTs).[71] In this case, TiO_2 nanotubes were vertically aligned on a Ti substrate by anodic oxidation and then DNA was immobilized onto the substrate. This sensor exhibits a high sensitivity (2.1 ppt – 32.8 ppb), good selectivity (Mn^{2+}, Mg^{2+}, K^+, Fe^{2+}, Fe^{3+}, Co^{2+}, Cd^{2+}, Al^{3+}, Ag^+, Zn^{2+}, Ca^{2+}, Ba^{2+}, Sr^{2+}, and Hg^{2+}), and a wide pH range. The superior characteristics for lead sensing were attributed to the immobilization of abundant target biomolecules, DNA, and the enhanced bioelectrical activity. The

controllable carbon hybridized of the TiO_2 NTs increases the conductivity of the electrode, while retaining the tubular structure, biocompatibility and hydrophilicity.[71] The electrode can then be regenerated for multiple uses including numerous environmental sites.

Bouw and colleagues reported a low cost electrochemical sensor based on clay modified by 1,10-phenanthroline within montmorillonite (MMT).[72] Pb^{2+} is sensed by a carbon paste electrode (CPE) by adsorptive stripping voltammetry through the exchange of saturated sodium ions by Pb^{2+}. The low cost materials, ease of preparation and use, and low detection limit (82.2 ppt) make this method an attractive one for testing environmental samples, however, the approach suffers from a 70% reduction in Pb^{2+} signal in the presence of Hg^{2+}.[72] Another low cost approach, developed by Abbaspour *et. al.*, uses reusable and disposable carbon composite PVC-based membranes, where a Pt wire was coated with phenyl hydrazone derivative-carbon composite in PVC membrane.[73] The membrane sensors have a fast response time and can be reused for up to 70 days, and is fairly sensitive with a detection limit of 65.8 ppb. The new developments in reusable, disposable, and affordable electrochemical sensors has been exciting, however, there is a room for improvement in their selectivity as well as sensitivity. Also, these electrochemical techniques do not provide any spatial information, which is of interest to better understand the cellular distribution of lead.

Nanoparticles

Gold nanoparticles have been used in sensors because of their extremely high extinction coefficient in the visible wavelength range. Typically, even at nanomolar concentrations, the color change of the particles can be observed by the naked eye. Recently, Yang *et. al.* reported a bromide capped gold nanoparticles for sensing lead.[74] In this case, Pb^{2+} reacts with bromide ions to form $PbBr_2$ on the surface of the gold nanoparticles that exhibits luminescence by absorbing in the UV region (300 nm) with visible emission (600 nm). With an increase in Pb^{2+} concentration the color of the particles changes from red to light blue and even become colorless which can be visualized with naked eyes. Alkali metals cause no spectral changes. However, alkaline earth and heavy metals show small changes, and even with 4 to 5 equivalents of these ions, Pb^{2+} has been detected.[74] In this case, no rigorous synthetic or biological procedures to be adopted; the sensor is water soluble, and has the very desirable visible region optical properties but the detection limit is above EPA limit. Wang and Guo reported a new nanoparticle based lead sensor that utilizes fluorescence resonance energy transfer (FRET) for Pb^{2+} detection.[75] It comprised of a positively charged CdTe-QDs capped with cystamine (CA-CdTe-QD) and negatively charged AuNPs capped with 11-mercaptoundecanoic acid (MUA-AuNPs).[75] The lead assay utilizes FRET efficiency of the positively charged quantum dots (QDs) and the negatively charged gold nanoparticles (AuNPs) which in the presence of Pb^{2+} the electrostatic interaction of inhibited. They are water soluble and biocompatible, easy to operate, and little interference from physiological metal ions but the working range of this sensor is parts per million although the detection can be as low as 30 ppb. Fe^{3+} and Ag^{+} ions interfere with Pb^{2+} detection, which can be improved in this exciting sensor.

DNAzymes

DNAzymes were first reported in 1994 showing approximately an 100-fold increase in a lead ion dependent cleavage process of a double stranded DNA that is linked with a flurophore or a chromophore and a quencher, and when the double strand is cleaved a fluorescence or a difference in absorption is observed.[76] In general, DNAzyme-based Pb^{2+} sensors are composed of an enzyme and substrate strand and the addition of Pb^{2+} enables the DNAzyme to cleave its substrate. Several lead-specific DNAzyme were built on the 8–17 base pair that are capable of catalyzing a phosphodiester bond cleavage in the presence of Pb^{2+}. In 2003 Liu introduced a DNAzyme adhered to gold nanoparticles that allows tuning of the detection level over several orders of magnitude.[77] In this case, the 3′ strand of a DNA is binds to gold nanoparticles (diameter, 13 nm), which causes aggregation of the nanoparticle exhibiting a blue color. In the presence of Pb^{2+}, the complementary 5′ strand that can recognize the Pb^{2+} catalyzes a hydrolytic cleavage preventing the formation of the NP aggregates. This results in a red color, sensing the presence of Pb^{2+}. This system allows detection with different dynamic range that are present in various environments in question; for example the EPA has a limit of 15 ppb while the CPSC has limits in the part per million (ppm). Lan *et. al.* developed a catalytic beacon sensor for Pb^{2+} based on the first 8–17 DNAzyme that exhibited a higher metal ion selectivity (~ 40,000 times), than the previously reported Pb^{2+} sensors.[78] Wen developed a “mix-and-detect” fluorescent sensor for Pb^{2+} ions by using graphine oxide nanoprobes.[79] Upon addition of Pb^{2+}, the substrate strand was cleaved causing significant quenching of the fluorescence. As the Pb^{2+} concentration was increased, the fluorescence signal decreased in response to increased cleaved DNAzymes. The dynamic range was tuned to high concentration range by appropriate mixing of enzyme strands.[79]

There has been considerable interest in developing portable and small devices for onsite testing. Chang and colleagues developed a miniaturized DNAzyme in a nanocapillary interconnected microfluidic device.[80] They combined a lead-specific DNAzyme with a microfabricated device containing a network of microfluidic channels that are fluidically coupled via nanocapillary array interconnect.[80] This sensor is a unique combination of DNAzyme and microfluid-nanofluid and it has been applied to the determination of lead onsite of an electroplating sludge and reference material. Another small and easy to use device was developed by Wang, a computer-readable DNAzyme Pb^{2+} assay on disc.[81] A conventional compact disc (CD) was used as the platform for preparing DNAzyme assays and an unmodified optical drive of ordinary computers as the readout device. Pb^{2+} specific DNAzyme was immobilized on the “transparent side” of a conventional CD-R via mild surface reactions. The concentration of Pb^{2+} was determined with a diagnostic program that checks the error distribution on the CD. The errors increase linearly over a wide range of concentrations, 2 ppb to 200 ppm.[81]

A recent report in lead specific DNAzymes took advantage of the optical properties of a water-soluble cationic polythiophene (PT) and designed a fluorometric sensing assay for the detection of Pb^{2+}.[82] A simple “mix-and-detect” approach enables the detection of Pb^{2+} within 20 minutes due to the distinguishable optical properties of PT–dsDNA and PT–ssDNA. The detection was well below the standard EPA at 0.2 ppb but this methods has a

wide detection range, 2 ppb to 20 ppm, enabling diverse functional.[82] This method avoids modification and separation thus making this simple, sensitive, specific, and cost-effective approach showed great potential in environmental monitoring, waste management and cellular understanding.

DNAzymes and Nanoparticles

Recent developments have been made using a combination of nanoparticles and DNAzymes. Aside from the optical properties of the gold nanoparticles and DNAzymes, nanoparticles' diameters are related to their disperse state. Thus a change of the disperse state from discrete nanoparticles to aggregates will lead to the increase of their average diameter, which can be monitored by dynamic light scattering (DLS).[83,84] Miao and colleagues reported a dynamic light scattering sensor for Pb^{2+}, which was constructed with oligonucleotide-modified gold nanoparticles based upon its cleavage property for DNAzyme.[85,86] The basis for this method was to determine the signal of the average diameter of AuNPs (Figure 3). There are two strands, the enzyme strand and the substrate strand, which can hybridize with each other to form duplex structure DNAzyme. This structure can then be adsorbed on the surface of the AuNPs, preventing them from aggregating in the presence of NaCl. In the presence of Pb^{2+} the substrate strand of DNAzyme can be cleaved into single strand DNA (ssDNA) fragments and these ssDNA fragments are adsorbed on the surface of the AuNPs to inhibit aggregation in the presence NaCl. Thus, as the concentration of Pb^{2+} increases the diameter of the aggregates decreases linearly from 2.1 to 61 ppt. This method is relatively simple and inexpensive because the DNA is unmodified and not separated.

Organic Molecules

In the past 20 years fluorescent sensors have been investigated intensely for their potential in real-time monitoring that helps in understanding cellular metal accumulation, trafficking, protein trafficking, small-molecule signaling, organelle distribution, and cell viability, along with the simple, quick, and determining environmental contamination.[87–93] Fluorescence-based sensors can offer unparalleled sensitivity and thus have garnered significant interest. Traditional methodologies require collection, transportation, occasional pretreatment of the sample, and in many cases, expensive instrumentation operated by trained personnel.[28,56–58,94] Small molecule sensors are valuable not only as they are cost effective and user-friendly, but also for real time monitoring and garnering special information.[94] Among the different chemical sensors, fluorescence-based ones present many advantages: fluorescence measurements are very sensitive, it is possible to detect a single molecule, typically low cost, easily performed, versatile, and allow subnanometer spatial resolution.[94,95] This approach has contributed greatly to explaining the roles of calcium and related s-block metals in biology,[95] but similar chemical tools for d- and p-block transition and heavy metals remain somewhat open for study.[96]

Chen *et. al.* reported a ratiomentric fluorescent sensor based on polypeptide scaffolds equipped with a microenvironment-sensitive fluorophore.[96] This sensor emits at visible wavelength and has a quantum yield of 0.35.[96] He *et. al.* reported another fluorescent based

sensor called, Leadfluor-1 (LF1), that shows promise in probing lead in biological samples.[97] It has a selective turn-on response, visible excitation and emission profile useful for real time monitoring of living cells.[97] Ranyuk *et. al.* reported a anthraquinone-based receptor that functions as a colorimetric chemosensor for the selective recognition of lead in water.[98] This sensor was developed using a systematic approach based on single modification of a one-step available chromogenic macrocyclic backbone, thus this is convenient for the development of selective sensors for different metal ions.[98] By changing the nature and number of side arms this backbone can be adapted to the nature of the metal of interest. In the presence of 2–3 ppm lead, a distinct change in color can be observed by the naked eye; a detection limit of 21 ppb can be achieved with a spectrophotometer.[98] Visible detection with the naked eye holds a great prospect for quick detection.

Alongside the development of devices, small organic molecules have been imbedded and immobilized in various substances. A most recent example of this immobilization was reported by Aksuner *et. al.*,[99] in which a novel triazolo-thiadiazin derivative was immobilized in PVC. The sensor displays a response for Pb^{2+} over a concentration range of 10 ppb to 78 ppm with the detection limit of 4.5 ppb.[99] In addition to high reproducibility and reversibility of the fluorescence signal, the sensor also exhibits good selectivity over common metal ions (Na^{+}, K^{+}, Ca^{2+}, Mg^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Mn^{2+}, Fe^{3+}). The membrane is easily prepared, stable, rapid, and is simple. The accuracy of the proposed sensor was confirmed by analyzing standard reference materials of natural water and surface water.

Another small organic sensor was developed in 2009 by Marbella *et. al.*[100] It is a unique fluorescent sensor both in structure and binding. Many fluorescent sensors have a flexible framework allowing the coordination to the metal ion, while this molecule has a rigid structure allowing alterations to be imposed without affecting the binding site. Intestingly, only a few metal ion sensors have solely a rigid framework. This sensor, called ‘leadglow’ (LG) was found to have a ‘turn-on,’ ratiometric response to Pb^{2+} in aqueous solution.[100] The free ligand has an excitation at 415 nm and an emission at 465 nm. Conversely, the Pb^{2+} bound ligand has an excitation at 389 nm and an emission at 423 nm.[100] Additionally, LG is able to detect Pb^{2+} at a wide pH range (4–10). This allows for the determination of Pb^{2+} in a variety of samples: slightly acidic, neutral, and basic pH levels. LG was compared with the EPA approved method. Determination of trace elements in waters and wastes by ICP-MS. By comparing the quantification of Pb^{2+} in SRM® 3128 Lead Standard Solution by both LG and ICP-MS, the two methods were found to be statistically equivalent. LG offers a wide variety of choices from tuning the excitation with the addition of functional groups to the incorporation into a matrix for ease of use. LG shows promise in becoming a simple method to detect Pb^{2+} in environmental samples.

As environmental and on site testing is of great interest to prevent and monitor lead contamination, advance in small and simple devices has grown. Zhao *et. al.* developed a micro-fabricated device for detection in water.[101] It was based on a selective and sensitive fluorescent molecular sensor for Pb^{2+}, Calix-DANS4.[101] The micro-chip based lead sensor detected by using a configuration in which the sensing molecules are excited by two optical fibers each one connected to a 365 nm UV LED source, and the light collection is made by

another optical fiber with a photomulitplier tube. The detection limit is below the EPA limit, permitting onsite testing of rivers and lakes. A recently developed devices used a calixarene bearing three dansyl groups and one long alkyl chain terminated by an alcohol function.[102] Calix-DANS3-OH was grafted on the wall of a PDMS microfluidic device. It has emission properties in the visible region and a detection limit ~42 ppb.

Polymeric materials with chromophore or flurophores have also garnered interest because of their potential applications. In 2005 Kim and co-workers reported a structurally simple polymer that was sensitive for lead in aqueous environments.[103] In the presence of lead, the polymer fluorescence is quenched. More recently, a polydiacetylenes (PDAs) were reported for lead sensing.[104] In the presence of lead the polymers displayed a selective colorimetric change and a significant fluorescence enhancement. PDAs have an intense blue color and when in the presence of lead a transition to a bright pink occurs, a change in color that can be easily seen with the naked eye.[104]

Concluding remarks

Lead, has been a major threat to human and environmental health and it continues to be a persistent problem, though its industrial usage has decreased drastically. Several countries are dealing with outbreaks of lead poisoning while others are dealing with high levels of lead in their water systems. New findings highlight the detrimental effect of lead even at a very low concentration. In order to better manage these problems new techniques for detection have been developed, and or modifications to more established techniques have been made, which also helps in understanding its mechanism of action.

Selection of the best probe is based on the testing environment and purpose. Detection limit of probe and necessary sensitivity, state of sample (solution, solid, biological, etc.), testing environment (access to laboratory or on-site testing), and information desired (real-time imaging, concentration, or simple detection) all must be considered when selecting a probe. Electrochemical techniques have been extensively used but with the development of new probes (DNA, organic, and Bismuth based) this method has become safer, easier, and significantly more accurate. Electrochemical probes are easily used in the analysis of aqueous samples and with the development of portable electronics electrochemical probes can now be applied to on-site testing. Among various detection techniques optical detection appear to be the most convenient methods due simplicity and detection limits. Among these techniques fluorimetry is highly impressive for its high sensitivity, fast kinetics, and high spatial resolution among in situ application, real-time monitoring in both environmental and in vivo imaging. DNAzymes and nanoparticles have become a widely growing field for their unprecedented detection abilities, the combination of the two also can produce personalized sensors. DNAzymes are usually resistant to hydrolysis and allow for easy modification for the detection of a range of metal ions.

Organic molecules, especially fluorescent molecules, offer the necessary real-time and sensitivity desired for living specimen. These molecules can be modified for use in multiple solvents. Small molecules also have been synthesized with high selectively, great for mechanistic understanding of *in vivo* studies. Through the compilation of the some of the

most promising techniques for the detection of Pb^{2+}, it is concluded that customized sensors can be developed using many aspects (DNAzyme, nanoparticle, fluorescent, organic, electrochemical) depending are their intended usage. More generally the development of sophisticated detection methods can lead to a better understanding of Pb^{2+} toxicity, through the real-time monitoring of lead in organisms.

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Acronyms

CDC	Center of Disease Control
BLLs	Blood lead levels
DBPs	Disinfectant by-products
EBLs	Elevated blood levels
EPA	Environmental Protection Agency
MCGL	Maximum containment level goal
FDA	Food and Drug Administration
CPSC	Consumer product safety commission
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-AES	Inductively coupled plasma atomic emission spectrometry
GFAAS	Graphite furnance atomic adsorption spectroscopy
ASV	Anodic stripping voltammetry
CSV	Cathodic stripping voltammetry
AdSV	Adsorptive stripping voltammetry
MFE	Mercury film electrode
HMDE	Hanging mercury drop electrode
Bismuth film electrode	
SPEs	Screen-printed electrodes
DPV	Differential pulse voltammetry
MMT	Montmorillonite
CPE	Carbon paste electrode
NP	Nanoparticles
DLS	Dynamic light scattering
AuNPs	Gold nanoparticles

ssDNA	Single strand DNA
PVC	Polyvinyl chloride
PVC	Polydiacetylenes

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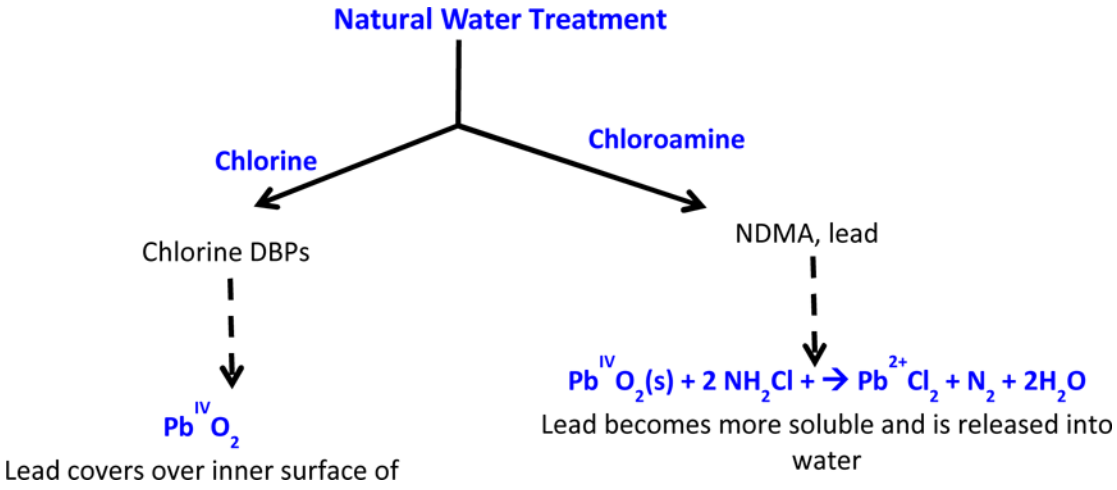

Figure 1.

A schematic of purification processes for drinking water. Chlorination generates chlorine disinfection by-products (DBPs) but oxidizes lead to a slightly insoluble Pb^{4+} state. Chloramine causes increased release of lead from plumbing, it is a weaker oxidant that does not oxidize Pb^{2+} to Pb^{4+}

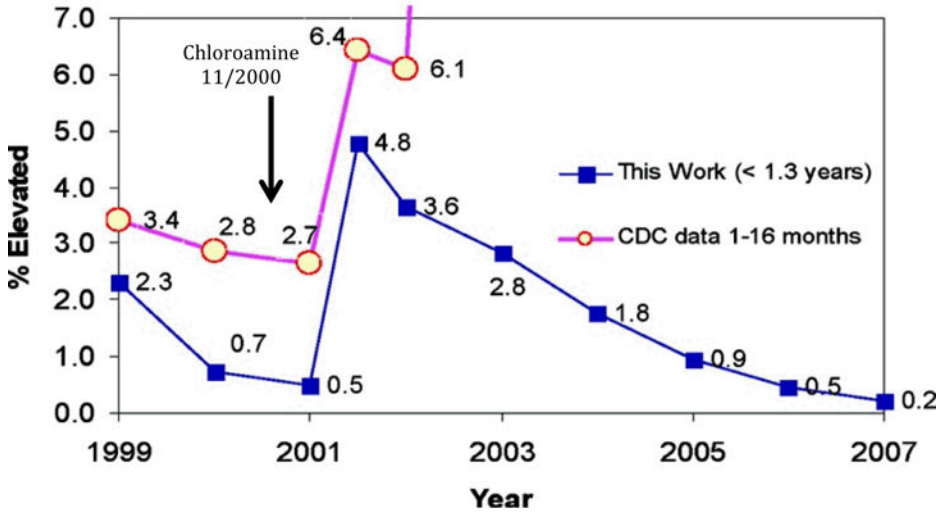

Figure 2.

Trends in elevated blood lead levels (EBL) incidence for children aged ≤1.3 years taken from reference[40] with permission.

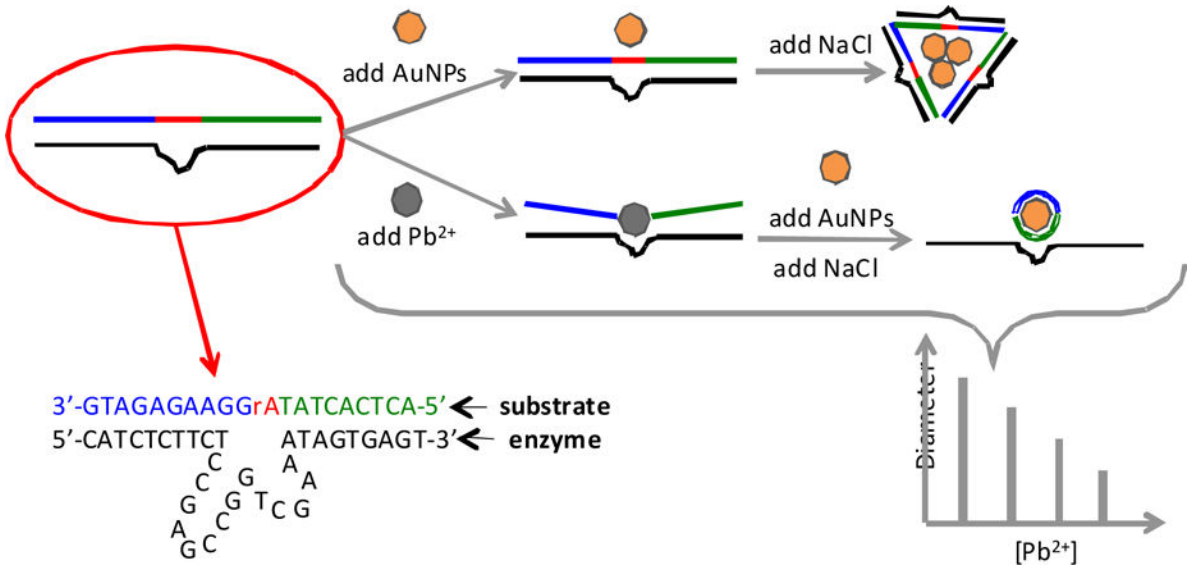

Figure 3.
Schematic illustration of Pb^{2+} detection using DLS.[85,86]

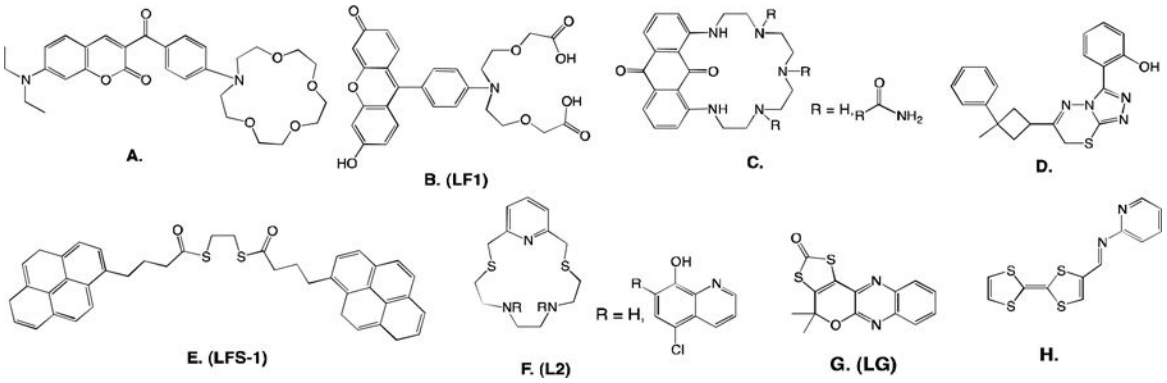

Figure 4.

Small organic lead sensors. A.) Ketoaminocoumarin[96] B.) Leadfluor-1, **LF1**[97] C.) 1,8-diaminoanthraquinone[98] D.) Triazolo-thiadiazi, imbedded in PVC[99] E.) Lead fluorescent sensor, **LFS-1**[104] F.) 5,8-bis((5′-chloro-8′-hydroxy-7′-quinolinyl)methyl)-2,11-dithia-5,8-diaza-2,6-pyridinophane, L2, imboilized in PVC[105] G.) Leadglow, **LG**[100] H.) Imine-bridged TTF-pi-pyridine derivative[109]

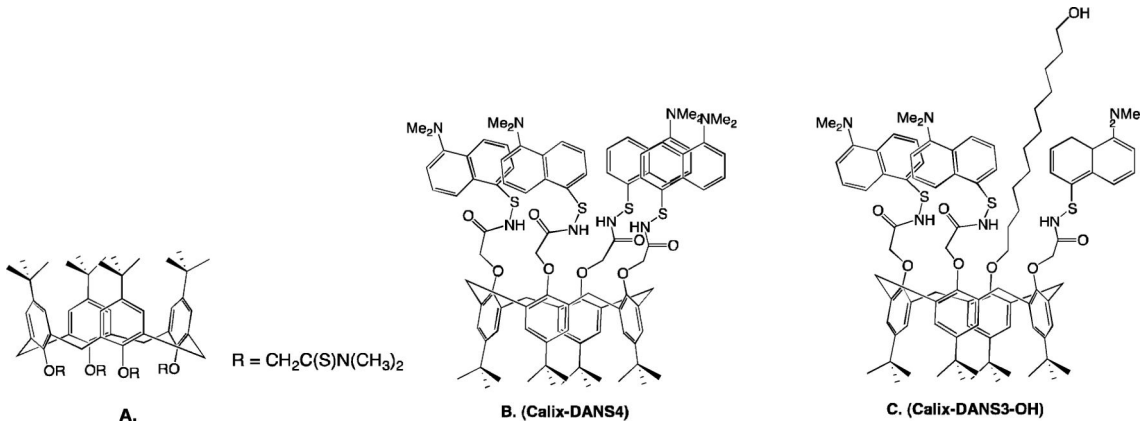

Figure 5.

Macro-organic lead sensors. A.) Ionophore imbedded in PVC[107] B.) Calix-DANS4[101] C.) Calix-DANS3-OH incorporated into a PDMS microfluidic chip[102]

Table 1

List of Standardized Lead Levels.

	Agency	Focus	MCL
United States	EPA	Drinking Water	15 ppb
		Air	1.5 μg/m^3
	CPSC	Children's Toys (12 or younger)	100 ppm
		Paint	600 ppm reduced to 90 ppm
	FDA	Food and Dishware	0.5 – 7.0 ppm leaching solution
Canada	Health Canada	Drinking Water	10 ppb
		Air	N/A
		Children's Toys (12 or younger)	90 ppm
EU	European Commission	Drinking Water	10 ppb
		Air	0.5 μg/m^3
		Children's Toys (12 or younger)	N/A
International	WHO	Drinking water	10 ppb

Table 2

List of different Techniques used in lead detection.

Class	Reagent (support matrix)	Method	Signal Properties	Detection Limit	Range	Selectivity	Year	Ref
Electrochemical	Bi-SPE	ASV	N/A	0.15 ppb	0.5 – 100 ppb	unknown	2011	69
	G-quadruplex with crystal violet	DPV	N/A	82.2 ppt	0.2 – 205 ppb	good	2011	70
	1,10-phenanthroline	ASV	N/A	82.2 ppt	N/A	nonspecific	2011	72
	DNA/C-TiO_2 NTs	ASV	TiO_2	0.7 ppt	2.1 ppt – 32.8 ppb	good	2010	71
	carbon composite PVC-based membrane	ASV	Pt wire	65.8 ppb	0.158 – 20,548 ppm	good	2010	73
Nanoparticles	Au nanoparticles	Fluorescence Absorbance	Ex: 330nm Em: 600nm	247 ppb	N/A	poor	2012	74
	Au nanoparticles and DNAzymes	DLS	Adsorption at ~540 nm	1.3 ppt, 7.2 ppt	2.1 – 61.1 ppt	good	2012, 2011	85,86
	CdTe-QDs	Fluorescence	Ex: 525nm Em: 560nm (QY =0.07)	30 ppb	0.22–4.51 ppm	good	2009	75
DNAzymes	cationic polythiophene (PT) DNAzyme	Fluorescence	N/A	0.2 ppb	0.002 – 20 ppm	good	2012	82
	DNAzyme with graphene oxide	Fluorescence	Em: ~565 nm	100 ppt	N/A	good	2011	79
	Computer-Readable DNAzyme on Disc	Error Distribution of CD	N/A	2ppb	0.002–205 ppm	good	2011	81
	GR-5DNAzyme	Fluorescence	N/A	0.76 ppb	N/A	good	2010	78
	DNAzyme in amicrofluidic device	LIF	Ex: 488 nm Em: 518 nm	2.3 ppb	0.020.5 – 20.5 ppm	good	2005	80
	DNAzyme-Au-NPs	Absorbance	Abs: 522 & 700 nm	can be tuned	can be tuned	good	2003	77
Small Molecules	Calix-DANS3-OH (PDMS microfluidic chip)	Fluorescence	Ex: 365 nm Em: 496 nm	42ppb	N/A	good	2012	102
	triazolo-thiadiazi (imbedded in PVC)	Fluorescence	Ex: 330 nm Em: 430 nm QY=0.039	4.5 ppb	0.010.2 – 78.1 ppm	good	2011	99
	PDA-polymer	Fluorescence	Ex: 254nm Em: 540 nm	0.8 ppm	N/A	good	2011	104
	LFS-1	Fluorescence	Em: 469 nm	N/A	N/A	good	2011	105
	L2 (immobilized on PVC)	Fluorescence	N/A	41 ppb	0.062 – 5137 ppm	N/A	2010	106
	Arsenazo III (immobilized on XAD-16)	Reflectance	N/A	10 ppb	0.205–20.5 ppm	N/A	2010	107
	Lead-selective ionophore (immobilzed on PVC)	Absorbance	N/A	5 ppb	0.007 – 10.7 ppm	N/A	2010	108
	BODIPY-functionalized Fe3O4.SiO2 nanoparticles	Fluorescence	Ex: 326&596 Em: 456 nm (QY=0.042)	1.5 ppb	0 – 30 ppb	good	2010	109
	Calix-DANS4	Fluorescence	Ex: 365 nm	5 ppb	N/A	N/A	2009	101
	1,8-diaminoanthraquinone	Absorbance	Abs: 524 nm	Eye: 2–3 ppm UVvis: 21 ppb	N/A	good	2009	98
	Imine-bridged TTF-pi-Py	Absorbance and Electrochemical	Abs: 508 nm	micromolar	N/A	Zn2+ interferes	2009	110

Class	Reagent (support matrix)	Method	Signal Properties	Detection Limit	Range	Selectivity	Year	Ref
	Leadglow (LG)	Fluorescence	Ex: 389 nm Em: 423 nm	10 ppb	1 –50 ppb	good	2009	100
	LF1	Fluorescence	LF1:Pb2+: Em:514 (QY=0.013)	<15 ppb	N/A	good	2006	97
	Ketoaminocoumarin (solution)	Fluorescence	Ex: 411nm Em:491 (QY=0.35)	N/A	N/A	good	2002	96

Selectivity: good (Mn^{2+}, Mg^{2+}, K^{+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Cd^{2+}, Al^{3+}, Ag^{+}, Zn^{2+}, Ca^{2+}, Ba^{2+}, Sr^{2+}, and Hg^{2+}), N/A (unknown - not known or only a few metal ions tested), nonspecific.