Environmental Chemistry for a Sustainable World 60

Vineet Kumar · Praveen Guleria
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Eric Lichtfouse *Editors*

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Preface

Food security is a major issue for human health in the context of climate change, global pollution, and rising population. In particular, the identification of contaminated food should improve food quality, yet classical analytical techniques are limited. This challenge has been solved by the recent development of nanosensors for food and the environment. Nanosensors enable ultrasensitive detection of multiple contaminants. Nanosensors are very specific because they are designed to bind selectively with some contaminants. Here, functional or biological recognition of the contaminant triggers an electric signal, which is converted into a readable computer graphic. This book gathers recent advances in the development of nanosensors for food, agriculture, and the environment. Nanosensors for the detection of heavy metals are reviewed in Chaps. 1, 2, and 3 by Bereli et al., He et al., and Xuyan et al., with focus on electrochemical, piezoelectric, optical, and colorimetric sensors and fluorescence sensors based on aggregation-induced emission (AIE). Biofilm-based nanosensors for monitoring pollutants such as toxins, hormones, and dioxins are presented by Nikoleli et al. in Chap. 4. Chapter 5 by Teodoro et al. reviews chemical sensors, including e-tongues (Fig. 1), and discuss the use of green composites, for example, cellulose and proteins.

Toxicity, risk assessment, and bioaccumulation of nanosensors are discussed in Chap. 6 by Heikal and Abdel-Aziz. Chap. 7 by Abdel-Aziz and Heikal reviews nanosensors and nanobiosensors in agriculture, with focus on the detection of bacteria, mycotoxins, pesticides, and drugs. Chapter 8 by Cimen et al. elaborates different sensing strategies for the detection of food contaminants. Chapter 9 by Manubolu focuses on sensing and removing mycotoxins from agricultural products and food samples. In Chap. 10, Karahalil discusses the use of nanomaterials for the detection of contaminants in food. Nanosensors based on quantum dots, carbon, dendrimers, liposomes, metal oxides, and dendrimers are reviewed in Chap. 11 by Sing and

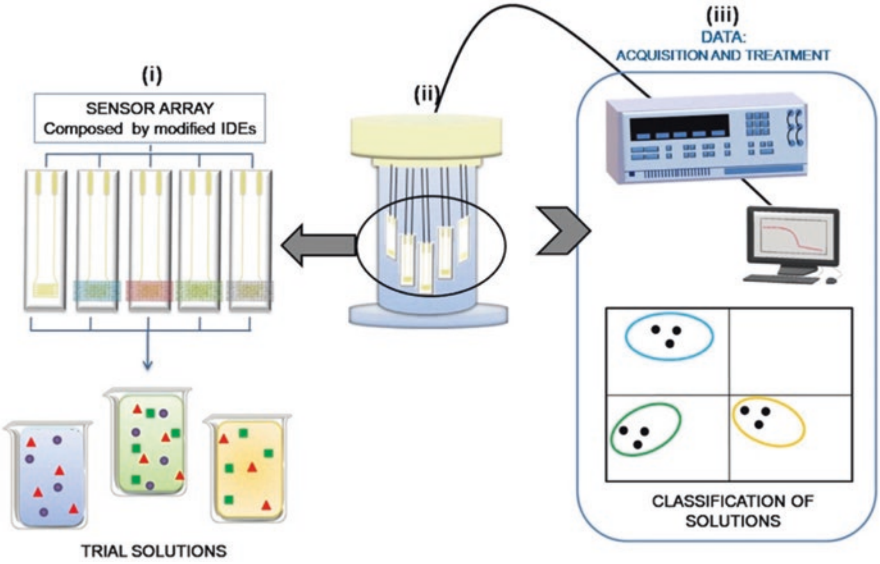

Fig. 1 The experimental setup of a typical e-tongue: (i) interdigitated electrodes (IDEs) modified with distinct materials, (ii) measurement cell containing the sensor array immersed in the liquid under investigation, (iii) data analysis of trial solutions collected using the e-tongue generates a large amount of data, which can be classified and distinguished by statistical analysis.

Sing. In Chap. 12,, Nikoleli et al. review biosensor with emphasis on size reduction of lipid film devices, new sensing techniques, and transduction.

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Contents

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Eric Lichtfouse is an environmental chemist at the University of Aix-Marseille, France, and visiting professor at Xi'an Jiaotong University, China. He has invented carbon-13 dating. Dr. Lichtfouse is teaching scientific writing and communication, and has published the book *Scientific Writing for Impact Factors*. He is founder and chief editor of scientific journals and series on environmental chemistry and agriculture. He received the Analytical Chemistry Prize from the French Chemical Society, the Grand Prize of the Universities of Nancy and Metz, and a Journal Citation Award by the Essential Indicators.

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Chapter 1
Sensors for the Detection of Heavy Metal Contaminants in Water and Environment

Nilay Bereli, Duygu Çimen, Handan Yavuz, and Adil Denizli

Contents

Abstract Environmental pollution by heavy metals is a global problem. The main sources of waste are industrial or domestic products and heavy metal–containing pesticides and fertilizers. Heavy metal contamination poses a serious danger to the human health and environment. Heavy metals are among the important environmental pollutants because of their toxic effects on plants, animals, and humans, even at very low concentrations. Moreover, they have non-biodegradable property and accumulation in the food chain. Currently available methods for determination of metal ion levels in water include chromatographic and spectroscopic methods. These chromatographic and spectroscopic methods are costly methods that require intense technical training because of their time-consuming and complicated proce-

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dures. The development of sensors for monitoring of toxic metals especially in water and environment is very important. The nano and functional material-based chemical sensors have been extensively employed for the detection of heavy metals. These sensors have advantages such as high selectivity, sensitivity, portability, on-site sensing capability, and improved performance of the devices. This chapter will outline the broad contours of heavy metals and the practical applications for their detection, with sensors, in the water and environment.

Keywords Heavy metals · Sensors · Sensitive determination · Monitoring · Waste water · Environment · Optical sensors · Electrochemical sensors · Colorimetric sensors · Piezoelectric sensors

1.1 Introduction

The growing number of pollutants requires the development of sensitive, rapid, precise, specific, and easy-to-use innovative analytical devices to meet the increasing demand for the environmental pollution control and early warning. Quantitative analysis of samples is usually carried out by conventional analytical methods such as spectroscopic and chromatographic techniques to detect different environmental contaminants. These methods are accurate and sensitive, but they require expensive instrumentation and also expert staff to operate them with multistep sample preparation. It is difficult to achieve on-site, real-time, and high-frequency monitoring of contaminants by these labor-intensive and time-consuming methods (Bellan et al. 2011). The potential for environmental pollution requires the development of rapid and simple detection methods for organic, inorganic, and pathogenic pollutants' monitoring. The pollutant recognition is vitally important in some emergent situations. Therefore, novel devices with superior sensing capabilities and increased spatial localization are needed urgently. Researchers have been striving for the development of cost-effective, robust, and automated water-monitoring devices for sensitive and rapid analysis of environmental pollutants.

Heavy metal ions are released to the environment through industrial activities or by end-user products. In the environment, they ultimately come in contact with water and accordingly they contaminate the water, including ground water, lakes, oceans, and rivers. The water contaminated by heavy metal ions (such as lead, mercury, and arsenic ions) can cause acute and chronic health problems in humans and seriously affect aquatic life (Kim et al. 2012; Lin et al. 2011; Song et al. 2016; Weng et al. 2014). Therefore, it is extremely important to monitor the toxic metal ion levels in drinking water as well as other water sources to improve public health and protect aquatic life (Chen et al. 2013). Currently available methods for determination of metal ion levels in water include inductively coupled plasma mass spectrometry (ICP-MS), high-performance liquid chromatography (HPLC), and atomic absorption spectrometry—AAS (Kim et al. 2001; Udhayakumari et al. 2014;

Bontidean et al. 1998; Erdem et al. 2018). While these chromatographic and spectroscopic methods offer high sensitivity and selectivity, these costly instruments require intense technical training because of their time-consuming and complicated procedures. Electrochemical or membrane-based methods have been also developed for detection of metal ions in water (Pesavento et al. 2009; Van Leeuwen et al. 2005). However, these methods often suffer from their poor selectivity.

Sensors that combine chemistry, biology, physics, nanotechnology, and electronics can follow developments in risk management approaches and environmental legislation because of their original characteristics such as specificity, sensitivity, real-time remote monitoring capability, and ease of use (Rogers 2006). Sensors provide fast, highly accurate, real-time, and high-frequency monitoring without any time-consuming sample enrichment, and sample pre-processing steps are effective alternatives to traditional analytical methods (Thevenot et al. 2001). Though their use in the field of environmental pollution control is still in the early stages, sensors have great potential applications in the areas of environmental monitoring, drug development, food safety, diagnosis, and biomedical research (Borisov and Wolfbeis 2008; Yılmaz et al. 2017a, b). Unfortunately, dispersed molecules that are diffusing freely into the solution are far from having sensitive surfaces in practical applications. In this regard, different types of sensors are promising devices, in that they combine their unique features such as high sensitivity, specificity, label-free and quantitative detection, inexpensiveness, and miniaturization.

1.2 Principle of Sensors

A sensor is a compact analytical device that consists of three parts: (i) a sensing receptor, (ii) a transducer, and (iii) a detector with a digital output (Goode et al. 2015). A sensor is a self-contained integrated device that is able to convert chemical signal depending on analyte concentration into a measurable analytical signal (Fig. 1.1). Figure 1.1 shows the basic components of the sensors. As can be concluded from the figure, sensors have unique advantages over conventional methods, like variety in the target structures, simple construct, and diversity in the detection techniques (Verma and Bhardwaj 2015; Altintas and Tothill 2013).

Sensors possess many advantages such as specificity, sensitivity, portability, quick response time, and so on, which are fabricated for various purposes, including heavy metal detection (Verma and Bhardwaj 2015). They are suitable for single analysis, multi analysis, short-term analysis, long-term implantable analysis, as disposable sensors, and also for environmental monitoring.

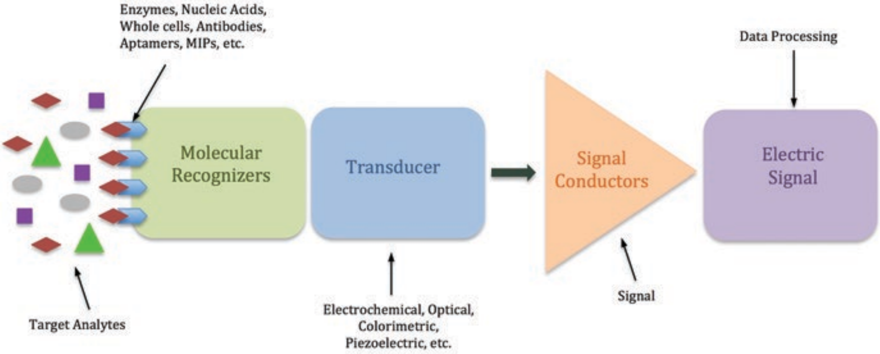

Fig. 1.1 The basic components of the sensor system

1.2.1 Electrochemical Sensors

In recent years, electrochemical sensors have exhibited several advantages over other analytical methods. Compared with the spectroscopic, chromatographic, and electrophoretic methods, electrochemical methods are more preferable and have attracted increasing attention because of their high sensitivity, low cost, fast response, portability, simple operation, and on-site operation (Kimmel et al. 2012; Yu et al. 2016a, b). Electrochemical sensors have been widely used for sensitive and selective determination of the environmental, clinical, and biotechnical targets. They are based on the control of electrical signal and its correlation to analyte concentration. These sensors represent a typical system for the construction of sensors, which include semi-conductors and screen-printed electrodes. These types of sensors can be classified into three major groups: (i) amperometric, (ii) potentiometric, and (iii) impedimetric transducers. In addition, these sensors have been employed to detect a variety of targets such as bacteria, pesticides, and heavy metal ions (Luo et al. 2013; Wang et al. 2015; Cui et al. 2015).

1.2.2 Piezoelectric Sensors

Mass-sensitive sensor devices work based on measuring the changes in properties of piezoelectric or magnetoelastic material via increased mass of molecules on sensor surface. Mass-sensitive sensors can work at both liquid and gas phases. Mass-sensitive devices can use quartz crystal microbalance (QCM), microcantilever, or magnetoelastic sensors (Nieuwenhuizen and Venema 1991; Li et al. 2010; Raiteri et al. 2001).

Figure 1.2 shows a schematic illustration of piezoelectric effect. In a piezoelectric material, the positive and negative charges are randomly distributed in each part of the surface. When some pressure on the material is applied, positive and negative

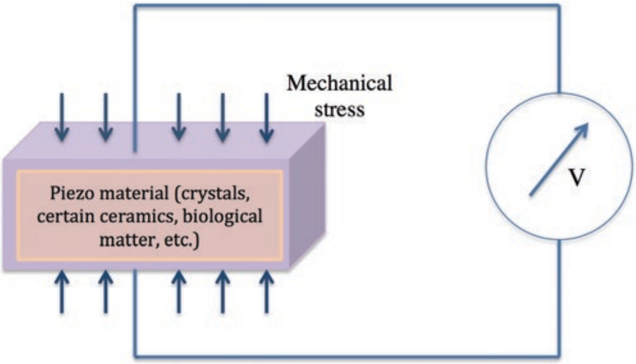

Fig. 1.2 Schematic illustration of piezoelectric effect

charges in the molecules are separated from each other. This polarization generates an electrical field and can be used to transform the mechanical energy used in the material deformation into electrical energy.

Piezoelectric biosensors, including the quartz crystal microbalance (QCM), utilize the sensitivity of piezoelectric crystal resonance to perturbations in the surrounding environment (Marx 2003; Cooper and Singleton 2007). The quartz crystal microbalance (QCM) as a piezoelectric sensor is a physical, nanogram-sensitive device that is able to detect variations in the resonance frequency of an electrically driven quartz crystal with changes in thickness or mass per unit area, when adding (loaded quartz) or removing (unloaded quartz) small masses, or when occurs oxide growth/decay, thin film growth/deposition, a biochemical interaction, or a catalysis at the surface of the quartz (Giamblanco et al. 2015; Karaseva et al. 2016).

1.2.3 Optical Sensors

Optical sensors focus on the measurement of a change in the optical characteristics of the transducer surface when target and recognition element form a complex. They have been widely used in fundamental biological studies, health science research, drug discovery, clinical diagnosis, food analysis, and environmental and agriculture monitoring (Shankaran et al. 2007; Saylan et al. 2017b; Yılmaz et al. 2017a, b; Saylan et al. 2017a). This sensor method of transduction has been used in many classes of sensors due to many different types of spectroscopy such as absorption, fluorescence, Raman Surface enhanced Raman spectroscopy (SERS), phosphorescence, refraction, and dispersion spectroscopy (Muslim et al. 2012). Optical-based biosensors are able to provide a label-free, real-time, and parallel detection.

1.2.4 Colorimetric Sensors

With the use of enzyme-linked sensitive thermistors, heat change was measured during enzyme substrate interaction for the first time by Danielson and Mosbach (1979). Colorimetric devices work on the basis of measurement of heat absorbed or evaluated during the chemical reactions between molecules (Mosbach 1991; Xie et al. 2000; Ramanathan and Danielsson 2001). Initially, the colorimetric transduction was employed for enzyme-based biosensor but has subsequently been applied in cells and immunosensors (Ahmad et al. 2010). The colorimetric sensors use thermistors that transform heat generated during a reaction into an electrical signal. The analyte is the substrate for the enzyme (Dinh and Cullum 2000). Recently, colorimetric sensor method has found uses in food industry and environmental monitoring (Kirchner et al. 2012).

1.3 Application of Sensors for Heavy Metal Detection in Environment

Usages of heavy metals have increased with industrialization, and this has caused heavy metal pollution, which is an important problem that needs to be solved. Heavy metals are non-degradable and accumulate in the environment. Arsenic, chromium, lead, copper, nickel, zinc, and cadmium are the most commonly found heavy metals in waste water, and all of these metals cause risk for human health. Heavy metal toxicity can damage the brain, liver, lungs, kidney, and other organs. Long-term exposure causes degeneration of muscular and neurological tissues (Zhao et al. 2012).

Accordingly, there is an expanding need for the development of innovative environmental monitoring and warning system enabling rapid, sensitive, and specific detection, cost-effective and field-portable screening methods. Recent developments in sensors, which allow for real-time, sensitive, and label-free detection, offer a promising alternative to conventional environmental analysis techniques, including spectroscopic, chromatographic, and electrochemical methods. Construction of the recognition element for interacting with the targets is the fundamental feature of sensors, with high affinity and high specificity used as recognition elements (Van Dorst et al. 2010; Wanekaya et al. 2008).

1.3.1 Electrochemical Sensing for Heavy Metals

Rudnitskaya et al. developed an array of potentiometric sensors with chalcogenide glass membranes for heavy metal ion detection. They reported 0.2, 0.4, 0.06, and 30 nmol/L for Cu(II), Pb(II), Cd(II), and Zn(II) in individual buffer solutions, respectively. They studied the capability of the sensor to detect these ions in combined buffer solutions at the background of 0.5 M NaCl or artificial seawater. They reported 1 nmol/L detection concentration value for copper and zinc and 2 nmol/L for lead and cadmium. They showed suitable detection sensor array for Cu(II) and Zn(II) detection at the concentrations corresponding to the chronic seawater criteria, and Pb(II) and Cd(II) at the acute seawater criteria (Rudnitskaya et al. 2008).

Avuthu et al. prepared an electrochemical sensor, which was screen printed on polyethylene terephthalate. The response of the sensor showed that conventional printing processes are used for heavy metal ion detection. Carbon- and silver-based inks were used for metallization of the working, counter, and reference electrodes. Cyclic voltammetry response of the sensor resulted in reduction peaks at 0.2 and −0.6 eV for the selective detection of Hg^{2+} and Pb^{2+}, respectively. An 87% and 9% change in the average peak currents were detected for the 50 μM concentration of Pb^{2+} and Hg^{2+}, respectively (Avuthu et al. 2016).

Lee et al. prepared an electrode by using Fe_2O_3 nanoparticle/graphene composite for the sensitive and selective detection of Cd^{2+}, Zn^{2+}, and Pb^{2+}. The linear range of the electrode was 1–100 μg L^{-1}. The detection limits were 0.08 μg L^{-1} for Cd^{2+}, 0.11 μg L^{-1} for Zn^{2+}, and 0.07 μg L^{-1} for Pb^{2+}. Repeatability was found to be 0.92% for Cd^{2+}, 1.68% for Zn^{2+}, and 1.69% for Pb^{2+} for single sensor with ten measurements and 1.15% for Cd^{2+}, 0.89% for Zn^{2+}, and 0.91% for Pb^{2+} for five different composite electrodes (Lee et al. 2016).

Shen et al. presented a highly selective and sensitive microfluidic electrochemical sensor for detection of heavy metals. Cd^{2+}/Pb^{2+} detection was achieved by this device using square-wave anodic stripping voltammetry. The detection limits were found to be 1.2 μg/L for Cd^{2+} and 1.8 μg/L for Pb^{2+} (Shen et al. 2017). Hwang et al. developed a modified nanoporous bismuth electrode sensor that measures successfully Cd^{2+} and Pb^{2+} in tap water even after over 40 times of measurements by a separate Bi/Sn electroplating process. The calibration curves showed strong correlations with respect to various concentrations of Cd^{2+} and Pb^{2+} with the limit of detection of 1.3 ppb for Cd^{2+} and 1.5 ppb for Pb^{2+} (Hwang et al. 2019). Liu et al. overviewed on recent advances in nanomaterial-enabled screen-printed sensors based on carbon, metal, and metal oxide nanomaterials. The modification strategies in heavy metal ion sensors and the application of these sensors for the analysis of heavy metal ions in real samples were discussed (Liu et al. 2019). Other studies for detection of heavy metal ions are summarized in Table 1.1.

1.3.2 Piezoelectric Sensing for Heavy Metals

Huang et al. developed a melanin-coated QCM sensor via cross-linking method to determine metal ions and they also examined the binding affinity of metal ions against melanin. The surface morphologies of melanin thin film upon binding to metal ions were characterized by atomic force microscopy (AFM), circular

Table 1.1 Different electrochemical sensor applications for heavy metal detection in literature

Methods	Metal ions	Linear range	LOD	References
Voltammetric	Pb^{2+}, Cu^{2+}, Cr^{2+}, As^{2+}	0.0071–0.0083 M	7.12, 8.12, 7.17, 7.34 × 10^{-9} M	Vimala and Vedhi (2019)
Graphene oxide-based	Pb^{2+}, Cu^{2+}, Hg^{2+}	12.8–200 ppb	0.4, 0.8, 1.2 ppb	Gong et al. (2014)
Bimetallic PtAu alloy Nanoparticles/ electrospun carbon Nanofibers	Cd^{2+}, Pb^{2+}, Cu^{2+}	0.50–1.0 μM	0.10 μM	Zhang et al. (2017)
Conducting polymer based	Na^{+}, K^{+}, Mg^{2+}, Sr^{2+}, Mn^{2+}, Al^{3+}, As^{5+}, Zn^{2+}, Fe^{2+}, Fe^{3+}, Pb^{2+},Cu^{2+}, Cr^{6+}	100 ppb–100 ppm	2.19 × 10^{-7} M	Dutta and Panda (2018)
Square-wave stripping voltammetry	Cu^{2+}	5–200 μg L^{-1}	2 μg L^{-1}	Wang et al. (2018)
Screen-printed electrode	Hg^{2+}	0.5–10 mg L^{-1}	0.2 mg L^{-1}	Fernández et al. (2015)
Square-wave voltammetry	Hg^{2+}	1.0 × 10^{-8} –1.0 × 10^{-5} M	5.8 × 10^{-9} M	Lahrich et al. (2016)

dichroism, and infrared spectroscopy. Detection of metal ions including Hg^{2+}, Sn^{2+}, Li^{+}, Zn^{2+}, Cu^{2+}, Ni^{2+}, Ge^{4+}, Bi^{3+}, Co^{2+}, Ag^{+}, Al^{3+}, and Fe^{3+} was carried out. The prepared piezoelectric sensor system showed sensitive detection for Hg^{2+} with 518 ± 37 Hz/ppm (Huang et al. 2007). Cao et al. developed copolymer-coated sensor that was used for detecting heavy metal ions via the quartz crystal microbalance (QCM) method (Cao et al. 2011). The copolymer was synthesized by free radical copolymerization of MBTVBC as a hydrophobic monomer and VIM as a main monomer. The surface morphologies of the copolymer-coated quartz crystal microbalance were characterized by atomic force microscopy. The experimental results showed that the prepared sensor has high sensitivity, stability, and selectivity for the detection of Cu^{2+} in aqueous solution. The lowest limit of detection was obtained at 0.01 mg/mL Cu^{2+}. They also studied repeatability and reliability of the QCM sensor and achieved stable adsorption equilibrium for each Cu^{2+} aqueous solution.

Sartore et al. reported an effective way to obtain surface-modified gold electrodes with high heavy metal ions' complexing capability. In order to achieve this, multifunctional polymers of polyamidoamine (PAA) type was grafted on preaminated gold via covalent bonding. For this purpose, they developed a flow-type quartz crystal microbalance (QCM) sensor. The unmodified and modified gold surfaces were also characterized by X-ray reflectivity (XRR) and total reflection X-ray fluorescence (TXRF). The developed polymer-grafted QCM sensors were managed to adsorb heavy metal ions, such as copper, chrome, cadmium, and lead, from solutions over a wide range, from 0.01 to 1000 ppm concentration selectively (Sartore et al. 2011).

Lou et al. designed a QCM sensor by using thiol-functionalized SBA-15 (SBA-15-SH) mesoporous silica materials, which have various pore sizes and specific surface areas, for the detection of Hg^{2+} ions in water (Lou et al. 2012). The QCM sensor loaded with thiol-functionalized SBA-15 (SBA-15-SH) was prepared via a post-grafting technique. All the materials were characterized by Fourier transform infrared (FT-IR) spectroscopy, small-angle X-ray scattering (SAXS), thermogravimetric analysis (TGA), transmission electron microscopy (TEM), and N_2 adsorption isotherms. The developed QCM sensor was able to detect 1 ppm Hg^{2+} in aqueous solution with the response frequency of 175 Hz and the response time was found to be as short as 1 min. Sun et al. aimed in their study to develop a quartz crystal microbalance (QCM) sensor with the fibrous polystyrene membranes functionalized by polyethyleneimine (PEI) for the determination of heavy metal ions in solution. The specific surface area (SSA) and morphology of the polystyrene membranes were controlled by way of adjusting the weight ratios of the blend solvents of tetrafuran, *N*,*N*-dimethylformamide (DMF). It was found that SSA of polystyrene membranes increased as DMF increased in mixture solvents. The experimental results indicated that QCM sensors have excellent selectivity for Cr^{3+} with a detection limit of 5 ppb. The sensor responses in the 5–200 ppb concentration range were obtained with good linearity. They also examined reproducibility of QCM sensors. More than 60% of the original response was maintained after five assays (Sun et al. 2012; Fig. 1.3).

Hüseynli et al. reported a new technique of quartz crystal microbalance nanosensor that is used for determination of Hg(II) ions in waste water (Hüseynli et al. 2019). For this purpose, they took advantage of the molecular imprinting method.

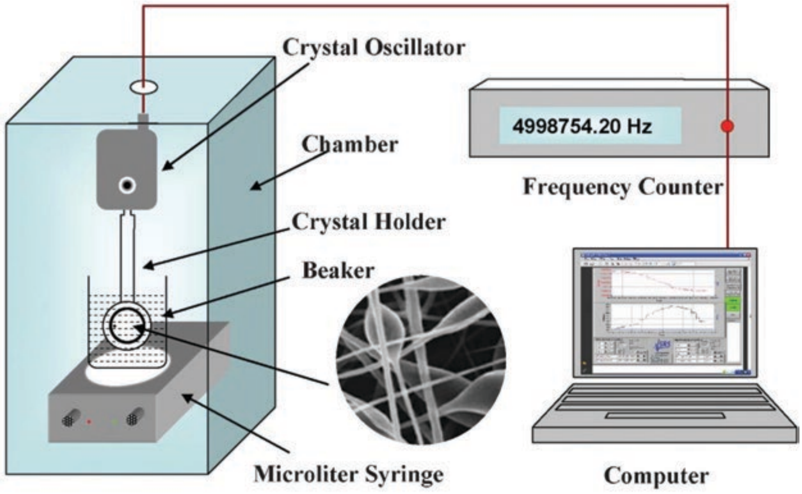

Fig. 1.3 Schematic diagram of a testing system for metal ions (Sun et al. 2012)

Firstly, a functional monomer and Hg(II) ions were co-complexed and then Hg(II) ions were imprinted into the polymeric film. Prepared QCM sensor for detecting Hg(II) ions was characterized by contact angle, Fourier transform infrared (FT-IR) spectroscopy, ellipsometer, and atomic force microscopy (AFM). In addition to selectivity and kinetic studies, reproducibility and recovery parameters were investigated. The linear working range was found to be 0.25–50 × 10^{-3} μM. The limit of detection was determined as 0.21 × 10^{-3} μM. The reproducibility of prepared sensor was reported as average %RSD 1.119 for 3 different days.

Sun et al. designed a QCM sensor, which was based on thioglycolic acid-modified CdTe nanoparticles, to determine heavy metal ions in aqueous solution. In this study, it was aimed to increase the detection limit of the sensor using CdTe nanoparticles and thioglycolic acid was the key factor in adsorption. It was also noted that the sensitivity of the prepared sensor was six times that of the quartz crystal microbalance sensor, which was based on the thioglycolic acid only. The limit of detection was obtained as 0.096 μg L^{-1} for Pb^{2+}, 0.089 μg L^{-1} for Cd^{2+}, and 0.189 μg L^{-1} for Cu^{2+}. In order to investigate reproducibility, the relative standard deviations of Pb^{2+}, Cd^{2+}, and Cu^{2+} were calculated as 4.2%, 3.1%, and 2.7%, respectively (Sun et al. 2019).

1.3.3 Optic Sensing for Heavy Metals

Forzani et al. detected a heavy metal ion by high-resolution differential surface plasmon resonance (SPR) sensor. They reported Cu(II) and Ni(II) detection in the ppt-ppb ranges of concentration. They developed the SPR sensor by coating with peptides NH_2-Gly-Gly-His-COOH and NH_2-(His)6-COOH. Also, they reported Cu(II) in drinking water using this sensor (Forzani et al. 2005).

Verm and Gupta developed an optical fiber SPR sensor for detection of Cd^{2+}, Pb^{2+}, and Hg^{2+} ions in drinking water. They used silver metal and indium tin oxide for fabrication of the SPR probe, which was further modified with the coating of pyrrole and chitosan composites. They reported strong binding for Cd^{2+} ions than the other ions. They reported a highly sensitive detection for the low concentrations (Verm and Gupta 2015).

Sadrolhossein et al. prepared a polypyrrole-chitosan/nickel ferrite (PPy-Chi/$NiFe_2O_4$) nanoparticle composite layer in order to detect iron, nickel, cobalt, manganese, mercury, aluminum, and lead ions. The thickness of the layers was detected as 6.3–83.1 nm. A gold surface layer of SPR chip was improved with the polymer composite. The detection of diamagnetic ions was conducted with a limitation of roughly 0.5 ppm. The synthesized polymer composite decreased the response time of the sensor. Thus, the prepared layer could detect the heavy metals strongly (Sadrolhossein et al. 2017).

In another study, Ullah et al. (2018) discussed sensor systems for the detection of heavy metal ions in different matrices, especially in water. They reported about properties of nanomaterial-based chemical sensors such as high sensitivity, portability, and selectivity. They severely engrossed on the recent progress with using various sensing strategies. The reported optical sensors focused and discussed in the review include fluorescent, surface plasmon resonance, and surface enhanced Raman scattering sensors.

Jalilzadeh et al. prepared Zn(II) ion-imprinted nanofilm on the SPR chip surface for detection of Zn(II) ions in aqueous solution and artificial plasma. Designed SPR sensor was applied for selective detection of Zn(II) ions in aqueous solution within the range of 0.5–1.0 mg mL^{-1}. The limit of detection and limit of quantification were calculated as 0.19 and 0.64 ng mL^{-1}, respectively (Jalilzadeh et al. 2019).

Safran et al. (2019) designed molecularly imprinted SPR biosensor for selective and label-free detection of Cu^{+2} in artificial urine and physiological serum samples to investigate the effects of metabolite residues. They synthesized Cu^{+2} imprinted poly(hydroxyethyl methacrylate-*N*-methacryloyl-(*L*)-cysteine methyl ester) nanoparticles, which they applied to the SPR sensor chip surface for the selective determination of Cu^{+2} ions.

1.3.4 Colorimetric Sensing for Heavy Metals

There is an ongoing research that utilizes metal nanoparticles and organic dyes to develop facile, rapid, and low-cost colorimetric assays for heavy metal ion detection (Du et al. 2013; Lin et al. 2011). In particular, gold and silver metal nanoparticles have attracted a great deal of interest due to their size- and shape-dependent optical properties and large absorption coefficients (Sepulveda et al. 2009; Saha et al. 2012). These assays are often based on aggregation of metal nanoparticles upon interaction of their surface functional groups (aptamers, peptides, proteins, small organic molecules, etc.) with metal ions (Lee et al. 2007; Ye and Yin 2008; Lee and Mirkin 2008; Li et al. 2008; Wang et al. 2010; Liu et al. 2008b, 2010, 2012). Aggregation changes the color of nanoparticle solution, which can be easily monitored by using a UV-Vis spectrophotometer or even with an untrained naked eye, without needing any complicated instruments. However, despite the extensive research in especially the last two decades, there is still need for improvements in the assay designs to improve their accuracy, reproducibility, as well as sensitivity and selectivity.

Mercury is widely released to the environment by industrial activities (e.g., gold mining) and combustion of fossil fuels and wastes. The most stable form of mercury in water is the solvated divalent mercuric ion (Hg^{2+}). Accumulation of mercury ions in the body can cause serious nervous system problems such as motor disorders and Minamata disease (Clarkson et al. 2003; Carvalho et al. 2008). Due to the serious effects of aqueous mercury ions on the human health and aquatic life, several colorimetric methods have been reported for its detection. One of the earlier methods for mercury ions was developed by Mirkin's group, where they prepared a method for the colorimetric detection of Hg^{2+} ions based on the thymidine–Hg^{2+}–thymidine bond formation using the melting point of DNA-functionalized gold nanoparticles.

The color change of the solution and the melting temperature of the DNA-gold nanoparticle aggregates are used to determine the concentration of Hg^{2+} ions. They reached a detection limit of 100 nM with good selectivity using this DNA approach (Lee et al. 2007).

Later, Merkoçi's group demonstrated a highly sensitive assay for the detection of Hg^{2+} ions by using gold nanorods. The gold nanorods were functionalized with *N*-alkylaminopyrazole, which can strongly and selectively interact with Hg^{2+} ions, and this interaction induced the formation of gold nanorod aggregates. They reported very low detection limit of 3 ppt for this method. In addition, the assay was very rapid and could be completed in a few minutes. Finally, they tested the selectivity of the assay against different metal ions: Cd^{2+}, Zn^{2+}, Cu^{2+}, Pb^{2+}, Hg^{2+}, and As^{3+} (Placido et al. 2013).

Şener et al. reported a simple, sensitive colorimetric method, which does not require any surface modification step, for simple detection of mercury ion. The system was based on the aggregation of citrate-capped gold nanoparticles in the presence of Hg^{2+} ions and the positively charged lysine. The proposed mechanism of this system is the spontaneous reduction of Hg^{2+} ions onto the gold nanoparticle surface, which causes nanoparticle aggregation in the presence of lysine. Using this assay, Hg^{2+} ions can be detected with naked eye within a few minutes, and the detection limit of this assay is 2.9 nM. In addition, selectivity of the assay was tested by using several competing metal ions or a mixture of competing metal ions: Zn^{2+}, Ca^{2+}, Al^{3+}, Cu^{2+}, Ni^{2+}, Pb^{2+}, Ag^{+}, $Na^{+}Co^{2+}$, K^{+}, Fe^{3+}, Cd^{2+}, etc. (Şener et al. 2014b).

In an interesting approach, Wei et al. prepared a sensitive and cost-effective smartphone-based Hg^{2+} sensor with the detection limit of 3.5 ppb. They determined Hg^{2+} ion concentration using gold nanoparticles and aptamer interaction in disposable test tubes by using green and red LEDs at 523 and 625 nm to analyze the color of the solution. In addition, they employed this portable sensor to test over 50 water samples in California, USA (Wei et al. 2014).

Another excessively studied heavy metal ion is lead (Pb^{2+}), which is released to the environment by end-user products such as gasoline, batteries, and dyes. Lead ions can get some serious health effects including cardiovascular, developmental, and neurological disorders, especially in children (Kim et al. 2012). Accordingly, several colorimetric assays were developed to detect aqueous lead ions. For instance, Chen et al. developed a label-free colorimetric method for the detection of Pb^{2+} ions in aqueous solution based on gold nanoparticles. Thiosulfate ($S_2O^{2-}{}_3$) was used to form a complex with gold nanoparticles. In the presence of Pb^{2+} ions and 2-mercaptoethanol (2-ME), Pb-Au alloy was formed on the surface of gold nanoparticles, which resulted in the aggregation of nanoparticles. The detection limit of this selective method is 0.5 nM. They also utilized this assay to detect Pb^{2+} ions in real samples such as soil and river water (Chen et al. 2009). Yu et al. reported a sensitive colorimetric sensor based on glutathione-functionalized gold nanoparticles for the detection of Pb^{2+} leaking from perovskite solar cells in the rain water. They detected Pb^{2+} by naked eye with the detection limit of 15 nM. The results of this selective and sensitive method were also compared with ICP-MS (Yu et al. 2016a, b). On the other hand, Zhu et al. utilized bifunctionalized gold nanoparticles for colorimetric detection of Pb^{2+} ions in aqueous solution and living cells (HeLa cells). Glutathione and pentapeptide (CALNN) were chosen as a functional group for Pb^{2+} sensing and as a stabilizing ligand for gold nanoparticles under physiological conditions, respectively. They found that the Pb^{2+} sensor was selective over different metal cations (Na^+, K^+, Ca^{2+}, Ba^{2+}, Zn^{2+}, Mg^{2+}, Cu^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cd^{2+} Mn^{2+}, $Hg^{2+}Al^{3+}$, and Fe^{3+}) in living cells (Zhu et al. 2012). Zheng et al. prepared a selective colorimetric method to detect and separate Pb^{2+} ions by using diethanolamine-modified gold nanoparticles (DEA-AuNPs) and *L*-(−)-malic acid-modified Fe_3O_4 nanoparticles (MA-NPs). They tested their sensor in different environmental sources such as drinking, river, and lake water. In the presence of Pb^{2+} ions, the color of the solution changed from red to blue after the interaction with modified gold nanoparticles in 10 min. Then with the addition of MA-Fe_3O_4 they successfully separated Pb^{2+}-Au aggregates and MA-Fe_3O_4 with a magnet in 15 min (Zheng et al. 2010).

Another very toxic heavy metal ion is arsenic, which can cause some several diseases, including bloody diarrhea, acute renal failure, cardiovascular diseases, and lung, liver, bladder, and skin cancer (Song et al. 2016; Weng et al. 2014; Domínguez-González et al. 2014). Wu et al. reported a sensitive and selective colorimetric method for the detection of As^{3+} ions in aqueous solutions by using polydiallyldimethylammonium (PDDA), aptamer, and gold nanoparticles. They chose a cationic polymer PDDA, which could aggregate gold nanoparticles and hybridize the aptamer through electrostatic interaction. In the presence of As^{3+} ions, the aptamer bound to As^{3+} to form an As^{3+}-aptamer complex. Addition of cationic polymer aggregated gold nanoparticles that resulted in color change from red to blue. In the absence of As^{3+} ions, aptamers hybridized with cationic polymer so gold nanoparticles were stable in the solution and the color of the solution did not change. The limit of detection of this selective method is 5.3 ppb (Wu et al. 2012b).

In another work, Kalluri et al. employed glutathione, dithiothreitol, and cysteine (Cys) modified gold nanoparticles for detection of arsenic in ground water. Interestingly, the authors observed an excellent selectivity against arsenic in the presence of these three ligands; when they modified the gold surface only with glutathione and dithiothreitol, they reported weak affinity with some other metal ions tested. More importantly, utilization of dynamic light scattering instead of common UV-Vis adsorption measurements improved the sensitivity of the assay about two orders of magnitude. Accordingly, they obtained a very good sensitivity of 3 ppt, which is almost three orders of magnitude lower than the WHO limit. Finally, they tested the assay with real samples using drinking water from different origin and found high levels of arsenic in the tap water sample from Bangladesh and bottled from Jackson (Kalluri et al. 2009).

Later, inspired by nature (i.e., odor and taste differentiation mechanism of mammalians), several sensing units with broad sensitivity to several metal ions have been employed with data-recognition methods. These assays allow selective detection of multiple ions using a single assay (Fig. 1.4). For instance, Şener et al. developed a colorimetric sensor array using mercaptoundecanoic acid (MUA)-capped gold nanoparticles to discriminate seven metal ions (Al^{3+}, Cu^{2+}, Hg^{2+}, Cd^{2+},

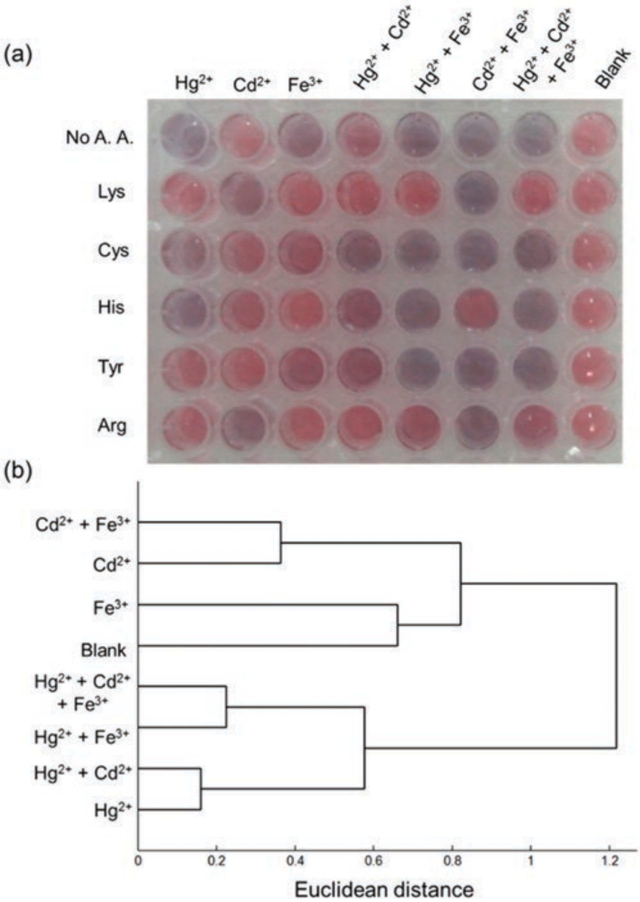

Fig. 1.4 Colorimetric response of the colorimetric array against Hg^{2+}, Cd^{2+}, and Fe^{3+} ions (20 M) and their binary and ternary mixtures: (**a**) representative photograph; (**b**) hierarchical cluster analysis (Şener et al. 2014a)

Fe^{3+}, Cr^{3+}, and Pb^{2+}) simultaneously with high selectivity. Amino acids (lysine, cysteine, histidine, tyrosine, and arginine) were employed to create several sensing units. Amino acids can bind to MUA-capped gold nanoparticles through their amino groups and form complexes with metal ions through their carboxyl and amino groups. The complex interactions between metal ions, amino acids, and MUA-capped gold nanoparticles resulted in enhanced or diminished nanoparticle aggregation and color changes from red to purple or blue (Şener et al. 2014a).

DNAzymes as an ideal recognition molecule toward specific targets with high selectivity are used for sensing. Because of their easy operation, high sensitivity, and easily detectable signals, numerous DNA aptamer-based sensors have been developed for the detection of heavy metals (Liu et al. 2008a; Wu et al. 2012a).

Kim et al. developed a high-affinity DNA aptamer for arsenic that can bind to arsenate [As(V)] and arsenite [As(III)] with a dissociation constant of 5 and 7 nM, respectively. The specific affinity interactions of the Ars-III aptamer to arsenic were verified against other heavy metals. They also applied Ars-III for removal of any arsenic present in the groundwater samples collected from the studied areas in Vietnam after obtaining successful removal results with a laboratory-prepared aqueous arsenic solution. They demonstrated that various arsenic concentrations ranging from 28.1 to 739.2 μg/L were completely removed after 5 min of incubation with the arsenic-binding aptamer Ars-III (Kim et al. 2009).

In another recent study, a selective colorimetric method was developed by using green silver nanoparticles that were synthesized from plant extracts (mango, neem, pepper, and tea plants) to detect Hg^{2+}, Pb^{2+}, and Zn^{2+} ions in aqueous solutions across a wide range of pH (2.0–11). The complicated interactions between surface-bound plant extracts and metal ions enable detection of Hg^{2+}, Pb^{2+}, Zn^{2+} ions across a wide pH range (Kumar and Anthony 2014). Similarly, a colorimetric method was reported for the detection of Cd^{2+}, Hg^{2+}, and Pb^{2+} ions at ppm level in aqueous solution through metal ion interacting functionality. They synthesized silver nanoparticles functionalized with different organic ligands such as *N*-(2-hydroxybenzyl)-valine and *N*-(2-hydroxybenzyl)-isoleucine (Slocik et al. 2008).

1.4 Conclusions

Recent advances in sensor technology have revolutionized our ability to characterize and quantify heavy metal contaminations, and undoubtedly offer benefits for environmental pollution control and early warning. Sensors have several significant and important advantages for such applications, for example: (1) the sensors provide rapid, sensitive, selective, and simple assay method; (2) novel materials may offer unique properties for real-time in-situ assays of binding kinetics between heavy metals and functional molecules; (3) rapid toxicity screening and multi-analyte testing of the environmental pollutants by more smaller, compact, adaptable, and robust sensors developed by sensing arrays can be enabled; (4) miniaturization of optical recognition elements by integration of microfluidics and microelectronics into sensors; and (5) emergence of environmental sensor networks facilitated by wireless-communication technology. Although various challenges still remain in creating improved, cost-effective, and more reliable sensors, sensors will provide the most productive means for heavy metal contamination control and early warning.

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Chapter 2
Nanosensors for Heavy Metal Detection in Environmental Media: Recent Advances and Future Trends

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Abstract Heavy metal pollution has long been an environmental and health problem for thousands of years. Although heavy metal contamination has been well studied and regulated nationally and internationally, remediation of heavy metal polluted environmental media remains a complicated challenge, as exposure to heavy metal continues. Novel heavy metal remediation has become a hot topic being vigorously researched in environmental science and engineering. The emergence of nanotechnology over the last two decades offers new solutions to the existing problems of the environment. Fabricated nanosensors are well recognized to be highly selective and sensitive toward certain heavy metal pollutants. Optical properties including light extinction, intensity, and scattering can be substantially altered and enhanced as a result of surface plasmon resonance phenomenon possessed by metallic nanostructures such as gold, platinum, and silver, and/or achieved by inner filter effect. Moreover, novel nanosensors could act as fluorescence quencher to produce strong fluorescence signals, or act as surface catalyzer to generate autonomous motion. These distinct mechanical, chemical, and electrical properties make many nanosensors promising candidates for environmental remediation. A variety of nanosensors, for example, surface-enhanced Raman spectroscopy and nanojets, has been designed and applied for heavy metal detection. In this review, we present a brief overview of the recent advances in the fabrication of novel nanosensors that provide potential solutions to heavy metal remediation. We also intend to provide perspective on strategies that are needed to assess and reduce the potential hazard of manufactured nanomaterials in a sustainable manner.

Keywords Heavy metal · Nanosensor · Surface plasmon resonance · Fluorescence quenching · Nanojets · Green synthesis · Nanotoxicology

2.1 Introduction

Heavy metal pollution has a long history associated with the development of human society (Hong et al. 1996; Nriagu 1996). Over the past century, due to the enormous mining activities and rapidly expanding industrial processing, environmental contamination with heavy metals has become a worldwide health issue. Main heavy metal pollutants reported in contaminated land and water include lead (Pb), mercury (Hg), arsenic (As), cadmium (Cd), copper (Cu), and chromium (Cr) (European Environment Agency 2016). According to the European Environment Agency (EEA), heavy metal in a total of 3.45×10^7 kg was released from Europe's industry (33,000 facilities in 33 countries including 28 European Union members) for the period 2007–2015 (European Environment Agency 2016). As shown in Fig. 2.1a, 1.55, 0.6, 7.99, 9.9, 13.82, and 0.65 million kg of As, Cd, Cr, Cu, Pb, and Hg were released, in which 50%, 48%, and 2% were directly released to water, air, and soil (Fig. 2.1b). By looking at the contribution to environmental pressure from releases of heavy metals, urban wastewater treatment plants, agriculture, and mining

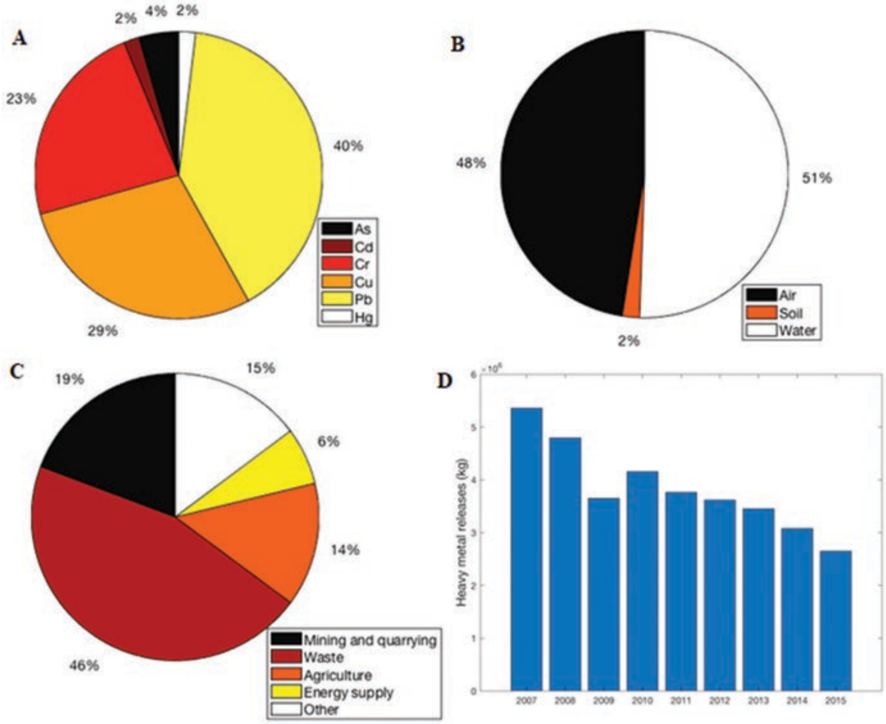

Fig. 2.1 Heavy metal releases from Europe's industry for the period 2007–2016. Total release: 3.45×10^7 kg. (**a**) Distribution of heavy metals. (**b**) Environmental pressure to water, air, and soil. (**c**) Contribution to environmental pressure from release of heavy metals to water (note heavy metal releases to air are mainly from industrial processing). (**d**) Annual release from 2007 to 2015. Data sources: European Environment Agency. The European Pollutant Release and Transfer Register (E-PRTR), Member States reporting under Article 7 of Regulation (EC) No 166/2006

contributed 78.8% of the total release to water, whereas industrial processing largely contributed to the total release to air (Fig. 2.1c).

These heavy metals are known to cause severe heavy metal poisoning and illness at toxic doses to plants, animals, and humans, as a result of air or water contamination and heavy metal contaminated food products. Many of the heavy metal pollutants such as inorganic arsenic can accumulate in the vitals of organisms, including liver, tissues, spleen, and kidneys. Acute and chronic heavy metal poisoning may lead to symptoms like skin irritation, nausea, and seizure, and life-threatening complications such as brain damage, hemolysis, and even death. Additionally, heavy metals released by anthropogenic practices tend to persist in the environment for a long time with little microbial degradation. Heavy metal pollution thus poses great risks and hazards to our ecosystem and humans.

Heavy metal contamination has been observed in almost every type of environment and all locations on earth, from breathing air (Li et al. 2013a) to drinking water (Mohan et al. 1996), land (Wuana and Okieimen 2011) to ocean (Mclntyre and He

2019; Millward et al. 2019), and Arctic (McConnell and Edwards 2008) to Antarctic (De Moreno et al. 1997). The effective monitoring and hazard assessment of heavy metal contaminants in a variety of environmental matrices is thus a prominent, yet challenging, section in ensuring environmental safety and human health (Gray et al. 2019). With the recent development in nanotechnology and nanoscience, engineered nanomaterials has received an ever-increasing attention with broad applications in many fields, including but not limited to biomedical researches (He et al. 2015b), environmental remediation (Ma et al. 2015; He et al. 2016a), transistor industry (Franklin 2015), energy application (Khan et al. 2017), and food and agriculture (He and Hwang 2016; He et al. 2019a). Nanotechnology has evolved to offer a potential solution to this challenging task: nanosensors (Su et al. 2012; Li et al. 2013b; Kumar et al. 2017). Recent market share forecasts that nanosensor market share is anticipated to grow from ~100 million USD to ~4 billion USD between 2017 and 2023, at a compound annual growth rate of 79.83% (Mordor Intelligence 2019). Nanosensors are engineered for chemical and mechanical applications because of the unique physicochemical properties at nanoscale. Successful examples have been reported in monitoring chemical pollution in our living environment (Su et al. 2012; Vikesland 2018) and agriculture practices (Baruah and Dutta 2009). Many nanosensors have also been designed and used to detect and monitor heavy metals in natural environmental media. Highly sensitive and selective nanosensors can be designed and modified to accommodate a large number of environmental applications.

Here we briefly present recent progress in nanosensor research and development for heavy metal contaminant detection. We aim to review mechanisms for detecting heavy metals and the potential contributions of nanotechnology-based sensors to human health in a sustainable manner.

2.2 Detection Mechanisms

2.2.1 Surface Plasma Resonance

Metallic nanoparticles are known to induce surface plasmon resonance as a result of electron oscillation due to light irradiation (incident electromagnetic wave E_o), as schematically illustrated in Fig. 2.2a. The electron cloud near nanoparticle's surface then displaces under the oscillating electric field relative to nuclei. The collective oscillation and displacement of the electron cloud of metallic nanoparticle induces electric dipole (Fig. 2.2b, c) for small nanoparticles or higher quadrupole modes (Fig. 2.2c, e) for large nanoparticles. Nanoparticle surface plasmon resonance ultimately leads to the amplification of the electric field near the metal surface (E_{out}), which can be characterized by (Kelly et al. 2003)

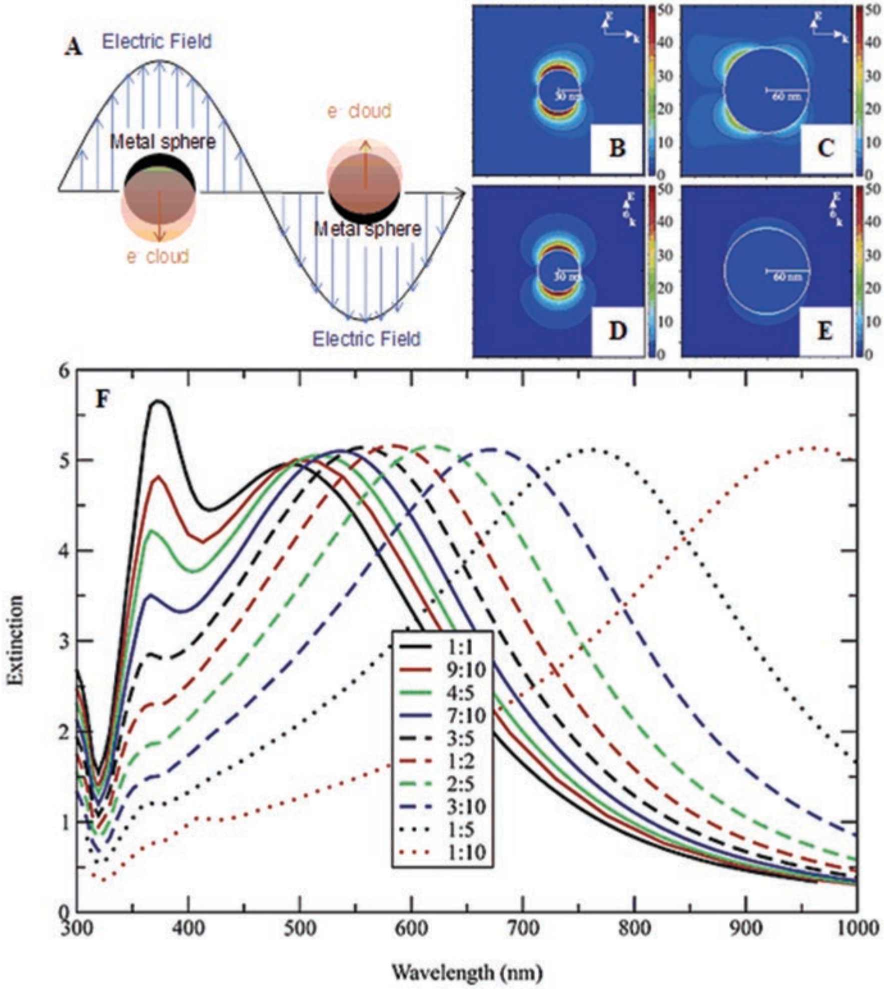

Fig. 2.2 (**a**) Schematic illustration of surface plasmon resonance showing the electron cloud displacement. (**b–e**) Electric field for Ag nanoparticles. (**b** and **c**) show the cross-section plane with propagation and polarization axes and (**d** and **e**) show the cross-section plane perpendicular to the propagation axis. (**b** and **d**) show 30 nm Ag at the main extinction peak of 369 nm and (**c** and **f**) show 60 nm Ag at the quadrupole peak of 358 nm. (**f**) shows the extinction spectra of nanoparticles with various shapes indicated by major to minor axis ratio (ranging from 1 to 10). Reproduced with permission from Kelly et al. (2003), American Chemical Society

$$E_{out} = E_o\vec{x} - \alpha E_o\left(\frac{\vec{x}}{r^3} - \frac{3x}{r^5}\left(x\vec{x} + y\vec{y} + z\vec{z}\right)\right)$$

where α is the nanoparticle polarizability, $x, y, z, \vec{x}, \vec{y}, \vec{z}$ are the Cartesian coordinates and unit vectors, and r is the radial distance. $E_o\vec{x}$ represents the contribution of the incident electromagnetic wave to electric field, and $\alpha E_o\left(\frac{\vec{x}}{r^3} - \frac{3x}{r^5}\left(x\vec{x} + y\vec{y} + z\vec{z}\right)\right)$ represents the contribution of the surface plasmon resonance to electric field. For quadrupole modes, E_{out} can be characterized by (Kelly et al. 2003)

$$\begin{aligned} E_{out} &= E_o\vec{x} + ikE_o\left(x\vec{x} + z\vec{z}\right) - \alpha E_o\left(\frac{\vec{x}}{r^3} - \frac{3x}{r^5}\left(x\vec{x} + y\vec{y} + z\vec{z}\right)\right) \\ &- \beta E_o\left(\frac{x\vec{x} + z\vec{z}}{r^5} - \frac{5z}{r^7}\left(x^2\vec{x} + y^2\vec{y} + xz\vec{z}\right)\right) \end{aligned}$$

where β is the quadrupole polarizability.

Optical characteristics including extinction, absorption, and scattering spectra exhibit distinct features for nanoparticles with different chemical and physical properties. Hence, a variety of methodologies have been used for the detection of nanoparticle surface plasmon resonance features. Noticeably, surface-enhanced Raman spectroscopy (SERS) has been shown to be highly sensitive to the electromagnetic fields at or close to the surface of nanomaterials (Ding et al. 2017), exhibiting distinct extinction spectra in response to different particle sizes and shapes (Kelly et al. 2003). For instance, the relatively large dipole plasmon peak for small Ag nanoparticles (30 nm; Fig. 2.2b, d) can lead to strong electromagnetic enhancements in SERS. One more example is given to illustrate the particle shape dependent extinction properties in Fig. 2.2e. By a given nanoparticle volume equivalent to that for an 80 nm radius sphere, an increasing red shift of the surface plasmon resonance is expected as the shape changes from sphere (ratio of major to minor axes = 1) to highly oblate (ratio of major to minor axes = 10), indicating a substantial dependency of diploe plasmon resonance on particle shape.

Among many metallic nanoparticles, Au, Pt, and Ag nanostructures are mostly studied and applied as nanosensors due to their distinct plasmonic characteristics. They possess similar plasmonic characteristics aforementioned, with dependency on nanoparticle morphology, oxidation states, and aggregation/agglomeration status (Amirjani and Haghshenas 2018). The highly selective and sensitive surface plasmon resonance features then can be used for the heavy metal detection with careful manufacturing. Here we briefly discuss some recent progress on the surface plasmon resonance based nanosensors. Four subcategories are divided to represent different properties exhibited by the surface plasmon resonance, including ultraviolet (UV)-visible spectroscopy, surface-enhanced infrared absorption (SEIRA), surface-enhanced Raman scattering, and surface-enhanced fluorescence.

2.2.2 UV-Visible Spectroscopy

UV-visible spectroscopy is readily accessible in most research facilities, which makes it the common method for quantifying the characteristic changes in plasmonic nanostructures. Agglomeration or aggregation often occurs when plasmonic nanoparticles meet certain heavy metal ions. UV-visible spectrum shift as a result of agglomeration or aggregation then can be observed by UV-visible spectroscopy. Zhang and coworkers reported that a colloidal graphite-like nitride doped carbon quantum dots-capped gold nanoparticle (Au@g-CNQDs) for selective detection of Cd^{2+} ions (Zhang et al. 2018). They found that Cd^{2+} ions were adsorbed onto Au@g-CNQDs, likely due to surface functional groups such as heptazine, carboxyl, and hydroxyl (Fig. 2.3a), leading to the formation of Au@g-CNQDs aggregates

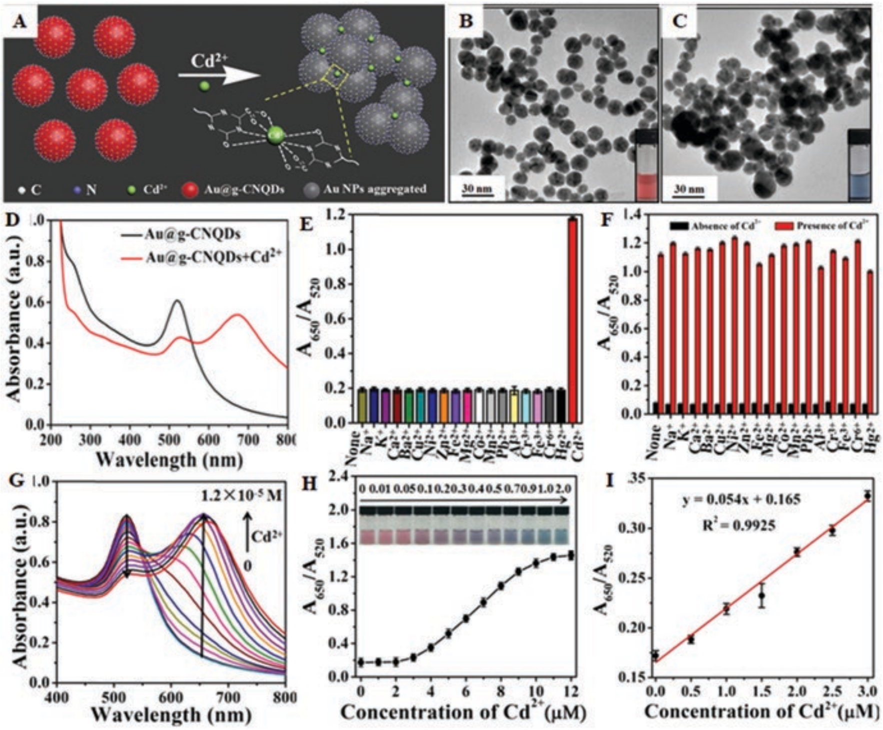

Fig. 2.3 (**a**) Schematic drawing that represents the Au@g-CNQD aggregation caused by Cd^{2+} ions, and (**b** and **c**) show the aggregation status of Au@g-CNQDs without (**b**) and with 1 mM Cd^{2+} ions (**c**). (D) UV-visible spectra of plasmonic characteristic shift of Au@g-CNQDs with Cd^{2+} ions. (**e** and **f**) Selectivity of Cd^{2+} ions to Au@g-CNQDs. (**g**) UV-visible spectra of the Au@g-CNQDs with different Cd^{2+} concentrations (0–12 μM). (**h**) The colorimetric and spectroscopic observations with different Cd^{2+} concentrations (0–12 μM). (**i**) shows a linear detection window with different Cd^{2+} concentrations (10 nM to 12 μM). Reproduced with permission from Zhang et al. (2018), Elsevier

(Fig. 2.3b, c). The change in aggregation status then resulted in subsequent plasmonic characteristic change. The feature change was recorded by UV-visible spectroscopy with an apparent red shift at 650 nm/520 nm (Fig. 2.3d). Notably, Au@g-CNQDs showed strong selectivity and sensitivity to the Cd^{2+} ions (Fig. 2.3e, f) with a detection limit of 10 nM and linear detection window up to 3 μM (Fig. 2.3g–i).

Similar UV-visible spectroscopy based on the aggregation or agglomeration of plasmonic nanoparticles was also employed by Ikram et al. (2019). They reported that epicatechin-capped silver nanoparticles (ECAgNPs) were highly selective to Pb^{2+} in blood and water matrices, among many other ions (Ikram et al. 2019). UV-visible spectroscopy shows that Pb^{2+} ion enhanced ECAgNP absorption at 412 nm with a detection limit of 1.52 μM and up to 100 μM (Ikram et al. 2019). Notably, UV-visible spectroscopy exhibits to be highly efficient and reliable in environmental samples, with a recovery rate of Cd^{2+} ranging from 97.7% to 99.8% in tap water samples and from 99.3% to 102.8% in lake water samples (Ikram et al. 2019).

2.2.3 Surface-Enhanced Infrared Absorption

Infrared (IR) absorption of the hybrid metallic plasmonic surface can also be enhanced in the presence of organic or biomolecules and heavy metal ions (Enders et al. 2006). The technique used for heavy metal detection is called surface-enhanced infrared absorption (SEIRA). Instead of inducing aggregation or agglomeration of nanoparticles, heavy metal ions could lead to a red shift in infrared plasmon of some nanomaterials, amplified by the nanostructure electromagnetic field (Enders et al. 2006). Literature survey shows little progress on the SEIRA-based nanosensor for heavy metal detection. We use the study from Hoang et al. (2013) as an example to illustrate how SEIRA-based nanosensor functions. Hoang et al. (2013) developed an Au plasmonic nanostructure with thiolated 15-base DNA oligonucleotides to monitor for the in-situ detection of Hg^{2+}. The binding of Hg^{2+} with DNA aptamer induced vibrational signal in the infrared spectra. Notably, Au nanostructures functioned as electromagnetic field amplifier and further enhanced the vibrational signal of the DNA aptamer in the presence of Hg^{2+}, even at ppt level in situ. The schematic of the Hg^{2+} binding with DNA aptamer is shown in Fig. 2.4a. The Hg^{2+} ion can bridge two thymine bases by N–Hg–N bonds, resulting in structural and chemical change in the DNA aptamer. Such conformational changes in DNA aptamer in the presence of Hg^{2+} ions subsequently cause the shift in infrared optical spectra (Fig. 2.4b). Altogether, infrared optical spectra features then act as the fundamental mechanism to detect Hg^{2+} ions.

IR spectral features in Fig. 2.4c clearly indicate the development of infrared spectra profile of the Au-DNA nanostructure with Hg^{2+} concentrations increasing from 37 ppt to 37 ppb. Although the peak shape and position of the infrared spectrum peak at $\omega_T = 1400\ \mathrm{cm}^{-1}$ (red solid line) remains unchanged, the intensity, but not the

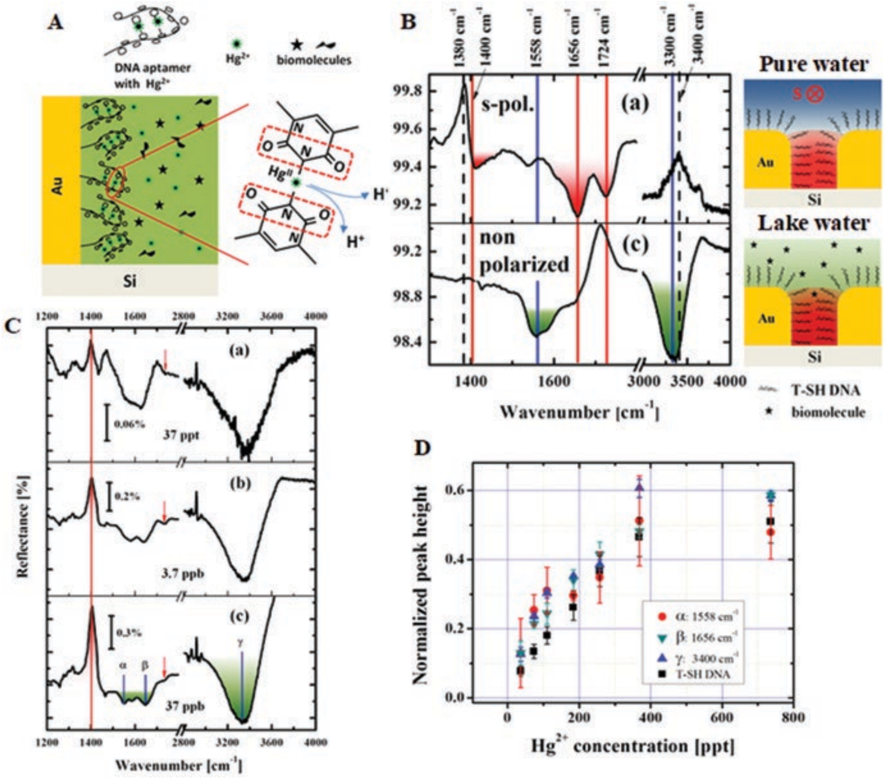

Fig. 2.4 (**a**) Schematic representation of the conformational changes in Au-DNA nanostructures caused by Hg^{2+}. The N–Hg–N bonds in the imide structures (red dotted rectangular) then lead to the IR signal change. (**b**) Infrared spectra of Au-DNA plasmonic nanostructure in pure water (upper panel) and lake water (lower panel). (**c**) IR spectral features in the presence of Hg^{2+} in lake water samples. (**d**) IR spectra intensity at $\omega = 1400\ cm^{-1}$ (DNA signal) and at α: 1558 cm^{-1}, β: 1650 cm^{-1}, and γ: 3300 cm^{-1} (Hg^{2+} induced signals) with different Hg^{2+} concentration. Vibrational IR signals from the DNA and Hg^{2+} are marked by red and blue lines, respectively. Reproduced with permission from Hoang et al. (2013), licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

peak shape, changes along with the Hg^{2+} concentration. Vibrational bands also occur at 1558 cm^{-1} (α: C–N stretching and N–H bending modes, Amide II), 1650 cm^{-1} (β: C=O Amide I), and 3300 cm^{-1} (γ: N–H stretching mode) in the presence of Hg^{2+} ions. The intensity of the infrared spectrum peak at those three wavenumbers also increases as the Hg^{2+} concentration increases (Fig. 2.4d).

2.2.4 Surface-Enhanced Raman Scattering

The amplified electromagnetic field near the plasmonic nanostructure surface induced by light irradiation (visible and near-infrared radiation) can be recorded as Raman signal and is known as enhancement in surface-enhanced Raman scattering (SERS). Notably, the electromagnetic field enhancement can magnify the light intensity, which in turn further increases Raman scattering signals. The overall SERS measurements can be as much as 10^{10}–10^{11}, making SERS possible for even single molecule detection. Plasmonic nanostructures such as Au and Ag with plasmon resonance frequencies within visible and near-infrared radiation are widely utilized for SERS measurement. The addition of heavy metals can reduce the SERS signal of plasmonic nanostructures, thus making SERS nanosensors possible to quantify the trace heavy metal concentrations. For example, the chemical interaction between methylthio moiety and plasmonic gold nanoparticles could be disrupted in the presence of copper(II) (Dugandžić et al. 2019). The conformational changes in the ligand can then be quantified by comparative SERS spectrum. Following the mechanism, trace metal ions can be detected as a function of SERS spectrum intensity at certain wavenumbers.

SERS-based nanosensors are rapidly growing in the last decade. Many other SERS nanosensors have been designed to monitor heavy metal ions in water samples with promising results (see selected studies in Table 2.1). Here we take a recent report from Zou et al. (2019) as an example. They reported a novel DNAzyme-Au nanocluster (AuNC) assembly coated on polystyrene microspheres (PSMPs) with DNA logic gates for theultrasensitive detection of Hg^{2+} and Pb^{2+} ion simultaneously (Zou et al. 2019). The newly constructed nanosensor uses Au nanostructured films as the SERS-active substrates. The 8–17 DNAzyme with enzyme strand (S1: 5′ACC TCTTCTTTGTTTCTTGCATCTCTTCTCCGAGCCGGTCGAAATAGTGAGT) and cleavage substrate strand (S2: 5′TGTCAACTCGTGACTCACTATGGAAGAG ATG) was conjugated with the short DNA sequence (S3: 5′GTTGTTTCTTTGTTC and S4: 5′CACGAGTTGACA) on the Au nanostructures. A number of 10 misaligned T−T base pairs in the short DNA sequence S3 were specifically engineered to bind Hg^{2+} by forming T–Hg–T bonds. Consequently, Raman reporter 5,5′-Dithiobis-(2-nitrobenzoic acid) labeled AuNCs were bond into the PSMP substrates, exhibiting a magnified SERS intensity at 1330 cm^{-1}. However, in the presence of Pb^{2+} ions, Au nanoconjugates were removed from the PSMP substrates, leading to a lower Raman signal at 1580 cm^{-1}. The binding and detaching of Raman labeled-AuNCs from the PSMP substrates is thus controlled by the presence of Hg^{2+} or Pb^{2+} ions, respectively. The DNA logic gate system is regulated by (0,0), (0,1), (1,0), and (1,1), indicating no Hg^{2+} or Pb^{2+} ions, with Pb^{2+} ions, with Hg^{2+} ions, and with both ions, respectively (schematically shown in Fig. 2.5a). The conformation changes in SERS intensity for four modes were then captured by the Raman spectroscopy, as shown in Fig. 2.5b. Clearly, as Hg^{2+} and Pb^{2+} ions were simultaneously presented, the SERS features at different shift wavenumbers were distinctly observed as detected in Fig. 2.5c, d.

Table 2.1 Selected reports on SERS nanosensors for the detection of heavy metals

Nanomaterials	Targeted heavy metal	Reported detection range	Detection limits	Recovery in environmental samples	Reference
Gold nanoparticle trimers	Hg^{2+}	Linear (log): 0.002–0.5 ng mL^{-1}	1.69 pg mL^{-1}	100–109%	Li et al. (2015)
	Ag^{2+}		1.71 pg mL^{-1}	95–101%	
Citrate-functionalized gold nanoparticle	Pb^{2+}	Linear: 50–1000 ng/L	25 ng/L	98.6%	Frost et al. (2015)
Porous anodic alumina membrane functionalized with CoFe$_2$O$_4$ nanoparticles and carbon nanotubes	Pb^{2+}, Hg^{2+}, and Cd^{2+}	1–100 ppb	1 ppb	N/A	Shaban and Galaly (2016)
Label-free Fe$_3$O$_4$@ag	Hg^{2+}	Linear (log): 10^{-5}–10^{-11} M	10 pM (2 ppt)	Tap water: 106–133%	Song et al. (2017)
				Regeneration water: 66.07–96.75%	
				Secondary sedimentation effluent: 93.2–106%	
				Ultrafiltration membrane effluent: 76.25–95.28%	
Aptamer-modified SiO$_2$@Au core/shell nanoparticles	Hg^{2+}	1 × 10^{-8} to 1 × 10^{-3} M	10 nM	N/A	Lu et al. (2018)
		Linear (log): 1 × 10^{-7} to 1 × 10^{-3} M			
NaYF$_4$@Yb,Ho,Au-nanohybrid	Pb^{2+}	Linear (log): 10^{-5}–10^{3} μg/mL	1.16 × 10^{-9} g/mL and	97.98–106.40	Annavaram et al. (2019)
NaYF$_4$@Yb,Ho,GO-nanohybrid			1.15 × 10^{-8} g/mL	97.76–116.80	
Poly(vinylidene fluoride) membrane decorated with silver nanoparticles	Cd^{2+}	0.2–20 mM	1 × 10^{-10} M	N/A	Liu et al. (2019)
L-cysteine-functionalized Au@Ag core-shell probes	Pb^{2+}	Linear range: 5 pM to 10 nM	1 pM	Drinking water: 96.2–103.5%	Xu et al. (2018)

(continued)

Table 2.1 (continued)

Nanomaterials	Targeted heavy metal	Reported detection range	Detection limits	Recovery in environmental samples	Reference
Oligonucleotide-functionalized and gold coated polystyrene microspheres	Hg^{2+}	0–10 μM	0.1 nM	Lake water: 97.2–103.3%	Zou et al. (2019)
				Tap water: 101.2–102.2% (Hg) (Pb) for	
	Pb^{2+}	0–100 μM	1 nM	Lake water: 94.6–106.3%	
				Tap water: 96.5–104.5%	
Aminobenzo-18-crown-6 (AB18C6)-AuNPs	Pb^{2+}	1 μM to 0.8 mM	0.69 pM	100–110% in the presence of other metal ions	Sarfo et al. (2018)
Dipicolylamine-based ligand plasmonic gold nanoparticles	Cu^{2+}	N/A	5×10^{-8} M	Drinking water: 88.83 ± 9.19%	Dugandžić et al. (2019)

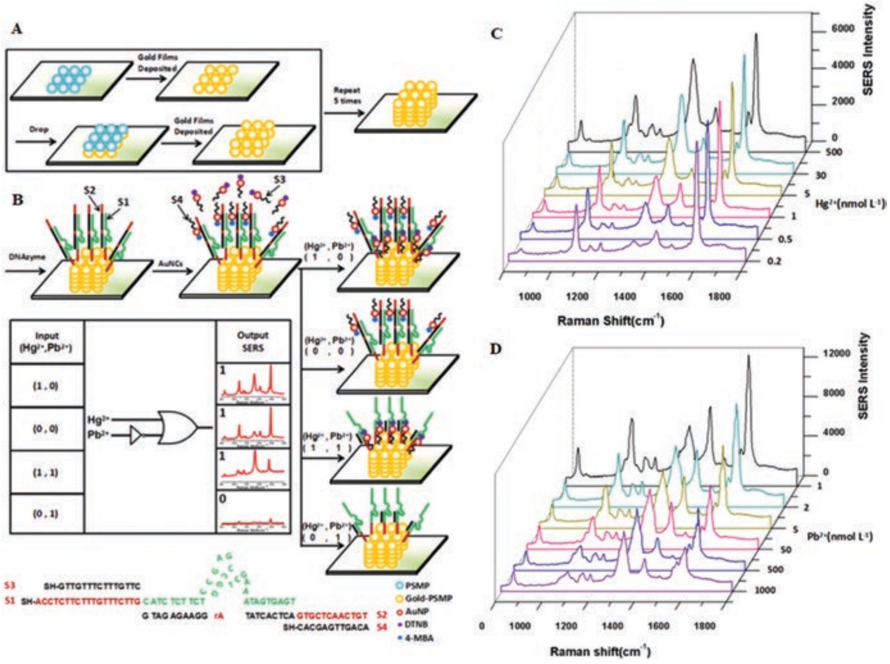

Fig. 2.5 Schematic representation of DNAzyme-Au nanostructure (**a**) and detection of Hg^{2+} and Pb^{2+} with engineered DNA logic gates (**b**). (**c** and **d**) show SERS spectra for Hg^{2+} with 100 nM Pb^{2+} (**c**) and for Pb^{2+} with 100 nM Hg^{2+} (**d**). Reproduced with permission from Zou et al. (2019), Elsevier

Moreover, SERS spectra also showed an excellent correlation between the heavy metal ions and SERS intensity. Good linear correlations were observed for both Hg^{2+} ions and Pb^{2+} ions with $R^2 > 0.99$ and 0.91, respectively. The nanosensor assembly exhibited an ultra-sensitivity and selectivity toward Hg^{2+} ions and Pb^{2+} ions with detection limit of 0.1 nM and 1 nM, respectively, meeting the World Health Organization standard of 10.0 ppb (31 nM) and 10.0 ppm (3.02×10^4 nM), respectively, for drinking water. Noticeably, the proposed AuNC nanosensor also showed excellent recovery in environmental water samples, with 97.2–103.3% (Hg) and 94.6–106.3% (Pb) for lake water samples, and 101.2–102.2% (Hg) and 96.5–104.5% (Pb) for tap water samples.

2.2.5 Surface-Enhanced Fluorescence

In addition to enhanced light absorption and scattering, metal surface enhanced fluorescence has also drawn broad attention. Although fluorescence spectroscopy is ultrasensitive, detecting fluorophore has often suffered from its limited quantum yield and low photostability (Aslan et al. 2005). Over the past decades, the surface plasmon electrons of plasmonic metals have been found capable of interacting with fluorophores and thus enhancing the fluorescence spectral properties such as intensity (Ray et al. 2006; Aslan et al. 2007), photostability (Aslan et al. 2005; Lakowicz 2005), and decay lifetime (Ray et al. 2006; Lu et al. 2012). Although excellent examples have been reported for surface-enhanced fluorescence in many biomedical and environmental studies (Aslan et al. 2005), most of them are focused on biomolecule or organic pollutant detection. Examples are detection of microcystin-LR (Li et al. 2014), bacteria sensing (Abdulhalim et al. 2009), single molecule on cell membrane (Zhang et al. 2008), RNA sensing (Aslan et al. 2006), and cellular imaging (Cui et al. 2010). However, few examples are seen in heavy metal detections.

Here we briefly discuss three successful applications of surface-enhanced fluorescence-based nanosensors to monitor heavy metal ions. Sui et al. (2014) developed DNA-Cy3 aptamer immobilized Ag@SiO_2-DNA-fluorophore nanostructure that is highly sensitive for Hg^{2+} and Ag^+(Sui et al. 2014), where Cy3 was used as the fluorophore. Hg^{2+} or Ag^+ could lead to the binding of T–Hg^{2+}–T or T–Ag^+–T in the DNA aptamer, thus placing the fluorophore Cy3 near the metal surface and enhancing the fluorescence of Cy3 at 2.5-fold. The nanosensor assembly showed high selectivity and sensitivity for Hg^{2+} and Ag^+ with a limit of detection at 1.4 nM. Taking advantage of a similar approach, a glutathione-stabilized gold nanoclusters/indium-based metal–organic frameworks modified with cysteine (AuNCs/MIL-68(In)-NH_2/Cys) was developed for the detection of Hg^{2+} ions (Wu et al. 2019), showing remarkably enhanced fluorescence emission. The red fluorescence intensity at 668 nm quenched in the addition of Hg^{2+}, making it possible to detect trace Hg^{2+} with an extremely low limit of 6.7 pM. The fluorescent AuNCs/MIL-68(In)-NH_2/Cys

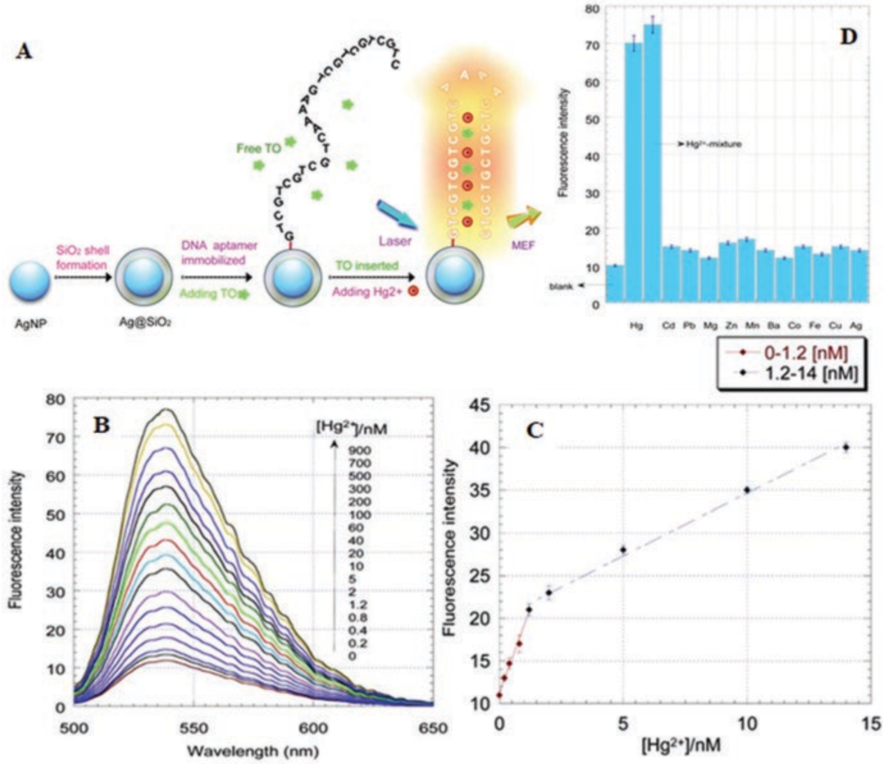

Fig. 2.6 (**a**) Schematic design of the metal surface enhanced fluorescence-based DNA aptamer-Ag@SiO_2 nanosensor for the detection of Hg^{2+}. (**b**) Florescence spectra of the aptamer-Ag@SiO_2 with Hg^{2+} (0–900 nM). (**c**) The detection range of Hg^{2+} from 0 nM to 14 nM. (**d**) Selective detection of Hg^{2+}. λ_{ex} = 482 nm, λ_{em} = 538 nm. Reproduced with permission from Panget al. (2015), licensed under a Creative Commons Attribution 4.0 International License

performed well in environmental water samples with a high recovery of 97.5–110.2% in lake water sample and 91.3–107.5% in tap water samples.

Another interesting study from Pang et al. (2015) demonstrated fluorescent core-shell Ag@SiO_2 nanosensors for the detection of Hg^{2+}, as the first label-free metal surface enhanced fluorescence-based aptasensor to detect heavy metal pollutants (Pang et al. 2015). The single-strand structure of the T-rich ss-DNA aptamer bound to Ag@SiO_2 NPs was folded to hairpin duplex structure that resulted from the formation of T–Hg^{2+}–T. Then the fluorescent reporter thiazole orange could bind the hairpin complex, resulting in higher fluorescence quantum yield (schematically illustrated in Fig. 2.6a). Moreover, the fluorescence intensity of the excited-state thiazole orange was further amplified by the surface-enhanced fluorescence of Ag@ SiO_2 nanosensors, therefore substantially increasing the sensitivity of the aptasensor. As shown in Fig. 2.6b, fluorescence intensity at 538 nm was enhanced by the increasing Hg^{2+} concentration (note the linear correlation window at 0–1.2 nM and

1.2–14 nM in Fig. 2.6c), with a limit at 0.33 nM, meeting the US EPA requirements of 10 nM. The hybrid fluorescence-enhanced Ag@SiO$_2$ nanosensors also showed high selectivity for Hg^{2+} among ten other metal ions (Fig. 2.6d), and great potential for in-situ environmental application.

2.2.6 Fluorescence Quenching–Based Nanoprobes

Besides the surface plasmon resonance enhanced nanosensors, many other properties have also been explored to engineer nanosensors. Fluorescence quenching based nanoprobes are among the noticeable nanosensors. In this case metallic nanostructures act as fluorescence quenchers for fluorophores, often at short distances (~0–5 nm; Aslan et al. 2005). The fluorescence quenching effect can then be quantified to indicate the presence of trace heavy metals. The small changes in the spatial distance between nanostructures and fluorophores can result in significant signal in fluorescence quenching. Heavy metal ions often can mobilize and detach nanoparticles from the hybrid fluorescent nanoprobes via disrupting electrostatic interaction between fluorophores and nanoparticles. The resulting fluorescence quenching is subsequently observed as the indicator for heavy metal concentration. Following this principle, metallic nanostructures have been successfully developed as fluorescent nanoprobes for a wide range of heavy metal ions (Wu et al. 2013; Kaewtong et al. 2014; Hormozi-Nezhad and Taghipour 2015).

Recently, Wang and coworkers engineered a *turn-on* fluorophore brilliant cresyl blue labeled-Au nanoparticle assembly to monitor Pb^{2+} in water samples (Wang et al. 2015). Au nanoparticles act as fluorescence quenchers that diminish brilliant cresyl blue fluorescence via electrostatic interactions. In the presence of Pb^{2+}, a chelating complex is formed between Pb^{2+} and negatively charged glutathione on the Au assembly, leading to the detachment of fluorophore brilliant cresyl blue from the Au nanoparticle assembly, and thus the recovery of fluorescence. The fluorophore labeled-Au nanoparticle assembly showed to be highly sensitive toward Pb^{2+} with a detection limit at 0.51 nM, among 12 other metal ions. Niu et al. (2018) also showed a *turn-on* graphene quantum dots and gold nanoparticle fluorescent sensor for detection of Pb^{2+}(Niu et al. 2018). A similar fluorescence-recovery mechanism was observed for the function of proposed graphene quantum dots and gold nanoparticle fluorescent sensor with Pb^{2+}. The proposed fluorescent nanosensor exhibited a high sensitivity with a wide detection range (50 nM to 4 μM), and a detection limit at 16.7 nM.

Another example from Wang and coworkers also demonstrated a fluorescent DNA-Ag nanosensor for Pb^{2+} detection (Wang et al. 2019). Similarly, Pb^{2+} ions specifically interact with rA cleavage site of the ds-DNA-AgNC nanosensor (Fig. 2.7a). Thus, the DNA segment was released from the ds-DNA-AgNC assembly, leading to fluorescence spectra shift from red to green (Fig. 2.7b). The strong fluorescence intensity peaks at 560 nm and 685 nm are shown in Fig. 2.7c with a linear correlation between 0.001 nM and 10 nM. As shown in Fig. 2.7d, the

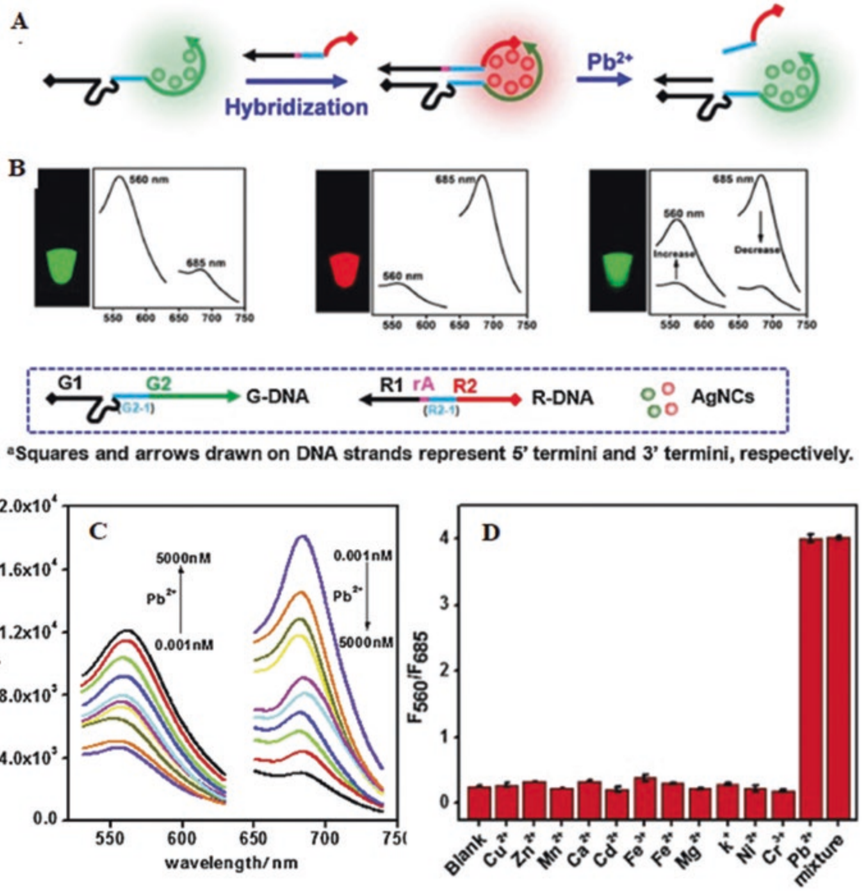

Fig. 2.7 Schematic illustration of ds-DNA-AgNC nanosensor detecting Pb^{2+} ions (**a**) and the fluorescence spectra response (**b**). The strong fluorescence intensity peaks at 560 nm and 685 nm for Pb^{2+} (0.001–5000 nM) (**c**). (**d**) shows the high selectivity of reported nanosensor toward Pb^{2+}. Reproduced with permission from Wang et al. (2019), Elsevier

ds-DNA-AgNC nanosensor was ultrasensitive and selective to Pb^{2+}, while all the other metal ions did not exhibit strong fluorescence response. Furthermore, the fluorescent signal of Pb^{2+} was not interfered by any of other metal ions, due to the high affinity and selectivity between Pb^{2+} and DNAzyme. The ultrasensitive nanosensor showed an exceptionally low detection limit at 1.0 pM in environmental samples, with recovery of 82–108% in lake water samples and 89–104.4% in tap water samples.

2.2.7 Self-Propelled Nanojets

Self-propelled nanojets (or nanomotors) are relatively new tools with vast promising applications in biomedical researches, with examples seen in drug delivery and medical diagnosis (Sanchez and Pumera 2009; Sánchez and Soler 2015). Those nanojets are autonomously self-propelled nanomachines with relatively quick autonomous motion and sufficient power output (Yang et al. 2015). The commonly studied models of self-propelled nanojets are bubble self-propulsion by enzymatic reactions (e.g., O_2 bubbles generated by catalytic decomposition of H_2O_2 [Solovev et al. 2012]), or bubble-free propulsion powered by an enzyme-controlled catalysis (e.g., internal flows generated by turnover of urea → $NH_{3(aq)} + CO_{2(aq)}$ in the presence of enzyme urease [Ma et al. 2016]), as partly illustrated in Fig. 2.8a (Sanchez and

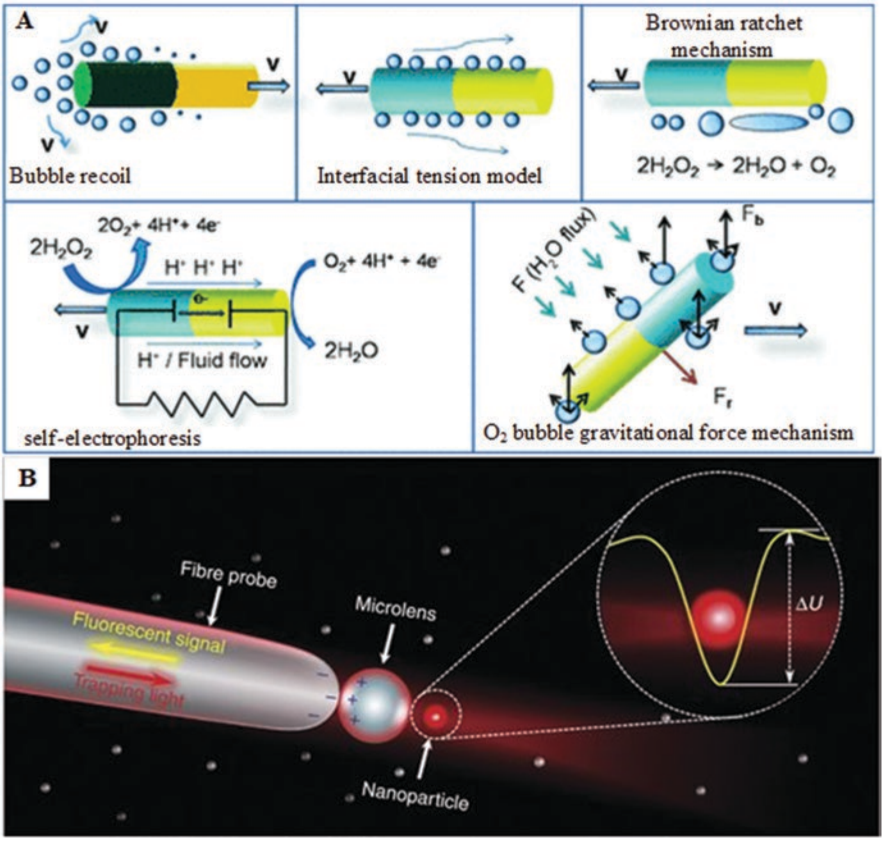

Fig. 2.8 (**a**) Mechanisms of self-propelled nanojets. Color scheme: Ni (green), Au (yellow), and Pt (blue). (**b**) Schematic illustration of photonic nanojets detecting a single nanoparticle by forming a potential well with maximum potential difference ΔU. (**a**) Reproduced with permission from Sánchez and Pumera (2009), John Wiley and Sons. (**b**) Reproduced with permission from Li et al. (2016), licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License

Pumera 2009). Alternatively, photonic nanojets supplied by optical power also show great potential for optical operation and detection as nanosensors (Li et al. 2016). The example shown in Fig. 2.8b illustrates a potential well can be generated by the probe-microlens complex, which is able to trap a single nanoparticle or biomolecule, operating at low optical power (Yang et al. 2015; Li et al. 2016; Gu et al. 2018). Recent studies have demonstrated that novel self-propelled nanojets can be applied for rapid detection of pollutants, at the single nanoparticle (Yang et al. 2015; Li et al. 2016; Gu et al. 2018) or single biomolecule (Li et al. 2016) level, in the environment.

As an example to illustrate the application of self-propelled nanojets for the detection of heavy metal contaminants in aqueous samples, Maric and coworkers reported a novel, highly sensitive Pt–Halloysite nanojet to monitor Hg^{2+} (Maric et al. 2019). The proposed Pt–Halloysite nanojets use Pt to catalyze the decomposition of H_2O_2, while large Halloysite nanoclay surface allows high adsorption for metal ions (Fig. 2.9a). The positive charges of metal ions can interact with the negatively charged Halloysite nanoclay outer layer by electrostatic interactions. Pt–Halloysite nanojets exhibited high velocities with an average of 227 $\mu m\ s^{-1}$, and preliminarily in the absence of heavy metal ions. However, the velocities of Pt–Halloysite nanojets drastically decreased in the presence of Hg^{2+} (Fig. 2.9e), while moderate decrease was observed for other metal ions (Fig. 2.9b–d). The decreased velocity was largely due to the less-exposed active sites for H_2O_2 decomposition of the adsorbed metal ions onto the Pt surface, as shown in Fig. 2.9f, g. The difference observed among the four tested metal ions was possibly due to the difference in metal ion atomic size and electronegative values. Hg^{2+} has the largest atomic radius and relatively higher electronegative values, making it having higher affinity toward Pt surface of the nanojets. The proposed Pt–Halloysite nanojet assembly also indicated a broad detection range for Hg^{2+} (0.25–1000 ppb), with a detection limit at 3.24 ppb.

2.3 Application Examples and Detection Limit

With understanding of fundamental mechanisms that are widely applied in nanosensors for detecting heavy metals, we further show a few examples from recent reports from 2017 to present. We intend not to repeat what we have discussed in the previous section. But we may use the same studies to emphasize the detection mechanism of each specific type of heavy metals. Therefore, applications of nanosensors for six major heavy metal contaminants, including Hg^{2+}, Pb^{2+}, As^{3+}, Cd^{2+}, Cu^{2+}, and Cr^{3+}/Cr^{6+} ions, are carefully selected from literature and briefly discussed in this section.

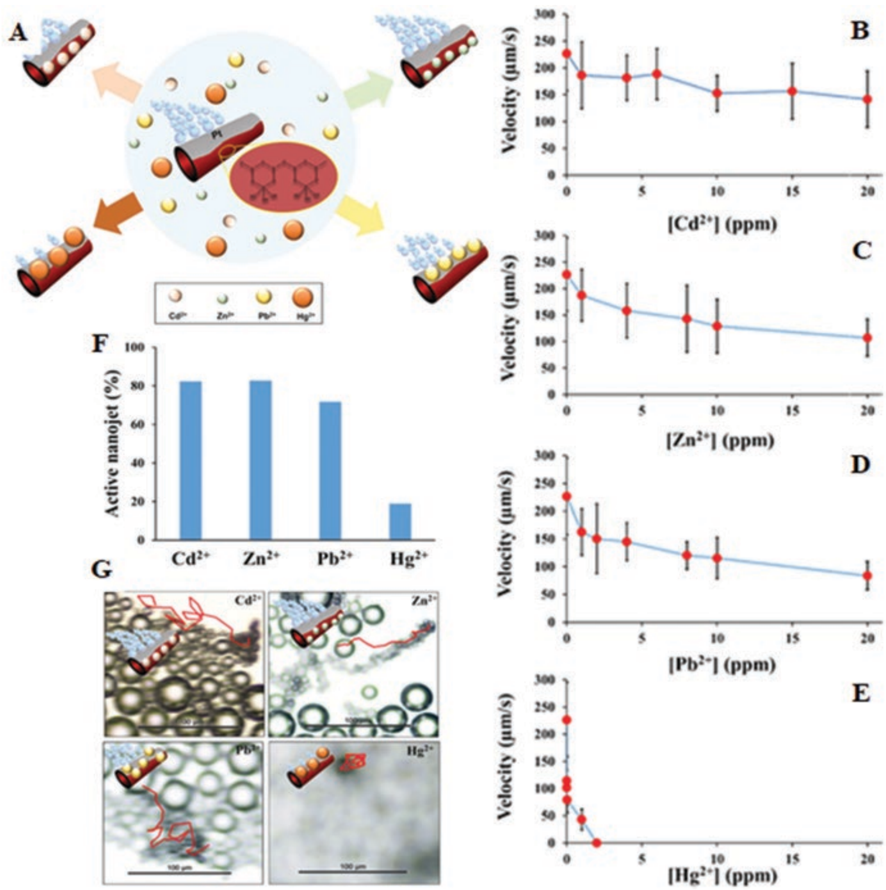

Fig. 2.9 (**a**) Schematic representation of self-propelled Pt–Halloysite nanojets for the detection of heavy metal ions. (**b–e**) show velocity changes of Pt–Halloysite nanojets in the presence of (**b**) Cd^{2+}, (**c**) Zn^{2+}, (**d**) Pb^{2+}, and (**e**) Hg^{2+}. (**f**) The percentage of active nanojets in different heavy metal ions. (**g**) Representative images of nanojets with different heavy metal ions at 1 ppm. Reproduced with permission from Maric et al. (2019), John Wiley and Sons

2.3.1 Hg^{2+} Detection

Hg normally presents in elemental (Hg^0), mercuric (Hg^{2+}), or alkylated form (methyl/ethyl mercury) after entering natural environment. In particular, methylmercury is more toxic than inorganic Hg as it tends to be bio-accumulative in living tissue, while many researches focused on detecting inorganic Hg (Amini et al. 2017; Cai et al. 2017; Satapathi et al. 2018). It is therefore important to detect Hg in various forms. Notably, Yang and coworkers developed a fluorescent nanoprobe named folic-acid-capped gold nanoclusters to detect mercury speciation between inorganic (Hg^{2+}) and organic (in form of CH_3Hg^+) forms in water and fish samples, showing a detection limit of 28 nM and 25 nM, respectively (Yang et al. 2018). The fluorescence quenching effect was observed for the Hg^{2+}, whereas CH_3Hg^+ exhibited strong fluorescence enhancement.

2.3.2 Pb^{2+} Detection

Pb is among the most heavy metals released in environment, with 13.82 million kg released from Europe's industry for the period 2007–2015 (European Environment Agency 2016). Ionic Pb^{2+}, PbO, $Pb(OH)_2$, and lead-metal oxyanion complexes are usually observed in natural environment. Pb poisoning may cause severe damage to the brain, kidney, and central nervous system, posing significant risk to physical and mental development. Detecting of Pb^{2+} is mainly based on the "detaching" mechanism as a result of the interaction between Pb^{2+} ions and nanosensors. For instance, unlike Hg^{2+}, the selectivity and sensitivity of Au nanoconjugates toward Pb^{2+} was due to the decreased Raman signal at 1580 cm^{-1}, as a result of mobilization of Au nanoconjugates from the PSMP substrates in the presence of Pb^{2+} (Zou et al. 2019). Similar detaching mechanism was also observed for many studies using fluorescence quenching nanosensors (Wang et al. 2015; Niu et al. 2018; Ikram et al. 2019; Wang et al. 2019). Fluorescence signal can be recovered for fluorophore by adding Pb^{2+}, due to nanostructures, as the fluorescence quencher, removing from the fluorophore via chelating interaction between Pb^{2+} and nanostructure assembly.

2.3.3 As^{3+} Detection

Arsenic exists in environment in a variety of forms, including inorganic As^{3+} and organic methylated derivatives, such as $HAs(CH_3)_2$ and $As(CH_3)_3$. As^{3+}-detecting nanosensors often are based on the *turn-on* effect resulting from chemical interaction between the As^{3+} ions and specific regions of nanosensor assembly (Nath et al. 2014; Zhang et al. 2017a). For instance, As^{3+} ions specifically bind $(GT)_{29}$ region of the fluorescent DNA quantum dots (Zhang et al. 2017a). As a result, organized structure evolution and conformational changes were developed for the nanosensor. Subsequently, fluorescence signal was largely enhanced due to the phenomena occurring at the nanostructure surface at which the stacking of nucleic acid–base pairs promotes radiative decay and fluorescence emission.

2.3.4 Cd^{2+} Detection

Cd^{2+} is believed to cause severe renal damage via chronic accumulation in kidney, with a well-known case of Cd^{2+} poisoning in the Jintsu River Valley, Japan. Severe bone diseases and kidney malfunction can occur as a result of Cd^{2+} poisoning. Cd^{2+} detection can also be achieved through recovering fluorescence signal. For instance, Cd^{2+} ions can break the complexation between the fluorescence quencher 1,10-phenanthroline and green emissive cadmium telluride quantum dots (CdTe QDs), thus turning on the green fluorescence signal (Qian et al. 2017). Similar mechanism was also reported in the L-cysteine-capped CdTe nanosensor. Adding Cd^{2+} can recover the fluorescence signal of CdTe QDs by replacing the fluorescence quencher dithizone (Li et al. 2017).

2.3.5 Cu^{2+} Detection

Copper is the second most released heavy metal from the European industry (Fig. 2.1a). The interaction between Cu^{2+} and environmental media is quite complex but usually in a form that is less toxic than other heavy metals. Nevertheless, it possesses high risks toward major organs such as kidney at high doses. Cu^{2+} detection can be achieved through many strategies and fluorescence is on the top list, followed by surface plasmon resonance and electrochemiluminescence (Wang et al. 2018). Cu^{2+} ions could act as fluorescence quencher (Elmizadeh et al. 2017; Shah et al. 2018), enhance surface plasmon resonance via aggregation (Deymehkar et al. 2018), and act as reaction catalyst in electrochemiluminescence ternary (e.g., $PTC\text{-}NH_2 + S_2O_8^{2-} + CoFe_2O_4$) system to substantially improve the detection sensitivity and limit (Lei et al. 2018).

2.3.6 Cr^{3+} and Cr^{6+} Detection

Detection of both Cr^{3+} and Cr^{6+} ions has been reported using a variety of methods. Carbon nanodots and cetyltrimethyl ammonium bromide capped-9,10-diphenyl anthracene nanosensors were used to determine Cr^{6+} concentration based on fluorescence quenching, showing a detection limit of 0.015 μM (Liu et al. 2017) and 0.01392 $\mu g\ mL^{-1}$ (Suryawanshi et al. 2019), respectively. Using colorimetric methods, the color change of 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol modified gold nanoparticles (AuNPs), due to the aggregation induced by Cr^{3+}, can be used as a quantitative tool for Cr^{3+} detection (Shahrivari et al. 2018). Similarly, Cr^{3+} could induce aggregation of methylene blue capped-AuNPs, which leads to surface plasmon absorption band red-shift signal with detection limit of 23.66 nM (Salimi et al. 2018).

2.4 Outlook

The increasing application of nanotechnology in many fields such as environmental remediation and pollution monitoring also comes with potential cost. The manufacturing, transportation, use, and disposal of nanomaterials may increase the exposure of nanoparticles to the environment and human beings. Yet, we do not have a full understanding of the fate and potential impact of nanomaterials on the environment and human, as the physicochemical properties of nanomaterials may be altered due to their dynamic interactions with surrounding environments. Many evidences have suggested nanomaterials may pose threat to non-target species and human with enhanced reactivity at the nanoscale, while others advocate the benefits of engineered nanomaterials. Questions on how we can design and manage nanoproducts in a sustainable manner remain unanswered at the present. Based on recent trends and progress on reducing adverse effects of nanomaterial production and use, we here provide insights on green synthesis and minimizing nanotoxicity.

2.4.1 Green Synthesis

Green synthesis of nanomaterials has evolved in efforts to reduce the use of toxic raw chemicals and adopt less extreme synthesis conditions (He et al. 2019b). Oftentimes the toxic reducing agent, stabilizing agent, and capping agent are replaced by non-toxic counterparts, particularly from natural products. In searching for sustainable and environment-friendly green synthesis method, biosynthesis has been long studied together with the development of nanomaterials. Biological hosts (e.g., plants and microorganisms) have been found suitable for synthesizing many types of nanomaterials, including Ag, Au, TiO_2, CuO, magnetic iron oxide, and ZnO nanostructures. Biological polymers, including chitosan, proteins, and lipids with functional groups, can serve as reducing agent, stabilizing agent, and capping agent (He et al. 2019b).

Notably, biosynthesized nanoparticles have been successfully used in environmental sensing for heavy metals. Maiti et al. (2016) reported biosynthesized silver nanoparticles for detection of Cu^{2+} ion. Furthermore, 3-mercapto-1,2-propanediol functionalized biosynthesized silver nanoparticles were able to detect Hg^{2+} ions at μM level (Maiti et al. 2016). Additionally, natural polymers can be directly used as reducing agent, stabilizing agent, and capping agent for green synthesis of nanoparticles without a biological host. Muthivhi et al. (2018) reported that Au, Ag, and Pt nanoparticles could be produced using gelatin and maltose as capping agent and reducing agent, respectively. The biosynthesized noble metal nanoparticles showed high-sensitivity Hg ions in lake water (Muthivhi et al. 2018). However, the exact underlying mechanism for nanomaterial production in biological hosts remains unclear. Biosynthesis of nanomaterials is therefore less productive and controllable. Future research on systematic study of biosynthesis may provide a possible green chemistry solution to the present chemical engineering approach for nanomaterials.

2.4.2 Minimizing Nanotoxicity

Nanotoxicology is an emerging multidisciplinary field in toxicology that focuses on assessing the risks of manufactured nanomaterials to the environment and human health. Nanomaterials are often highly reactive compared to their bulk counterparts because of the large surface-area-to-volume ratio and they are always present as complicate systems (Deng et al. 2018). The enhanced chemistry may cause unintentional toxicity toward environmental species (Dasari and Hwang 2010; Hu and Zhou 2013; He et al. 2014a, 2016b, c; Hu et al. 2014, 2015; Chen et al. 2015; Zhang et al. 2017b; Zhou and Hu 2017; Yuan et al. 2018) and possibly the ecosystem (Hu and Zhou 2013; Ouyang et al. 2018). Thus, it is important to ensure the safe application of novel nanotechnology for commercial use (Hwang et al. 2013; He et al. 2014b, 2015a, 2018, 2019a). It is imperative to study the complex nature of nano-bio-eco interface with an effort to deliver an accurate comprehension on the toxicological behavior of engineered nanomaterials (He et al. 2015a, 2018).

A comprehensive database is needed, which describes the physicochemical properties of the enormous amounts of nanomaterials being engineered. Then the toxicity can be studied and correlated to those properties in the database (Puzyn et al. 2011; Pathakoti et al. 2014). Traditional in vitro and in vivo toxicological studies on countless nanomaterials being generated everyday are often resource-limited and time-consuming. Emerging *omics* studies, including genomics, transcriptomics, proteomics, and metabolomics, are powerful tools to reveal the potential metabolic pathways using model biological species. Lastly, recent trend on machine learning and data mining has revealed many previously unknown patterns hidden in the data collected. The comprehensive database can be useful to explore hidden patterns using data mining and predict new features using machine learning. One recent example is from Ban et al. (2018) who reported random forest-based machine learning approach to determine the priority factors underlying the reproductive toxicity of 18 nanomaterials. They found that Fe_3O_4, Fe_2O_3, and ZnO nanoparticles tend to accumulate in living organism at a much higher level than other nanoparticles, but induce less reproductive toxicity. Such finding somewhat contrasts to the intuitive as higher dose may cause severer damage. Their model also predicts that Ag nanoparticles have a weak dependency on dosage over a wide range (1–100 mg/kg), which is useful to assess the toxicity of Ag nanoparticles. Nevertheless, data heterogeneity and uncertainty is a challenge for the current machine learning algorithm to accurately represent the reality (Ban et al. 2018). Novel computational algorithms may aid in analyzing dataset with high diversities, uncertainties, and incompleteness of different degree, and discovering new features and patterns (Valdés 2018).

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Chapter 3
AIE-Based Fluorescent Nanosensors for Detection of Heavy Metal Ions

Xueyan Huang, Bin Feng, Tang Gao, Anyao Bi, Liu Huang, Rong Song, Meihui Liu, and Wenbin Zeng

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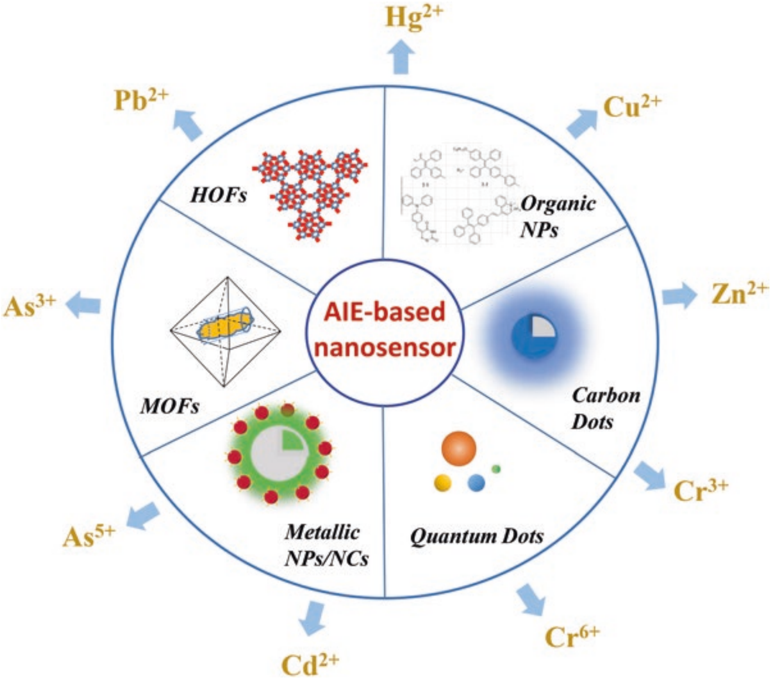
Abstract Heavy metal pollution is a serious global environmental problem that causes irreversible damage to the ecological environment and harms the human health. It is clearly imminent to develop an efficient and simple method for detecting heavy metals in the environment. Aggregation-induced emission (AIE)-based nanomaterials are excellent as a sensing platform, which enables rapid detection of heavy metals with high sensitivity and selectivity in aqueous solution, overcoming the drawbacks of traditional sensors such as poor solubility in water, aggregation-caused quenching, and insufficient signal-to-noise ratio. Herein, we summarize the recent efforts to develop AIE-based nanosensors for detecting heavy metal ions (including mercury, lead, zinc, copper, cadmium, chromium, and arsenic) with a focus on the sensing materials and mechanisms. Organic nanoparticles, metallic nanoclusters or nanoparticles, metal-organic frameworks, hydrogen-bonded organic frameworks, carbon dots, and quantum dots have been applied in the construction of AIE-based nanosensors to achieve the trace analysis of heavy metal ions, acting more in a fluorescence enhancement or quenching behavior. Moreover, some ratiometric nanosensors based on coupling two or more nanomaterials have shown some superiorities in selectivity, sensitivity, and accuracy. Despite the report that AIE-based nanosensors exhibit sufficient sensitivity to detect heavy metal ions in aqueous environment, the insufficient selectivity and specificity affect the capability of specially sensing in complex matrices.

Keywords Nanosensor · AIE · Heavy metal · Detection · Fluorescence

3.1 Introduction

Heavy metal contamination is a major global environmental issue (Bashir et al. 2019). Owing to the non-biodegradability, long half-life, and the ability to accumulate in the body, heavy metals (mercury, lead, copper, cadmium, chromium, zinc, arsenic, etc.) often cause severe damage to the organs, tissues, bones, and nervous systems once they enter the human body (Jarup 2003; Wu et al. 2010). For instance, mercury, lead, and arsenic can cause schizophrenia and neurological disorders; copper, cadmium, mercury, and lead can cause kidney and liver failure; copper, lead, and cadmium can cause dermatosis; and so on (Aragay et al. 2011; Cui et al. 2015). Even in the presence of merely trace amounts of heavy metals in the environment, the human would be exposed to high levels of heavy metals ultimately due to their permanent retention in the ecosystem (Izah et al. 2016). In view of this, it is urgent to develop effective method for detecting heavy metal ions with high sensitivity, high selectivity, and simplicity in practical application (Soodan et al. 2014; Kumar et al. 2017). Fluorescent analysis provides an effective platform for heavy metal detection, which possesses unique physical and chemical properties, high specificity for heavy metal ions, cost-effectiveness, and portability, to break through the limitations of traditional methods such as the demand for expensive instruments and skilled professionals, long detection time, etc. (Zhang and Fang 2010; Ullah et al. 2018; De Acha et al. 2019). However, the traditional fluorophores suffer from aggregation-caused quenching (ACQ) in aqueous solution, which severely restricts the practical application in aqueous solution (Gao and Tang 2017). Fortunately, the concept of aggregation-induced emission (AIE) first proposed by Tang et al. can effectively alleviate the pressing problem (Luo et al. 2001; Hong et al. 2009). In the AIE process, structural rigidification in aggregation state blocks the non-radiative decay, thereby causing the excited electrons to return to the ground state mainly by radiation transition (Mei et al. 2014). The AIE material is capable of maintaining strong fluorescent emission in aggregated state, which makes it possible the assembly of those materials into nanoparticles (NPs) to construct the AIE-based nanosensors for metal detection (Zhao et al. 2019; Liu et al. 2019a, b). Actually, those nanosensors hold great benefits for heavy metals' detection: strong fluorescence emission in aqueous solution, anti-photobleaching, high sensitivity, low background interference, etc. (Zhang et al. 2015a, b; Huang et al. 2019). These fluorescent nanosensors are able to quantify heavy metal ions by analyte-induced fluorescence quenching or enhancement (Wang et al. 2018a, b). Furthermore, the aggregation process can be actively utilized to achieve the collective effect, which is definitely favorable to trace analysis (Gu et al. 2018; Yang et al. 2019a, b). This review will outline recent advances in nanosensors with AIE property in the detection of heavy metal ions, with a focus on Hg^{2+}, Pb^{2+}, Zn^{2+}, Cu^{2+}, Cr^{3+}, Cd^{2+}, and As^{3+}, and pay special attention to the sensing materials and related mechanisms (Scheme 3.1).



Scheme 3.1 Schematics depicting the AIE-based nanosensors for heavy metals' detection. *MOFs* Metal-organic frameworks, *HOFs* Hydrogen-bonded organic frameworks, *NPs/NCs* nanoparticles/clusters

3.2 AIE-Based Nanosensors for the Detection of Hg^{2+}

Many different types of AIE nanosensors for Hg^{2+} detection have been reported, generally based on the following strategies: (1) complexation with ligands such as Schiff base, sulfhydryl, thymine-like group, sulfonamide group, aldoxime, and other sulfur atom-containing, oxygen atom-containing, or nitrogen atom-containing compounds; (2) utilizing specific reactions such as Hg^{2+}-induced cleavage of the vinyl group, desulfurization reaction, dethioacetalization, ring-opening reaction of spirolactam, etc.; and (3) utilizing the ability to quench the metallic nanosensors' emission through metallophilic interactions. In this section, these nanosensors are reviewed according to the classification of materials in terms of organic molecule nanoparticles, supramolecular system, nanoparticles (NPs), nanoclusters (NCs), and carbon dots (CDs).

3.2.1 Organic Molecule Nanoparticles

Organic molecule nanoparticles refer to nanoparticles formed by aggregation of single organic molecules, multiple different molecules, or polymers. They usually involve typical fluorophores such as cyanostilbene derivative, rhodamine, rhodol, and the classical AIE skeleton tetraphenylethylene (TPE). Some fluorophores themselves can be used as ligands for complexing with Hg^{2+} while some need to incorporate specific recognition groups.

Wei et al. (2018) designed a TPE-based aggregation-induced enhanced emission (AIEE) nanosensor **1** for sensing Hg^{2+}; it was composed of molecular polymer and introduced thiazole as the recognition unit through Pd-catalyzed Sonogashira coupling reaction. Similar to AIE effect, AIEE effect means stronger fluorescence in aggregation state compared with that in solution state. Since Hg^{2+} has a high affinity for sulfhydryl group, the reduction of the π-conjugation system of **1** was induced by the coordination with thiazole upon the addition of Hg^{2+}. Consequently, the original bright yellow fluorescence of **1** was observed to gradually quench in tetrahydrofuran (THF) and water mixture (water fraction 90%). However, this "turn-off" behavior was nonlinear due to the failure to guarantee uniform distribution of coordination between Hg^{2+} and any polymer chain.

Schiff base has the advantage of simple synthetic procedure, and the nitrogen atoms of which can efficiently coordinate with Hg^{2+} (Bhalla et al. 2013; Ni et al. 2013). Wang et al. (2018a, b) prepared two TPE-based fluorescent nanosensors **2-1** and **2-2**, which formed by aggregation of small molecule functionalized with Schiff base (Fig. 3.1). The AIE effects of both sensors were investigated in THF-H_2O solution. The fluorescence intensity of **2-2** was stronger due to its possession of alkyl chain and longer conjugation. With the addition of Hg^{2+}, the complexation of the diaminomaleonitrile moieties with Hg^{2+} resulted in the decrease in electron-withdrawing effect, which further inhibited the intramolecular charge transfer (ICT)

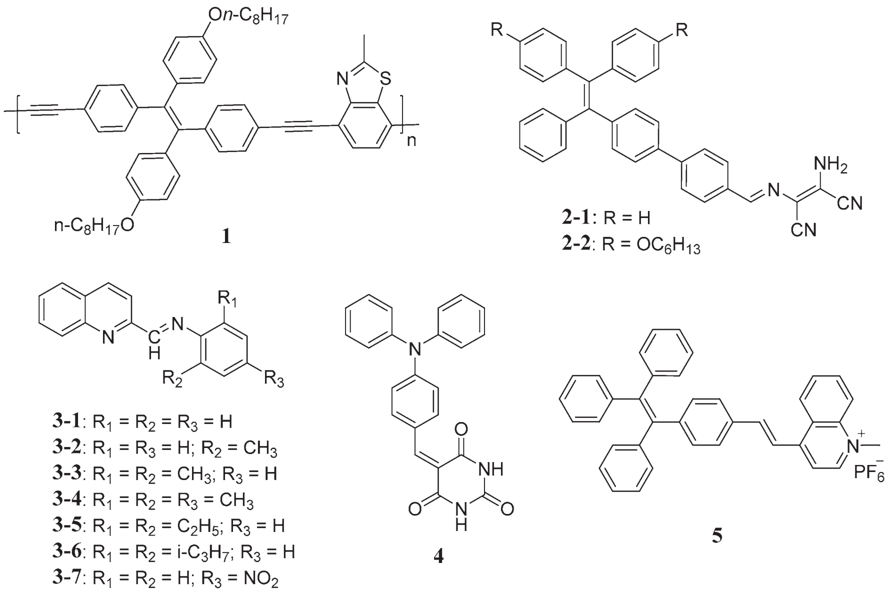


Fig. 3.1 Monomer chemical structures of AIE-based nanosensors **1**-**5** for Hg^{2+} detection

from TPE to the diaminomaleonitrile unit. In consequence, fluorescence intensity decreased gradually thereby achieving the quantification of Hg^{2+}. Further the detection limit of **2-2** was as low as 9.84 nM. These two sensors were shown to be cell permeable, leading to the success of detection of Hg^{2+} in living cells.

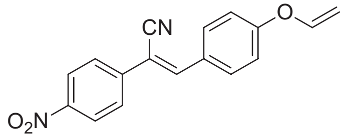
In another separate work, Wang et al. (2019a, b) synthesized seven different substituted Schiff base-based fluorescent sensors from **3-1** to **3-7** with AIE properties via a simple one-step reaction (Fig. 3.1). These sensors could coordinate to Hg^{2+} and aggregate into nanoparticles for achieving fluorescence "turn-on." They prepared *L*-coated test paper by uniformly coating the *L* powder on filter paper. The test paper showed good stability in sensing Hg^{2+}, which proved its potential for commercial use.

Besides, thymine-like amide groups are excellent specific binding sites for Hg^{2+}. Shi et al. (2016) prepared a triphenylamine-barbituric acid adduct **4** with AIEE features through a simple Knoevenagel reaction under mild conditions without a catalyst for sensing Hg^{2+} (Fig. 3.1). Exposure of **4** to Hg^{2+} resulted in the formation of polymer-like complex of thymine-like group in **4** with Hg^{2+} and the significant increase in fluorescence intensity at 600 nm. The formation process of the nanoaggregates exhibited good linearity over the range of Hg^{2+} concentration from 0.5 to 4μM, and **4** possessed excellent anti-interference ability in selectivity experiments.

Further, Hg^{2+} shows high affinity for iodide ion due to the ability to form HgI_2. Zhang et al. (2016) constructed an AIE nanosensor **5** with high sensitivity and selectivity containing a TPE fluorophore, which was functionalized by quinolinium salt with hexafluorophosphate as anion, for Hg^{2+} detection (Fig. 3.1). As a typical quencher, the addition of I^- could quench the red fluorescence emitted by **5** nanoaggregates in aqueous solution. However, the addition of Hg^{2+} could cause the formation of HgI_2 to restore fluorescence, making **5** a "turn-on" fluorescent sensor. The sensing behavior was observed having a good linear relationship at Hg^{2+} concentration of 0.5–4.0μM with a detection limit as low as 71.8 nM. These attributes made **5** suitable for the analysis of Hg^{2+} in water or urine.

The sensors based on special reaction appear to be more selective than those based on ligand complexation. Wang et al. (2015a, b) designed a "turn-off" fluorescent nanosensor **6** with AIE properties and good selectivity based on cyanostilbene derivative by taking advantage of the ability of Hg^{2+} to selectively cleave vinyl groups for sensing Hg^{2+} (Fig. 3.2). As the Hg^{2+} concentration increased, the fluorescence signal of **6** gradually changed from the original strong yellow fluorescence emission to weak emission. This quenching behavior showed good linearity in the range of Hg^{2+} concentration from 0 to 50μM with a low detection limit of 37 nM. Besides, the sensor has been successfully applied to the detection of Hg^{2+} in river, lake, and tap water samples.

Detection of Hg^{2+} based on Hg^{2+}-induced dethioacetalization has been documented, but it usually tends to aggregate and quench the fluorescence in aqueous solution (Gao et al. 2018; Cheng et al. 2010). Recently, our group developed a fluorescent nanosensor **7** functionalized with 2-mercaptoethanol for the detection of Hg^{2+} (Gao et al. 2019). In aqueous solution, **7** exhibited good solubility with weak



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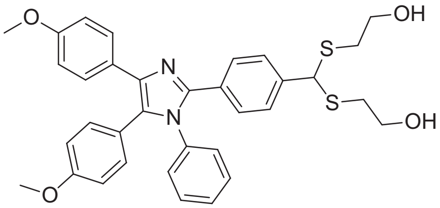

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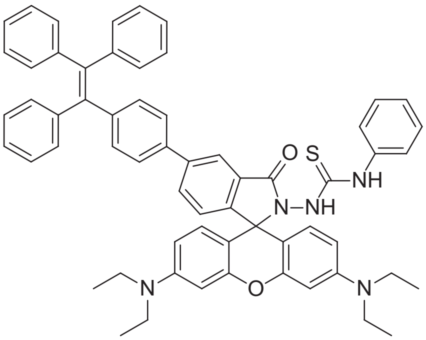

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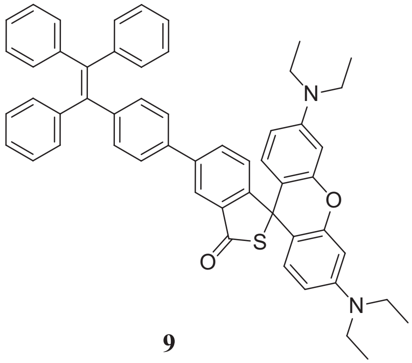

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Fig. 3.2 Monomer chemical structures of AIE-based nanosensors **6**-**9** for Hg^{2+} detection fluorescence emission. Besides, addition of Hg^{2+} caused the hydrolysis reaction to expose the aldehyde group, which changed its solubility and ICT efficiency, resulting in fluorescence "turn-on." The detection limit was as low as 1.45 nM, indicating it is of extremely high sensitivity. Good recovery rate was obtained in recovery experiments of real water samples and urine samples, and the prepared paper test strips were capable of detecting Hg^{2+} with the lowest concentration of 0.3μM. Moreover, **7** was able to image the Hg^{2+} in MDA-MB-231 cells and zebrafish models in a concentration-dependent manner.

Chen et al. (2017) combined TPE and rhodamine to prepare a highly efficient ratiometric nanosensor **8** for the detection of Hg^{2+} (Fig. 3.2). They firstly proposed the dark through-bond energy transfer (DTBET) mechanism; the characteristics of possessing rigid linker, dark donor with low quantum yield, and large torsional angle endowed DTBET-based system with the advantages of high energy transfer efficiency. Furthermore, it could effectively resolve the paradox of the conventional Förster resonance energy transfer (FRET) system that the requirement of large Stokes shift always decreases FRET efficiency. TPE as a dark donor did not leak fluorescence emissions exhibiting high energy transfer efficiency. In the absence of Hg^{2+}, only the blue fluorescence induced by TPE aggregate was observed in aqueous solution. Addition of Hg^{2+} would result in a significant ratiometric change in fluorescent emission due to the DTBET. The detection limit was as low as 0.3 ppb. It is worth mentioning that the nanosensor was applied to evaluate and visualize the bioaccumulation of Hg^{2+} in vivo within the rotifer in subsequent related work (Jiang et al. 2017).

Similarly, another ultrasensitive ratiometric fluorescent nanosensor **9** based on AIE and DTBET was developed by Jiang et al. (2019), which incorporated a rhodamine B thiolactone unit as acceptor (Fig. 3.2). The fluorescence enhancement could reach 30,000-fold when the reaction was saturated. Notably, the detection limit could be as low as 43 pM, which was the lowest among the currently reported ratiometric sensor for Hg^{2+}. Moreover, the absorption spectrum showed that colorimetric detection was also feasible. Paper strips prepared using Whatman filter paper were also developed, which appeared purple when Hg^{2+} was as low as 400 nM and became darker as the concentration increased. The potential utility of **9** for biological application and environmental monitoring was demonstrated through fluorescence imaging in onion tissues and tap water sample recovery study.

Compared with conventional polymers, supramolecular polymers formed by directional and reversible noncovalent interactions have been paid high attention in sensor field due to their advantages of simple preparation, recyclability, and self-adjustability. Macrocycles that are intimately associated with supramolecular polymers play a critical role in providing cavities to accommodate guest molecules. In addition to some conventional macrocycles such as cyclodextrins (Harada et al. 2009), crown ethers (Zheng et al. 2012), calixarenes (Baldini et al. 2007), novel macrocycles such as pillararenes have also been developed recently (Ogoshi et al. 2016).

Wang et al. (2016) have exploited the self-assembled AIE micelles to construct a FRET-based ratiometric sensor **10** for sensing Hg^{2+} in water. They chose

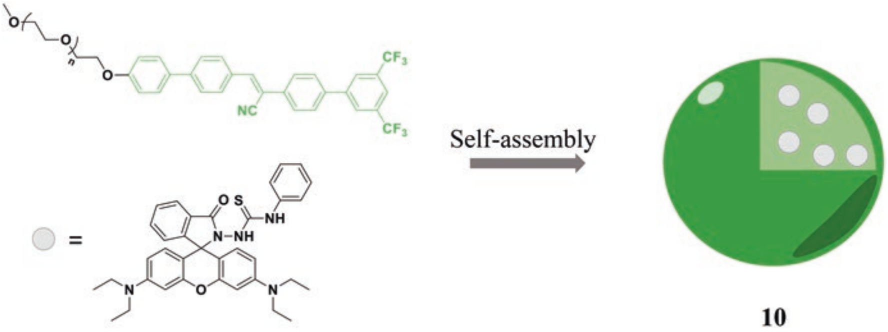


Fig. 3.3 Self-assembled AIE micelles to construct FRET-based ratiometric sensor **10**. Cyanostilbene modified with hydrophilic methoxypolyethylene glycol and trifluoromethyl group (donor) acted as nano-carrier to form a rod-coil. Rhodamine B derivative (acceptor) was encapsulated inside the carrier. Adapted from Wang et al. (2016) with permission from Royal Society of Chemistry

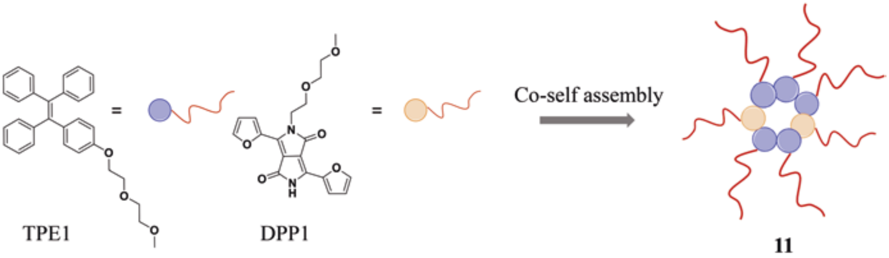
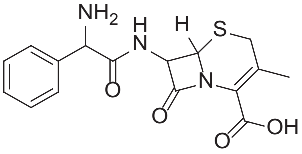


Fig. 3.4 Nanosensor **11** was prepared by co-self-assembly of amphiphilic diketopyrrolopyrrole DPP1 and tetraphenylethylene TPE1 derivatives. The complexation of DPP1 with Hg^{2+} caused aggregation thus quenching its fluorescence but had no effect on the TPE1, thereby achieving ratiometric sensing. Adapted from Nie et al. (2018) with permission from Elsevier

cyanostilbene modified with hydrophilic methoxypolyethylene glycol and trifluoromethyl group capable of increasing hydrophobicity to form a rod-coil self-assembled system as donor and nano-carrier. The rhodamine B derivative was encapsulated inside the carrier (Fig. 3.3). The addition of Hg^{2+} caused the spirolactam ring to open and the maximum fluorescence intensity at 490 nm gradually decreased accompanying the increase in orange emission at 585 nm, which demonstrated the FRET process. The value of $I_{585\ \mathrm{nm}}/I_{490\ \mathrm{nm}}$ had a good linear correlation with the concentration of Hg^{2+} in the range of 0–1.2μM. Besides, the sensor exhibited superior selectivity toward Hg^{2+}.

Interestingly, a novel approach for Hg^{2+} sensing was introduced by Nie et al. (2018). They prepared nanosensor **11** with two-photon property by co-self-assembly of two different molecules, amphiphilic furyl diketopyrrolopyrrole (DPP1) and TPE1, in water (Fig. 3.4). In aqueous solution, DPP1 could self-assemble into loose nanoaggregates and maintain stable fluorescence emission at 540 nm while TPE1



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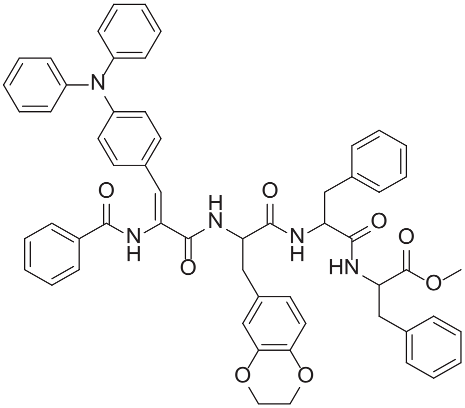

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Fig. 3.5 Monomer chemical structures of AIE-based nanosensors **12**-**13** containing peptide backbone for Hg^{2+} detection

exhibited the AIE effect at 470 nm. The nanosensor, which possessed cavities provided for loading drugs, could be easily obtained by co-self-assembly. The complexation of DPP1 with Hg^{2+} caused aggregation thus quenching its fluorescence but had no effect on the fluorescence of TPE1, thereby achieving ratiometric sensing with a detection limit as low as 13 nM. In view of the fact that DPP1 endowed **11** two-photon absorption characteristic, they achieved the two-photon fluorescence sensing of Hg^{2+} with good linearity. The further recovery experiment in tap water sample made **11** potential for practical application.

Bioorganic compounds have been widely used for fluorescence sensing due to their good biocompatibility, biodegradability, and inherent optical properties (Zhang et al. 2014). Among them, biologically derived materials that can support the AIE effect have received strong interest in the field of materials. Singh et al. (2015) developed a fluorescent nanosensor **12** based on cephalexin self-assembly for Hg^{2+} detection (Fig. 3.5). Notably, the preparation was very convenient in which it only required a pulsed ultraviolet (UV) laser to irradiate the cephalexin aqueous solution. The sulfur moiety of the sensor could be combined with Hg^{2+} to cause fluorescence quenching, thus achieving the Hg^{2+} detection with good selectivity and the detection limit low up to 10^{-7} M.

The peptide is an attractive material in the sensing field due to their unique advantages, such as the simplicity of preparation, the adjustability of the peptide backbone, biocompatibility, degradability, and low toxicity. Besides, they possess multiple sites for metal building (Oliveira et al. 2011; Wang et al. 2015a, b). Given all that, Tomar et al. (2018) synthesized a self-assembling tetrapeptide **13** with an overlapping turn of type III/III for sensing Hg^{2+}, the fluorophore of which was the dehydrophenylalanine residue (Fig. 3.5). The peptide monomers could self-assemble into spherical nanoparticles with a hydrophobic hollow core. The accumulation of Hg^{2+} in the hollow core induced aggregation accompanying enhanced fluorescence, which illustrated the AIE property of the tetrapeptide. It is worth mentioning that the overlapping β-turn scaffold was essential for specific sensing of Hg^{2+}.

3.2.2 *Metallic Nanoparticles/Clusters*

In recent years, metallic nanoclusters such as Au nanoclusters (Au NCs) and Ag nanoclusters (Ag NCs) have proven their application value in the field of material science due to their simplicity of preparation, modifiability, high surface area, and dielectric constant. They generally consist of a several to hundreds of Au/Ag atoms-containing metal core and a ligand shell, and they are smaller than 5 nm in size. Importantly, they possess molecular-like photoluminescence (PL) behavior adjusted by different size, oxidation states, and species of capping agents (Saha et al. 2012; Wilson 2008; Zhang et al. 2020). Considering the advantages of fluorescence stability, large Stokes shift, and biocompatibility, a large majority of researchers applied Au/Ag NCs to fluorescence detection of heavy metal ions based on metal ions induced fluorescence enhancement or quenching.

Au NCs have attracted tremendous attention in detecting mercury because of the high affinity from metallophilic Hg^{2+}-Au interactions (Xie et al. 2010). AIE organic fluorescence nanoparticles (OFNs) and Au NCs were combined by electrostatic interaction to obtain a ratiometric fluorescent sensor **14** for detecting Hg^{2+} (Niu et al. 2015). A 9,10-stilbene-ruthenium (9,10-di((E)-styryl)anthracene [DSA]) derivative was applied to bind ε-polylysine to form positively charged nanoparticles Ply-9,10-bis(3-formylstyryl)anthracene (BFSA) OFNs as a reference material, while bovine serum albumin (BSA) stabilized nanoclusters as a responsive material with negative charge (Fig. 3.6). OFNs possessed stable green emission with the DSA derivative aggregates while red-emitting nanoclusters would quench when sensing Hg^{2+}, resulting in the entire sensing system eventually turning green-emitting. Moreover, this change appeared observable to the naked eyes. The sensing process exhibited excellent linearity in the range of Hg^{2+} concentration from 0 to 1μM with detection limits as low as 22.7 nM. Cell experiments confirmed the good biocompatibility, and the nanosensor was found to be predominantly localized in the cytoplasm. Moreover, the stability verification experiment in human serum indicated the obvious practicability.

Ag NCs are also regarded as important sensing materials for Hg^{2+} detection due to their good stability and low cost. Besides, some possess the property of AIE such as thiolate-protected nanoclusters (Zhang et al. 2015a, b). Interestingly, hydrophilic ligand-protected nanoclusters have good solubility in aqueous solution and cannot maintain strong stable emission. Pan et al. (2018) demonstrated for the first time the hydrophobic interaction-induced AIE Ag NCs **15**. It was capped with thiosalicylic acid acting as hydrophobic capping ligand for detecting Hg^{2+} (Fig. 3.7). When the ratio of thiosalicylic acid to silver ion was 1:4, the optimum luminescence was obtained at 612 nm. The addition of Hg^{2+} could cause the fluorescence quenching,

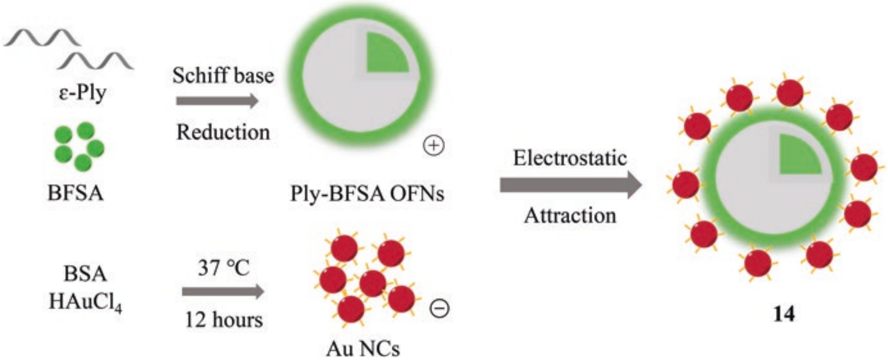

Fig. 3.6 Schematic illustration of the synthesis of the dual-emission ratiometric nanosensor **14** for the detection of Hg^{2+}. Ply-BFSA OFNs were synthesized through the reaction between ε-Ply and BFSA. Red-emitting Au NCs were prepared via a simple procedure using BSA. Through the electrostatic adsorption, Ply-BFSA OFNs with positive charge and Au NCs with negative charge assembled into **14**. Adapted from Niu et al. (2015) with permission from Royal Society of Chemistry

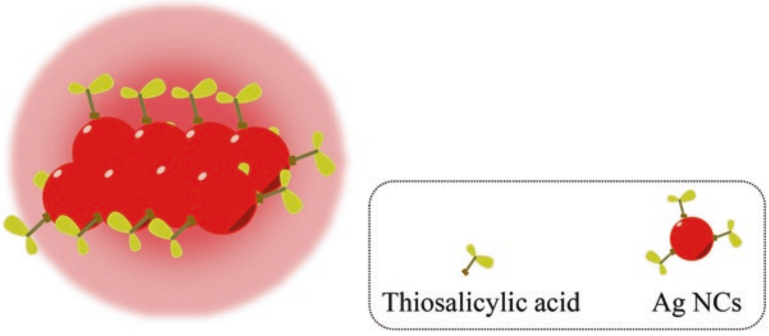

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Fig. 3.7 Schematic composite of AIE Ag NC **15**. Sensor **15** was capped with thiosalicylic acid acting as hydrophobic capping ligand, for the detection of Hg^{2+}. Upon addition of Hg^{2+}, the fluorescence of **15** would be quenched in a linearity behavior from 0.3 to 2.2μM. Adapted from Pan et al. (2018) with permission from Royal Society of Chemistry

and the quenching behavior exhibited good linearity in the range of 0.3–2.2μM (limit of detection [LOD] = 91.3 nM). Moreover, **15** possessed good cell permeability and excellent anti-photobleaching ability.

Copper nanoparticles (Cu NPs) have also attracted considerable attention due to their relatively low price and large abundance in nature. Hatamie et al. (2016) synthesized **16** by using D-penicillamine (DPA) as stabilizing agent and ascorbic acid as reductant under dark condition, which overcame the obstacles of the instability and tendency of Cu NPs to oxidize (Fig. 3.8). The obtained aggregates exhibited strong red fluorescence emission, which benefited from the ligand-to-metal charge

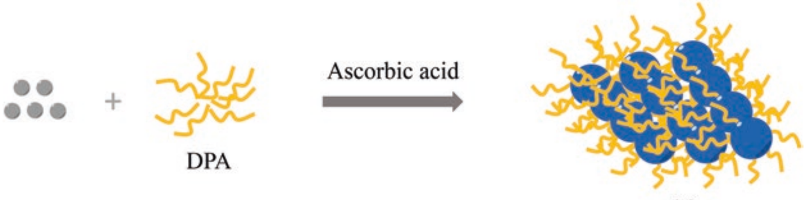

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Fig. 3.8 Synthetic strategy of AIE-based Cu NPs **16**. Red-emitting **16** was prepared by using DPA as a stabilizing agent and ascorbic acid as reductant. Adapted from Lin et al. (2016) with permission from Elsevier

transfer between the thiolate ligands in the DPA and Cu atoms. Upon the addition of Hg^{2+}, the high-affinity metallophilic interaction promoted the formation of the closed-shell complexes, which further inhibited the binding of the thiolate ligands with the Cu atoms. In consequence, the aggregates were dispersed into the small homogeneous particles accompanying the fluorescence quenching. The quenching behavior exhibited good linearity in the range from 1.0 to 30μM of Hg^{2+} concentration (LOD = 32 nM). The superior properties made **16** capable of detecting Hg^{2+} in tap water.

3.2.3 Carbon Dots

Carbon dots, a newly emerged nanomaterial consisting of carbon (C), oxygen (O), nitrogen (N), hydrogen (H), and some doped elements, have been widely concerned in the field of sensing and bioimaging because of their simple synthesis, unique PL feature, excellent photostability, and good biocompatibility (Hola et al. 2014). Moreover, compared with Au/Ag nanoclusters, carbon dots are more environment friendly. The PL properties of carbon dots can be tuned by modulating the size and surface of chemical groups, and higher quantum yields can be obtained by doping other elements or inorganic salts (Wang et al. 2014).

As widely acknowledged, the carbon dots based on fluorescence enhancement generally showed better selectivity and higher accuracy in contrast with those sensors based on fluorescence quenching. Xu et al. (2018) studied the nitrogen and sulfur co-doped fluorescent carbon dots (N,S-CDs, **17**) prepared in glycerol for quantification of Hg^{2+} based on fluorescence “turn-on” method (Fig. 3.9). They took a one-step microblog-assisted method to obtain N,S-CDs with glycerol and cystine as reactants, and the average size was at 1–6 nm. Glycerol was used here not only as a solvent but also as a passivator proved by the presence of hydroxyl groups derived from glycerol on the surface of N,S-CDs. The specific interaction between sulfur-containing groups and Hg^{2+} led to aggregation, which induced AIEE at 385 nm thereby achieving detection with good selectivity (Table 3.1).

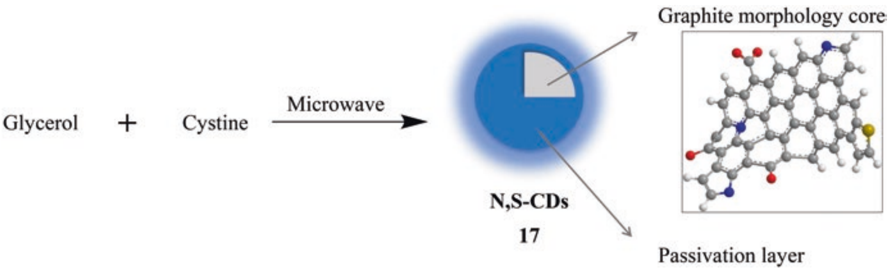

Fig. 3.9 Synthesis process and structure of nitrogen and sulfur co-doped fluorescent CDs (N,S-CDs, **17**). Sensor **17** was obtained by a one-step microblog-assisted method using glycerol and cystine as reactants. It composited of two fragments: graphite morphology core and passivation layer. Adapted from Xu et al. (2018) with permission from Springer

3.3 AIE-Based Nanosensors for the Detection of Cu^{2+}

Another promising direction of AIE-based nanosensors for practical application is the establishment of methods for Cu^{2+} detection. Unlike sensor for Hg^{2+}, nanosensor for tracing Cu^{2+} acts more in a “turn-off” behavior since Cu^{2+} itself is a fluorescence quencher due to its paramagnetic nature (Glaser et al. 2007). Besides, the chelation between Cu^{2+} and identification groups has effect on the nanoaggregates of nanosensors, leading to the attenuated intensity of fluorescence (Singh et al. 2016; Liu et al. 2017). As a result of both aspects, the fluorescence emission is quenched, also called chelation-enhanced quenching. Utilizing this strategy, numerous nanomaterials have been employed to construct “On-Off” nanosensors to detect Cu^{2+}, including organic molecule nanoparticles, metal-organic frameworks, hydrogen-bonded organic frameworks, and organic dots.

3.3.1 *Organic Molecule Nanoparticles*

Considering the difference in the identification units, it can be divided into several categories: (1) imine groups, for instance, Schiff bases, hydrazones, or salicylaldehyde Schiff base scaffold; (2) pyridine units; (3) multiple carboxyl groups; and (4) aza-crown ether. Exploiting these units as ligands for complexing with Cu^{2+}, the fluorescence emission of AIE fluorophores could be tuned after response behavior happens.

Among these recognition components, imine groups are the parts mainly deployed. Since the imine group has strong affinity to Cu^{2+}, coupling the AIE fluorophores and imine groups paves an interesting pathway to construct an AIE nanosensor for Cu^{2+} detection (Zou et al. 2012; Huo et al. 2012). Besides, some hydrazones derived from salicylaldehyde have even been reported to exhibit a typical AIE feature, meaning no need for further introduction of AIE units (Liu et al.

Table 3.1 List of characteristics of nanosensors with AIE properties developed for Hg^{2+} detection

Nanosensor	Emission wavelength	Concentration of sensors	S:A	LOD	Linear range	System	Real water examples	References
1	525 nm	10μM	1:1	–	–	THF/water (1:9 v/v)	–	Wei et al. (2018)
2	–	10μM	2:1	9.84 nM	–	THF/water (1:9 v/v)	–	Wang et al. (2018a, b)
3	550 nm	–	1:1	0.20 nM	0–120μM	Water	Y	Wang et al. (2019a, b)
4	600 nm	50μM	–	3.4μM	0.5–4.0μM	THF/water (3:7 v/v)	–	Shi et al. (2016)
5	610 nm	10μM	–	71.8 nM	0.5–4.0μM	DMSO/water (1:99 v/v)	–	Zhang et al. (2016)
6	537 nm	20μM	–	37 nM	0–50μM	PBS	Y	Wang et al. (2015a, b)
7	490 nm	10μM	–	1.45 nM	0–302.4 nM	DMSO/water (1:99 v/v)	Y	Gao et al. (2019)
8	595/485 nm	10μM	–	0.3 ppb	–	CH_3CN/water (4:6 v/v)	–	Chen et al. (2017)
9	592/485 nm	10μM	–	43 pM	2–10μM	CH_3CN/water (4:6 v/v)	Y	Jiang et al. (2019)
10	585/490 nm	–	–	0.11μM	0.1.2μM	Water	–	Wang et al. (2016)

11	540/470 nm	–	–	Ca. 13 nM	–	Water	Y	Nie et al. (2018)
12	460 nm	–	–	0.1μM	–	Water	–	Singh et al. (2015)
13	500 nm	50μM	1:1	10μM	–	Acetonitrile	–	Tomar et al. (2018)
14	625/525 nm	–	–	22.7 nM	50–1000 nM	THF/water (0.5:99.5 v/v)	–	Niu et al. (2015)
15	612 nm	6.6 ug/mL	–	91.3 nM	0.3–2.2μM	Water	–	Pan et al. (2018)
16	620 nm	–	–	23 nM	1.0–30 nM	Water	Y	Lin et al. (2016)
17	385 nm	–	–	0.5μM	1–75μM	Water	Y	Xu et al. (2018)

S:A stoichiometric ratio; *LOD* lowest limit of detection, *THF* tetrahydrofuran, *DMSO* dimethyl sulfoxide, *PBS* phosphate buffered saline; Y means successful practical application in real water samples

2015; Tiwari et al. 2018; Liu et al. 2017). Regrettably, the fluorescent intensity of such nanosensors sometimes showed abnormal fluctuation in the presence of Al^{3+}, Fe^{2+}, or Fe^{3+}, which limits its further practical application (Xu et al. 2019).

Feng et al. (2014) designed and synthesized a Schiff base macrocycle by the condensation reaction of TPE dialdehyde and 1,2-benzenediamine (Fig. 3.10). In an aqueous solution, the macrocycle (**18**) aggregated into nanofibers emitting strong fluorescence. After addition of Cu^{2+} at 13μM, the quench of fluorescence emission accompanying a color change from colorless to intense yellow-brown could be observed by the naked eyes. Sensor **18** was capable of achieving the nM level detection since the interspace in the macrocyclic framework between the two circumjacent imine groups just accommodated one Cu^{2+} ion. Moreover, the high selectivity toward Cu^{2+} among various metal ions allowed detection in various matrix, including real water and pork juice-containing water.

Singh et al. (2016) developed nanosensor **19** by taking advantage of the strategy involving excited state intramolecular proton transfer coupled AIE effect (Fig. 3.10). Sensor **19** could self-assemble into nanorods and exhibited intense green fluorescence in aqueous solution, but the presence of Cu^{2+} could disrupt the self-assembled aggregates via the metal chelation with Schiff base unit. Consequently, the nanorods were disassembled showing nearly no emission. Moreover, **19** could also be used for colorimetric assay along with the discernible color transition from light green to dark green.

Sharma et al. (2017) developed a Cu^{2+} nanosensor **20** based on the diimino dicarbazole derivatives with AIEE properties (Fig. 3.10). The aggregates of **20** could selectively sense Cu^{2+} in the nanomolar range and mediate the reduction of Cu^{2+} to Cu nanorods via the interaction with the nitrogen atoms of the imines. Along with the conversion, the fluorescence was quenched accompanying with the color change from light yellow to dark yellow. Further, ensembles of **20** and Cu nanorods were utilized for selective sensing of CN^- ions, which could itch the Cu nanorods and recover the aggregation state of **20**.

Huang et al. (2018) designed a chiral molecule **21** with AIEE characteristics by introducing a chiral alanine to hydrazone derivative (Fig. 3.10). Cu^{2+} exhibited high affinity to the nitrogen atom of the imine moiety and oxygen atom of the phenolic hydroxyl. Addition of Cu^{2+} resulted in fluorescence quenching due to the photoinduced electron or energy transfer process. Meanwhile, the self-assembly of **21** was transformed from long nano-helical fibers into irregular polyhedral particles. The "On-Off" behavior allowed detection of Cu^{2+} in concentration ranging from 0 to 0.6μM with an LOD calculated to be 67 nM. It is worth mentioning that the chiral component endowed **21** with the properties of aggregation-induced circular dichroism and circularly polarized luminescence.

The Cu^{2+}-induced AIE fluorescence of 5-chlorosalicylaldehyde azine (**22**) quenching was first illustrated by Liu (2015) and the salicylaldehyde azine provided a new platform for Cu^{2+} detection. For instance, Liu et al. (2017) synthesized two Schiff base compounds via the condensation of salicylaldehyde or 2-hydroxy-1-naphthaldehyde with hydrazine hydrate (Fig. 3.10). The two AIE active compounds (**23** and **24**) could aggregate into needle-like particles in pure aqueous environment

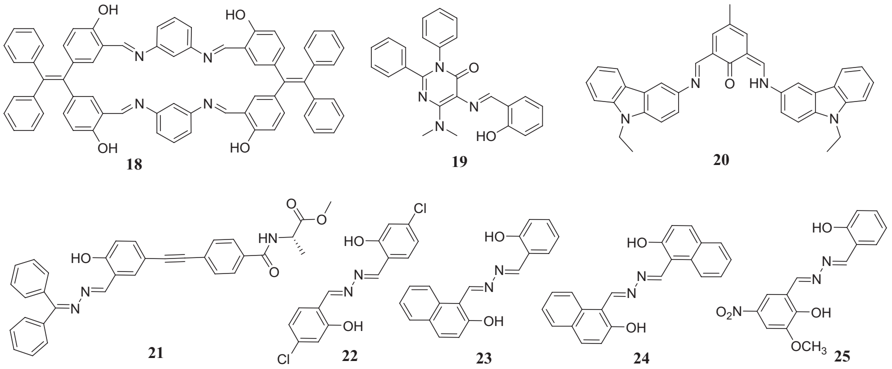

Fig. 3.10 Monomer chemical structures of AIE-based nanosensors **18**-**25** containing Schiff bases or hydrazones for Cu^{2+} detection

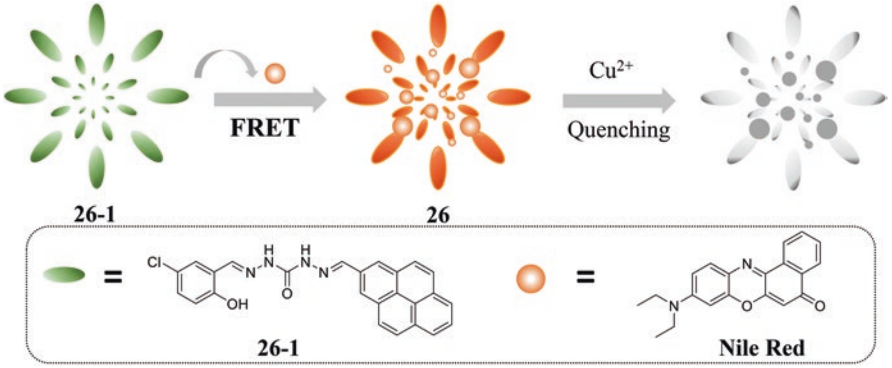

Fig. 3.11 Novel AIE plus FRET strategy for Cu^{2+} detection with elevated sensitivity. Sensor **26-1** was combined with the Nile red to construct a FRET system (**26**) in which the energy of the excited state was transferred from **26-1** to Nile red. Upon addition of Cu^{2+}, the green fluorescence of **26-1** could be quenched thus disrupting the FRET process, making the sensitivity to be elevated hundreds of times. Adapted from Yang et al. (2019a, b) with permission from Elsevier

exhibiting intensive green fluorescence. Addition of Cu^{2+} promoted the further self-assembly to form more stable complexes, thus quenching the fluorescent emission. The “Off-to-On” response happened when the concentration of Cu^{2+} was as low as 10 ± 0.3 nM. More recently, Xu et al. (2019) reported an asymmetric hydrazone **25** based on salicylaldehyde for fluorometric “turn-off” detection of Cu^{2+} (Fig. 3.10). Owing to the introduction of an electron acceptor (nitro group), the fluorescence of **25** exhibited a little red-shift with a strong orange emission in the aggregate state. Sensor **25** was shown to have high sensitivity for Cu^{2+} (LOD = 74.5 nM).

Yang et al. (2019a, b) synthesized a material **26-1** derived from carbohydrazide displaying strong green emission in the nanoaggregates, which could be quenched upon addition of Cu^{2+}, as depicted in Fig. 3.11. Regrettably, the LOD of **26-1** was higher as 13.2μM, which lacked sufficient sensitivity to meet the need for practical

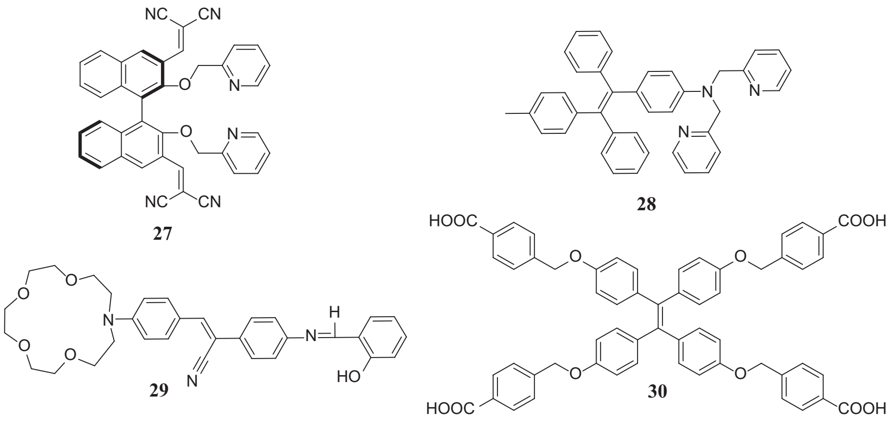

Fig. 3.12 Monomer chemical structures of AIE-based nanosensors **27**-**30** for Cu^{2+} detection

application. In view of this, they combined **26-1** with Nile red to construct a FRET system (**26**). Consequently, the LOD of **26-1** was elevated into nano level (9.12 nM). Meanwhile, as the green emission of **26-1** acted as excitation energy for Nile red, the fluorescent signal of the mixed aggregates was red-shifted to 630 nm. This novel AIE plus FRET strategy provided a well-anticipated avenue to improve some poor properties and disadvantages of AIE active nanosensors.

Besides imine groups, some nanomaterials could also serve as a superior nanosensor for Cu^{2+} after introduction of multiple pyridine units (You et al. 2011; Zhang et al. 2013a, b), and act like the nanosensors containing Schiff bases in a chelation-enhanced quenching behavior (Dasgupta et al. 2008). Li et al. (2015a, b) utilized AIE active binaphthol to develop a Cu^{2+} nanosensor **27** with the assistance of the pyridine moieties (Fig. 3.12). Upon addition of Cu^{2+}, the morphological structure of aggregates of **27** is transformed from nano-polyhedra into micro-branches, and the strong ligand-to-metal charge transfer also contributed to the quenching of fluorescence. Besides the fluorophore of **27**, binaphthol is a well-known chiral fluorophore, thus allowing the circular dichroism signal as well.

Dipicolylamine unit is another multi-pyridine moiety with high affinity to Cu^{2+} and serves as an identification group in some sensors for Cu^{2+} detection (Choi et al. 2009). For example, recently a dipicolylamine unit was attached with TPE group to prepare a Cu^{2+} nanosensor **28** (Fig. 3.12) (Li et al. 2017). The nanoaggregates of **28** emitted intense green fluorescence in aqueous solution and could be effectively quenched by the presence of Cu^{2+}. This quenching process was highly selective toward Cu^{2+} over other metal ions thus guaranteeing its high anti-interference. The linear concentration of Cu^{2+} ranged from 0 to 8.0μM while LOD was found as 4.29 nM, all validating its possibility in practical application in complex water matrix and living cells.

Crown ether group is another choice to constitute a moiety with high affinity to Cu^{2+} (Zheng et al. 2012). In Zhang's works, aza-crown ether was selected as a ligand to Cu^{2+} and coupled with Schiff base to construct a Cu^{2+} nanosensor **29** (Fig. 3.12;

Zhang et al. 2017a, b). In aqueous media, **29** aggregated into irregular globular-like aggregates emitting strong fluorescence but quenched in the presence of Cu^{2+}. Although the sensitivity was not ideal (LOD = 2.32μM), **29** exhibited rather higher selectivity while the interference of other coexisting metal ions was nearly negligible. The superior performance was ascribed to the appropriate characteristics of aza-crown ether such as the cavity of the macrocycle, the number of binding sites, or the variety of oxygen and nitrogen atoms on the crown. These all contributed to the practical detection of Cu^{2+} in real water.

TPE derivative **30** with quadruple carboxyl groups was illustrated having specific selectivity for Cu^{2+} ions in Geng's work, as shown in Fig. 3.12 (Geng et al. 2019). In aqueous solution, the aggregates of **30** exhibited intense blue emission but the addition of Cu^{2+} could lead to the fluorescence quenching. The quench efficiency of fluorescence exhibited linearity in the large range of 0–15μM with detection limit as low as 4.5 nM. Sensor **30** has been applied in fabricating test strips for detecting Cu^{2+} attributed to its strong emission in solid states.

3.3.2 Metal-Organic Frameworks

Although numerous nanosensors involving AIE scaffolds salicylaldehyde azines exhibited high affinity to Cu^{2+}, their pH-dependent emission still limited their practical application (El-Sherif and Aljahdali 2013). Lu et al. (2016) provided a facile strategy to surmount this obstacle by confining them within metal-organic frameworks. The complex **31** was formed via the integration of **31-1** into a zirconium(IV) dicarboxylate porous material (UiO-66) exhibiting concentration and pH-independent fluorescence emission, as shown in Fig. 3.13. Owing to the nano-space confined effect, the space torsion of **31-1** was restricted, thereby exhibiting strong

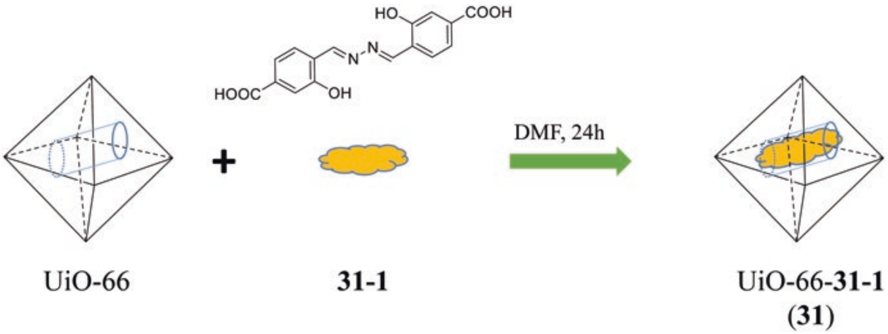

Fig. 3.13 Formation process and structure of complex **31**. Complex **31-1** was integrated into UiO-66 to obtain UiO-66-**31-1** complex (**31**). Via the host-guest process, encapsulation of **31-1** into the metal-organic frameworks could enlarge its application in pH and concentration-independent behavior. Adapted from Lu et al. (2016) with permission from Royal Society of Chemistry

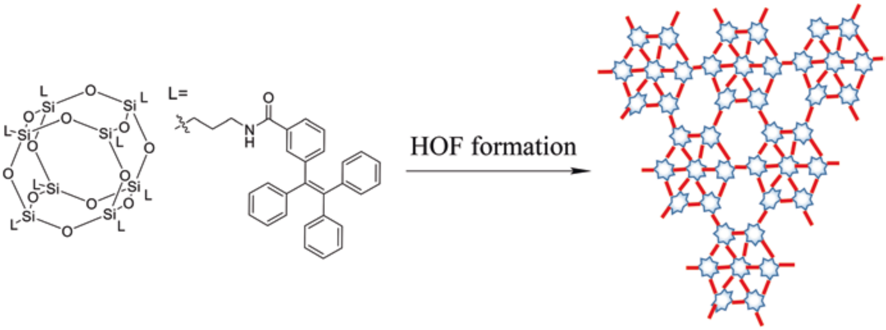

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Fig. 3.14 Structural illustration of the formation of hydrogen-bonded organic frameworks **32** for Cu^{2+} sensing. With amide linkages, it was formed without employment of any guest molecules. Owing to the restriction of intra- and inter-molecular rotation, the blocked non-radiative channel led to the intensive emission of **32**. Adapted from Zhou et al. (2015) with permission from Royal Society of Chemistry

fluorescence over a wide pH range (pH = 4.0–8.0) as well as at low concentration, which could enlarge their application in some extreme environments. Since the guest **31-1** possessed a high affinity to Cu^{2+}, **31** served as a sensitive and selective nanosensor for Cu^{2+} detection in aqueous solution (LOD = 50 nM).

3.3.3 Hydrogen-Bonded Organic Frameworks

Hydrogen-bonded organic framework is another pathway to detect Cu^{2+} with increasing interest as stimuli-sensitive nanomaterials. For example, **32** could form a stable structure without the employment of any guest molecules, and disperse well in organic solution (Zhou et al. 2015). Owing to the restriction of intra- and inter-molecular rotation, the non-radiative channel was blocked, leading to high fluorescence (Fig. 3.14). Nevertheless, Cu^{2+} ions could coordinate with the amide groups and impair the interaction of hydrogen bond, thus causing the dissociation of frameworks. Subsequently, the intramolecular rotation of TPE moieties was allowed and the non-radiative channel was opened. Regrettably, the detection was performed in DMSO, which largely limited its practical application.

3.3.4 Metallic Nanoparticles/Clusters

As mentioned above, Cu NPs/NCs have been used widely in metal detection. Generally, highly fluorescent Cu NCs are formed by adding ligands into Cu^{2+} solution, with the “Off-to-On” fluorescence change (Kasana et al. 2017). In view of this unique transformation, Li et al. (2015a, b) employed the fast formation process of Cu NCs (**33**), in which penicillamine was chosen as ligands, to detect Cu^{2+}. Due to the high specificity, no fluorescence could be triggered upon addition of metal ions, except for Cu^{2+}. Even the introduction of Ag^{+} and Au^{3+}, two of noble metal ions often used for the construction of metal nanoparticles/clusters, had no impact on the detection process. In light of this strategy based on the formation process of Cu NCs, it may provide a new means for developing a low-cost, real-time, and easy-to-use sensor for evaluation of Cu^{2+}.

3.3.5 Organic Dots

Similar to hydrogen-bonded organic frameworks that could modulate the property of AIE materials, organic dots provided another way to pave for the development of novel functional AIE materials (Dasgupta et al. 2017). Jiang et al. (2018) prepared poly(acrylamide-co-acrylic acid) (PSMA)-coated organic dots **34** in which 9,10-di((E)-styryl)anthracene (DSA) was employed as the AIE fluorescent material. As shown in Fig. 3.15, the hydrophobic moieties were encapsulated inside while the carboxyl groups were exposed on the surface in the self-assembly process of AIE dots. In water, the suspension of **34** displaying intense green-yellow fluorescence could be quenched by Cu^{2+} with LOD calculated as 107 nM. The response was attributed to the high-affinity coordination of carboxyl groups with metal ions. Nonetheless, similar efficiency of quenching also happened to Fe^{3+} and other ions (Table 3.2).

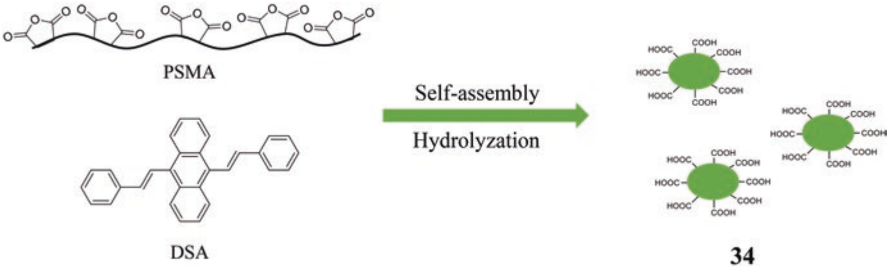

Fig. 3.15 Proposed self-assembly process and structure of organic dots **34**. DSA was encapsulated inside while the carboxyl groups were exposed on the surface of **34**. DSA was an AIE fluorescent material and these carboxyl groups were provided by PSMA. Adapted from Jiang et al. (2018) with permission from MDPI

Table 3.2 List of characteristics of nanosensors with AIE properties developed for Cu^{2+} detection

Nanosensor	Emission wavelength	Concentration of sensors	S:A	LOD	Linear range	System	Real water examples	References
19	526 nm	1μM	1:1	0.26 ppb	0–2.5μM	CH_3CN/water (1:99 v/v)	Y	Singh et al. (2016)
20	447 nm	10μM	–	90 nM	–	THF/water (3:7 v/v)	–	Sharma et al. (2017)
21	586 nm	10μM	1:1	67 nM	0–0.6μM	THF/water (1:9 v/v)	–	Huang et al. (2018)
24	530 nm	10μM	4:1	(10 ± 0.3) nM	–	CH_3CN/water (1:99 v/v)	–	Liu et al. (2017)
25	570 nm	10μM	1:1	74.5 nM	0.5–5.0μM	CH_3CN/water (1:99 v/v)	–	Xu et al. (2019)
26	525 nm	10μM	1:1	132 nM	–	CH_3CN/water (1:99 v/v)	–	Yang et al. (2019a, b)
27	511 nm	10μM	1:1	148 nM	–	DMSO/water (2:8 v/v)	–	Li et al. (2015a, b)
28	500 nm	10μM	1:1	4.29 nM	0–8.0μM	DMSO/water (1:4 v/v)	–	Li et al. (2017)
29	570 nm	10μM	1:1	2.32μM	–	DMSO/water (1:99 v/v)	Y	Zhang et al. (2017a, b)
30	432 nm	10μM	1:2	4.5 nM	0–15μM	Ethanol/water (1:9 v/v)	–	Geng et al. (2019)
31	560 nm	10μM	1:1	50 nM	0.1–4.0μM	Water	Y	Lu et al. (2016)
33	673 nm	–	–	0.3 ppm	0.95–6.35 ppm	–	Y	Li et al. (2015a, b)
34	524 nm	–	–	107 nM	0.025–6μM	–	–	Jiang et al. (2018)

S:A stoichiometric ratio
LOD lowest limit of detection, *THF* tetrahydrofuran, *DMSO* dimethyl sulfoxide; Y means successful practical application in real water samples

3.4 AIE-Based Nanosensors for the Detection of Zn^{2+}

Although it has been documented that dipicolylamine, 8-aminoquinoline, semicarbazide, and carboxyl were superior recognition components toward Zn^{2+} (Carol et al. 2007; Jia et al. 2012; Liu et al. 2013), their roles in AIE organic molecule nanoparticles were still rarely illustrated. By contrast, metallic NPs/NCs have been greatly developed. Au NCs, Ag NCs, and Cu NCs were all employed in the detection of Zn^{2+}. Besides, the combination of Au NCs with metal-organic frameworks appeared as a good way to elevate the detection sensitivity and selectivity (Li et al. 2018).

3.4.1 Organic Molecule Nanoparticles

As one of the well-known building blocks of AIE fluorophores, the terpyridine moiety is also a metal-chelating group (Swiegers and Malefetse 2000; Schubert and Eschbaumer 2002). Jung et al. (2015) constructed a terpyridine-based nanosensor **35** for detecting Zn^{2+} (Fig. 3.16). The chelation between the terpyridine moieties and the Zn^{2+} induced the nanosensor **35** aggregation from the fibrillar structure into a spherical structure. This molecular aggregation by coordination bonding led to the restriction of intramolecular rotation (RIR) without π-π stacking. Therefore, the aggregated **35** could be utilized as a "turn-on" fluorescent nanosensor for Zn^{2+}. The fluorescence intensity showed tenfold enhancement when the concentration of Zn^{2+}

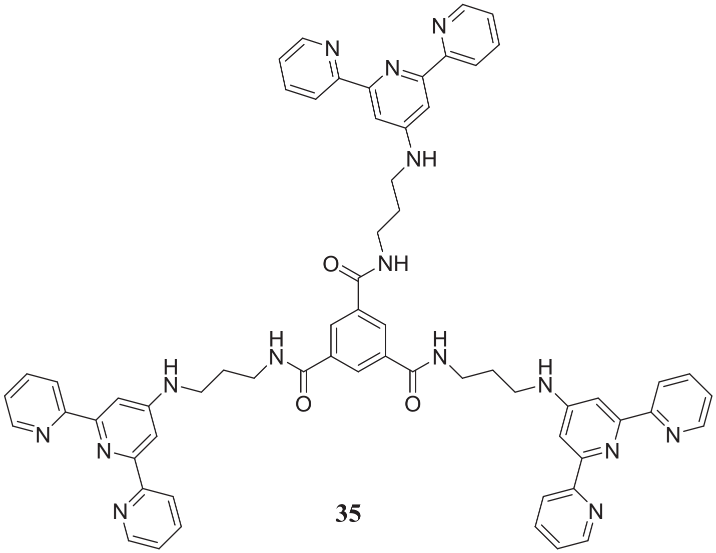

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Fig. 3.16 Monomer chemical structures of AIE-based nanosensors **35** for Zn^{2+} detection

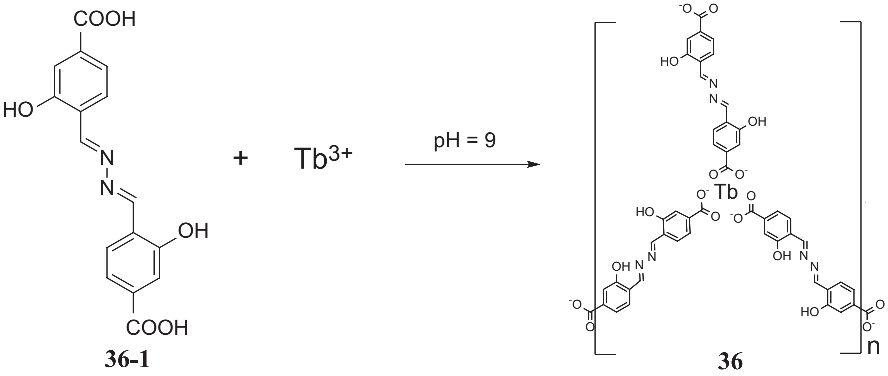


Fig. 3.17 Schematic representation of the preparation of metal-organic frameworks **36**. Sensor **36** was formed by self-assembly due to the coordination of carboxylate groups to Tb^{3+} ions

was increased to 15 nM, while a strong fluorescence emission could still be observed as low as 1.1 nM. In addition, **35** was used to detect Zn^{2+} in urine samples successfully.

3.4.2 Metal-Organic Frameworks

Metal-organic frameworks have played an indispensable role in Zn^{2+} detection as well. For instance, Lin et al. (2017a, b) utilized an AIE fluorophore, **36-1**, to prepare a Zn^{2+} ratiometric fluorescent nanosensor **36** (Fig. 3.17). The nanosensor was formed by self-assembly due to the coordination of the carboxylate groups to metal ions. Interestingly, **36-1** exhibited different wavelength emission in combination with different ions, with Tb^{3+} emitting at 590 nm and Zn^{2+} at 470 nm. In view of the cation exchange process of **36** with Zn^{2+}, the complex was developed as a ratiometric fluorescent nanosensor with high selectivity for the detection of Zn^{2+}. The ratiometric biosensor could be applied for detection of Zn^{2+} in real water samples. Worth to mention, this strategy using the cation exchange process of metal-organic frameworks paved a way toward AIE nanomaterials with ratiometric fluorescence response.

3.4.3 Metallic Nanoparticles/Clusters

In the preparation process of metallic NPs/NCs, ethanol or some external stimulants were required to induce pre-aggregation (Kasana et al. 2017; Kong et al. 2017). For mercaptopropionic acid or glutathione (GSH)-capped metallic NPs/NCs, Zn^{2+} could act as cross-linker to bridge components, promoting further aggregation of these nanoparticles. As a result, the tighter aggregates yielded stronger fluorescence.

Additionally, elevated sensitivity, higher selectivity, or even ratiometric behavior could be achieved via combining with other active nanomaterials.

Recently, Kuppan, and Maitra (2017) reported rapid room temperature synthesis of 3-mercaptopropionic acid-capped Au NCs (**37**) in aqueous solution. Since the carboxylate groups of 3-mercaptopropionic acid acted as a ligand with high affinity to Zn^{2+}, the electrostatic binding with Zn^{2+} could rigidify the Au NCs, causing the million-fold enhancement of yellow fluorescence ($\lambda_{em} = 580$ nm). Then, further self-assembly took place to yield highly ordered NCs, and the emission of yellow would transform into green ($\lambda_{em} = 500$ nm). According to the unique behavior, it has been applied for visual and fluorimetric detection of Zn^{2+} with rather high sensitivity (LOD = 9 nM).

In another work, Li et al. (2018) revealed that GSH-capped Au NCs/Zn-MOF composite (**38**) could be of analytical applications in Zn^{2+} detection (Fig. 3.18). In the mixture of Au NCs and 2-methylimidazole (**2-MIM**), the addition of Zn^{2+} could induce the generation of Zn-MOF in situ within which Au NCs were confined. Compared with sole Au NCs, the quantum yield, sensitivity, and selectivity were all elevated, presenting a relatively large linear range (12.3 nM to 24.6 mM) and considerably low LOD as 6 nM. In view of these superior characteristics, **38** was further applied to detect Zn^{2+} in various complex matrixes, including human serum, syrup samples, and milk. The success of unconventional combination of Au NCs with metal-organic frameworks provides a novel nanoscale platform for Zn^{2+} detection, although these metal-organic frameworks were not stable under acidic media.

In order to reduce the costs of metal nanoparticles/clusters using noble metals, Lin et al. (2017a, b) utilized $Cu(NO_3)_2$ to prepare Cu NCs (**39**) capped by GSH with red emission for "turn-on" detection of Zn^{2+}. The presence of Zn^{2+} could cross-link the Cu NCs by electrophilic interaction to form aggregates, inducing the fluorescence enhancement. Compared with Au NCs mentioned above, the Cu NCs exhibit a faster response toward Zn^{2+} and a wider detection range (4.68–2240μM). Moreover, taking the advantages of red emission, large Stokes shift, and good biocompatibility, the attempt to develop a nanosensor based on Cu NCs other than Au NCs is meaningful. Besides, Ag NCs were also proved capable of detecting in Zn^{2+} as well. One

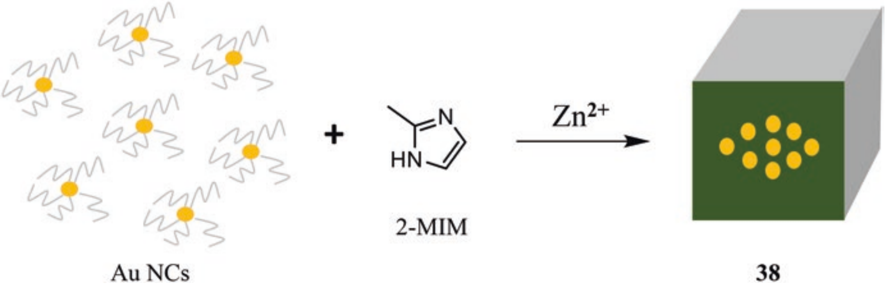


Fig. 3.18 Detection strategy of Zn^{2+} based on AIEE process of Au NCs-MOFs **38**. In a mixture of Au NCs and **2-MIM**, the addition of Zn^{2+} induced the generation of Zn-MOF in situ through enclosing Au NCs. The intensity of fluorescence was highly dependent on the amount of Zn^{2+} existing. Adapted from Li et al. (2018) with permission from Elsevier

attempt is GSH-capped Ag NCs (**40**), which were employed as a "turn-on" nanosensor with fluorescence enhancement of red emission (Liu et al. 2019a, b).

3.5 AIE-Based Nanosensors for the Detection of Pb^{2+}

Although phosphate group could incorporate with Pb^{2+} (Khandare et al. 2014), its potential in constructing AIE-based nanosensors was still waiting for being explored. In recent years, compared with the limited progress in organic molecule nanoparticles, the sensor for tracing Pb^{2+} was mainly dependent on metallic NPs/NCs and carbon dots.

3.5.1 Metallic Nanoparticles/Clusters

Ji et al. (2015) firstly reported a kind of glutathione-capped Au NCs (**41**) with AIEE property for sensing Pb^{2+}. The Au NCs showed ethanol-induced aggregation and emitted more intensively. Furthermore, addition of Pb^{2+} led to the aggregation of Au NCs accompanying with bright fluorescent emission due to the strong coordination between GSH and Pb^{2+}. The "turn-on" response exhibited good linearity in the range of 5.0–50 mM. It is worth to mention that the sensing process could be completed just in 1 min. More importantly, **41** showed satisfactory selectivity toward Pb^{2+} over various divalent metal ions, guaranteeing its application in real water.

Based on the ethanol-induced further aggregation of the GSH-capped Au-NCs, our group optimized the working system and developed a Pb^{2+} nanosensor (**42**) with higher sensitivity and shorter response time (Zhang et al. 2017a, b). The detection sensitivity was largely enhanced with a higher fraction of ethanol due to the formation of dense Au nanoparticles other than loose clusters. The critical point of the fraction of ethanol was exploited. Upon the addition of Pb^{2+}, the nanosensor would turn to be denser and more rigid, showing stronger fluorescence emission. Moreover, the detection of Pb^{2+} could be realized in not only real water but also human serum, with minimal interference from the other matrixes.

3.5.2 Carbon Dots

Tian et al. (2018) developed a "turn-on" nanosensor **43** via immobilizing carbon dots into the shell of the spherical polyelectrolyte brushes for detection of Pb^{2+}. The electrostatic interaction between carbon dots and brushes could induce the quenching of original fluorescence emission. Upon addition of Pb^{2+}, the AIEE-based fluorescence "turn-on" could be achieved due to the mutual contribution of aggregation of the spherical polyelectrolyte brushes particles and the aggregation of carbon dots in shell. Sensor **43** could detect Pb^{2+} in a wide range of concentration and has been applied in real water. Regrettably, the short-wavelength emission of **43**, which means its strong background signal interference, greatly limited its further application (Table 3.3).

3.6 AIE-Based Nanosensors for the Detection of Cr^{3+} and Cr^{6+}

Chromium (Cr) is an ecological pollutant with valence states ranging from chromium(II) to chromium(VI), while elemental chromium (0) is not naturally occurring (Vincent 2000). As a naturally occurring element, Cr^{3+} exhibits fewer influences in toxicology (Tchounwou et al. 2012). However, excessive intake of Cr^{3+} will lead to genotoxic effects, and its deficiencies could also cause sugar metabolic disorders like engendering diabetes (Flora et al. 1990; Nickens et al. 2010). Accordingly, a number of nanosensors have been constructed for sensing of Cr^{3+}. Unfortunately, currently reported Cr^{3+} nanosensors with AIE characteristics are almost based on the imine bond, which shows high affinity to trivalent cations, which means, however, rough selectivity (Liu et al. 2014; Islam et al. 2019).

Recently, Yu et al. (2019) reported a novel AIE-active nanosensor **44** composed of a TPE unit and rhodamine spirolactam, in which thiophene ring was used as a conjugated electron-rich linker (Fig. 3.19). Compared with the conventional chelation-induced manner, the interaction of nano-aggregated **44** with Cr^{3+} was a comprehensive result of proton-induced ring-opening followed coordination interaction. The Lewis acid characteristics of Cr^{3+} induced the acidic hydrolysis of loop-locked spirolactam and gave rise to loop-open response exhibiting AIEE. While, due to the perpendicular configuration and steric hindrance, the monovalent and divalent metal ions could not trigger the chelation-induced ring-opening, so **44** showed good selectivity to these metal ions. Regrettably, the response of **44** was inevitably triggered by other trivalent metal cations or H^+ for the same reason. Nonetheless, AIE-active rhodamine B-based nanoaggregates were still promising for practical applications due to their high selectivity and visible color change.

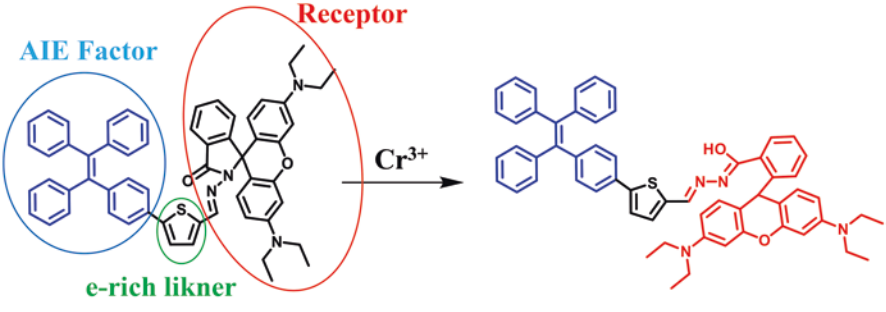
Although chromium occurs mostly in the trivalent [Cr^{3+}] form, the detection of hexavalent [Cr^{6+}] form, which is less stable but more toxic, is still of significance (Tchounwou et al. 2012; Stohs and Bagchi 1995; Salnikow et al. 2008). Recent reported AIE nanosensors for detection of Cr^{6+} were mainly based on the oxidability of Cr^{6+}. The Cr^{6+} sensing ability of GSH-Au NCs was assumed to be ascribed to the reduction of Cr^{6+} under acidic conditions while ligand GSH behaved as a reducing agent (Fournier-Salaün and Salaün 2007). The "turn-off" effect was a result of the disruption of the inter-Au(I) interactions; subsequently, the destruction of core-shell structure happened to lead to the quenched fluorescence (Zhang et al. 2017a, b). The reduction process occurred under acidic condition, while there was no response at neutral condition due to the lower redox potential.

Yin et al. (2019a, b) provided a solution for this limiting condition utilizing the mechanism of polymer-salt aggregate self-assembly chemistry to entrap the GSH-Au NCs inside micron-sized capsules (Fig. 3.20). Polymer-salt aggregates **45** were formed via the electrostatic interactions between phosphate anions and the

Table 3.3 List of characteristics of nanosensors with AIE properties developed for Zn^{2+} or Pb^{2+} detection

Nanosensor	Analytes	Emission wavelength	Concentration of sensors	S:A	LOD	Linear range	System	Real water examples	References
35	Zn^{2+}	442 nm	10μM	2:3	1.1 nM	1.1–15 nM	DMSO/water (1:99 v/v)	Y	Jung et al. (2015)
36	Zn^{2+}	470/590 nm	0.02 mg mL^{-1}	–	50 nM	0.1–60 nM	Water	Y	Lin et al. (2017a, b)
37	Zn^{2+}	580 nm	–	1:1	9 nM	0.2–1.0μM	–	Y	Lin et al. (2017a, b)
38	Zn^{2+}	570 nm	20μM	–	40μM	12.3 nM to 504.6 mM	Water	Y	Li et al. (2018)
39	Zn^{2+}	630 nm	–	–	1.17μM	4.68–2240μM	Water	Y	Lin et al. (2017a, b)
41	Pb^{2+}	590 nm	–	–	5μM	5.0–50μM	Water	Y	Ji et al. (2015)
42	Pb^{2+}	595 nm	–	–	0.1μM	2.0–350μM	Ethanol/water (57:43 v/v)	Y	Zhang et al. (2017a, b)
43	Pb^{2+}	491 nm	–	–	22.8μM	0–1.67 mM	Water	Y	Tian et al. (2018)

S:A stoichiometric ratio
LOD lowest limit of detection, *DMSO* dimethyl sulfoxide; Y means successful practical application in real water samples



44

Fig. 3.19 Monomer chemical structure of AIE-based nanosensor **44** and its proposed response to Cr^{3+}. The interaction of nano-aggregated **44** with Cr^{3+} was a comprehensive result of proton-induced ring-opening followed coordination interaction. In the presence of Cr^{3+}, the Lewis acid characteristics of Cr^{3+} induced the acidic hydrolysis of loop-locked spirolactam and gave rise to loop-open response exhibiting AIEE. Adapted from Yu et al. (2019) with permission from Royal Society of Chemistry

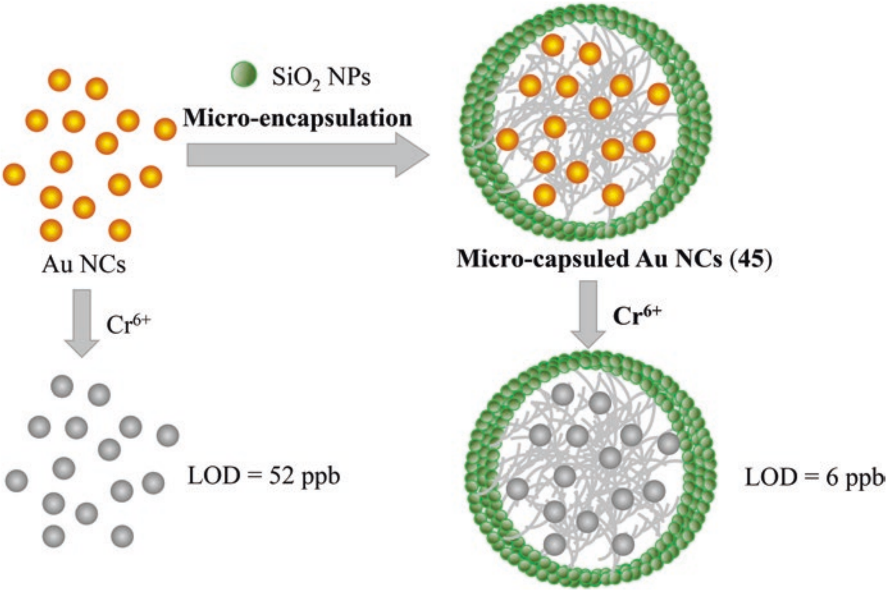


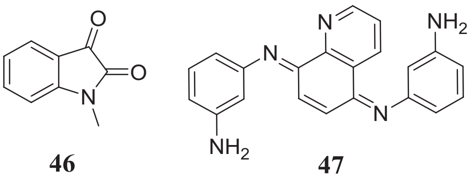
Fig. 3.20 Schematic depiction of micro-encapsulation of Au NCs (**45**) for Cr^{6+} detection. The Au NCs were entrapped inside micro-capsules via polymer-salt aggregate self-assembly. SiO_2 NPs diffused and deposited within the surface to form the shells. Through the micro-encapsulation, the limit of detection was optimized from 52 ppb to 6 ppb. Adapted from Yin et al. (2019a, b) with permission from American Chemical Society

amine groups of poly(allylamine hydrochloride), and GSH-Au NCs were incorporated within their cross-linked network structure. Subsequently, SiO_2 NPs diffused and deposited within the surface to form the shells. Owing to the high density of poly(allylamine hydrochloride) throughout the micro-capsule wall and interior, these components carrying protonated amine functional groups provided the acidic environment required for reduction of Cr^{6+} and no acidification was needed before testing. Besides, compared with these free Au NCs, the fluorescence of microcapsuled Au NCs was five times more intensive owing to the Mie scattering of multilayer-thick and semipermeable shell. Consequently, the sensitivity was elevated a lot after encapsulation. Furthermore, **45** could be immobilized on paper and successfully extended to a test strip system exhibiting similar Cr^{6+}-induced fluorescence quenching behavior with an LOD estimated to be 30 ppb.

3.7 AIE-Based Nanosensors for the Detection of Cd^{2+}

Selective detection of Cd^{2+} has long been a challenge. The nanosensors based on the supramolecular systems such as metal-organic frameworks, nanoparticles, nanoclusters, and carbon dots are rarely reported, while the main papers developed are on the basis of organic molecule nanoparticles, which need be preorganized. For example, Mahajan et al. (2015) developed a small organic molecule **46** based on Isatin and further converted it into nanoparticles by reprecipitation method (Fig. 3.21). Due to the coordination of functional keto moiety with Cd^{2+}, these organic nanoparticles assembled more tightly, which restricted the free rotations of the carbonyl, which largely appeared as a significant enhancement of emission. Similar response has been observed in real water samples as well. Regrettably, **46** could be only used in a weak acid condition, otherwise, the ring-open of **46** would happen and the structural cavity would be disrupted.

Recently, Aguilar et al. (2018) reported a preorganized Schiff base **47**, which exhibited an enhanced fluorescence response to Cd^{2+} ions at sub-micromolar concentration after it was converted to organic nanoparticles (Fig. 3.21). Sensor **47** showed high selectivity to Cd^{2+} from other metal ions owing to the stereochemistry of **47**, which contained a molecular cavity suitable for chelation with Cd^{2+} ion. The interaction occurred between nitrogen atoms of **47** and the electron acceptor Cd^{2+}, which led to the formation of structurally rigid coordination complexes exhibiting "turn-on" behavior. Moreover, these organic nanoparticles of **47** showed less cytotoxicity in living cells than the free **47**, which suggested that the conversion of organic nanoparticles modulated the elevated sensitivity and higher biocompatibility. The practical potential of **47** in Cd^{2+} detection has further been verified in real water and aqueous solution of cigarette tobacco leaves.



46 **47**

Fig. 3.21 Monomer chemical structures of AIE-based nanosensors **46-47** for Cd^{2+} detection

3.8 AIE-Based Nanosensors for the Detection of As^{3+} and As^{5+}

Arsenic (As) is a ubiquitous metalloid whose contamination in groundwater is a serious global problem threatening the health of more than 150 million people (Jackson et al. 2012; Mohan et al. 2007). The major inorganic salts of arsenic are trivalent arsenite (AsO_3^{3-}) and the pentavalent arsenate (AsO_4^{3-}), while little exist in organic form (Cullen and Reimer 1989). As^{3+} has been reported with higher affinity to thiol or sulfhydryl groups of biomolecules and macromolecules (Mandal and Suzuki 2002; Smedley and Kinniburgh 2002), and some sensors based on the Cys-modified fluorophores have been elucidated (Tian et al. 2017). Unfortunately, similar strategies have not been employed in the development of AIE-based nanosensors for As^{3+} and As^{5+} detection.

Lately, Pathan et al. (2019) exploited Fe_3O_4 nanoparticle functionalized graphene quantum dots as a nanosensor (**48**) for tracing As^{3+} ions in contaminated water. The surface of magnetic dots was full of carboxyl, hydroxyl, and amide groups, which provided high affinity to heavy metal ions. After addition of As^{3+} ions, the coordination of the hydroxyl and Fe_3O_4 nanoparticles to As^{3+} ions via intramolecular or extra-molecular interactions or adsorption induced the formation of rigid structure of the ion-mediated complex. As a result, the fluorescence of **48** was enhanced largely. It is worth noting that **48** exhibited high selectivity for As^{3+} over a relatively wide pH range and the resultant LOD value was 5.1 ppb, which render this nanosensor of practical significance (Table 3.4).

3.9 AIE-Based Nanosensors for the Detection of Multiple Heavy Metals

Apart from these AIE nanosensors for single heavy metal ion detection, designing such nanomaterials with different responses toward multiple cations has also caused extensive concern (Srivastava et al. 2018). In view of the advantages like cost-effectiveness, labor reduction, and reduced analytical time, developing versatile nanomaterials with AIE characteristic for multiple heavy metals' detection is meaningful for practical application as well (Wang et al. 2013; Samanta et al. 2015). From the perspective of design strategy, the multi-response nanosensors could be implemented in various ways, such as varying work solvents, differential response behaviors or subsequent recognition processes.

3.9.1 Organic Molecule Nanoparticles

As mentioned earlier in the section concerning detection of Cu^{2+}, salicylaldehyde Schiff base scaffold showed high affinity to Cu^{2+}(Zou et al. 2012). In Yang's work, anthryl-contained Schiff base derivative **49** exhibited additional affinity toward Zn^{2+} (Yang et al. 2015). Due to the differential electronic configuration of Zn^{2+} and Cu^{2+},

Table 3.4 List of characteristics of nanosensors with AIE properties developed for Cr^{3+}, Cd^{2+}, or As^{3+} detection

Nanosensor	Analytes	Emission wavelength	Concentration of sensors	S:A	LOD	Linear range	System	Real water examples	References
44	Cr^{3+}	588 nm	10μM	1:6	11.9μM	–	CH_3CN/water (3:2 v/v)	–	Yu et al. (2019)
46	Cd^{2+}	417 nm	10μM	2:1	11.8μM	8.9–443.6μM	Water	Y	Mahajan et al. (2015)
47	Cd^{2+}	436 nm	0.1μM	2:1	0.09 nM	0–0.1μM	Water	Y	Aguilar et al. (2018)
48	As^{3+}	430 nm	10μM	–	5.1 ppb	–	–	–	Pathan et al. (2019)

S:A stoichiometric ratio,
LOD lowest limit of detection; Y means successful practical application in real water samples

49 served as an “Off-On” nanosensor for Cu^{2+} detection in methanol-H_2O mixture solution while acted as an “On-Off” nanosensor for Zn^{2+} sensing in pure methanol solution. Especially, other competing cations had nearly no effect on the fluorescence intensity of **49**.

Similarly, Yin et al. (2019a, b) reported a 2-hydroxyl phenyl imino-modified imidazole derivative **52** possessing salicylaldehyde Schiff base scaffold (Fig. 3.22). The coordination sites composed of the N atoms of imine group, imidazole ring, and the O atom of the hydroxyl group, which exhibited high affinity to Cu^{2+}. Upon addition of Cu^{2+}, the original regular aggregate of **52** was disrupted and then the emission was quenched along with the colorimetric change from colorless to light yellow. Subsequently, upon the sequential addition of Cr^{3+} to the solution, the quenched fluorescence was recovered because of the cation exchange. The whole detection procedure was validated in real water samples. The strategy based on subsequent recognition provided a wider pathway for construction of nanosensor for heavy metal ion detection.

In another work, Pannipara et al. (2018) developed a novel pyrazolyl derivative **50**, which was capable of detecting Cu^{2+}, Ni^{2+}, and Hg^{2+} ions in different behavior (Fig. 3.22). Similarly, the emission of **50** in nanoaggregates could be quenched upon addition of Cu^{2+}, and Ni^{2+} displayed higher efficiency of quenching. Contrary to the fluorescent changes corresponding to Cu^{2+} and Ni^{2+} ions, the blue shift in the emission spectra occurred in the presence of Hg^{2+}, which meant the ratiometric sensing was available. It was a result of this that the charge transfer from **50** to Hg^{2+} could lower the energy of lowest unoccupied molecular orbital (LUMO) but not cause fluorescence quench, whereby **50** could be applied for Cu^{2+} and Ni^{2+} detection via “On-Off” mode but could trace Hg^{2+} in ratiometric behavior.

As introduced earlier in the sections discussing Hg^{2+} and Cr^{3+}, the ring-open of spiro would be induced by both Hg^{2+} and Cr^{3+}, leading to the “turn-on” of rhodamine fluorescence (Wang et al. 2016; Yu et al. 2019). Similar situation arose with **51**,

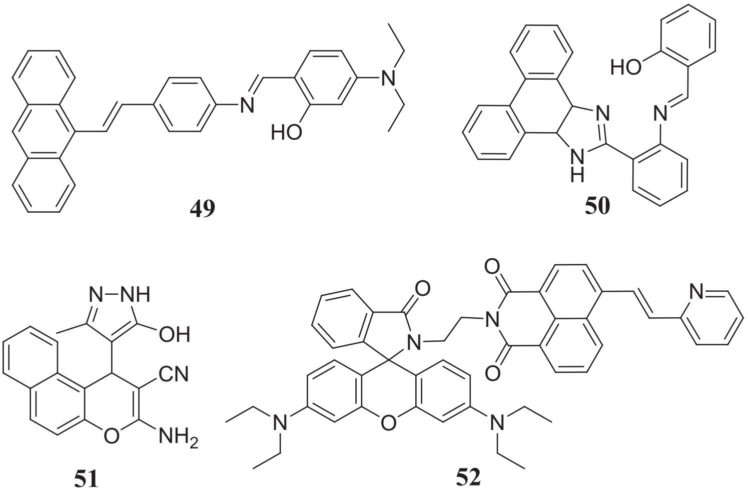


Fig. 3.22 Monomer chemical structures of AIE-based nanosensors **49–52** for detection of multiple metal ions

which was based on the modulated naphthalimide linked with rhodamine through a flexible non-conjugated spacer (Fig. 3.22; Sun and Qian 2016). Prior to the addition of Cr^{3+} or Hg^{2+}, only a weak fluorescent emission of **51** could be observed due to the photo-induced electron transfer process from the N atom of spiro ring on the rhodamine to the naphthalimide moiety. Otherwise, since the electrons were absorbed to the metal cations in the chelation with the hetero atom, the electron transfer process was blocked and the emission of naphthalimide was recovered. On the basis of the above mechanism, **51** served as a multi-responsive nanosensor for detection of Hg^{2+} and Cr^{3+} simultaneously in ratiometric behavior and dual-channel.

3.9.2 Metallic Nanoparticles/Clusters

GSH-Au NC mentioned above is one of the typical luminophores with AIEE properties but needs some "triggers" to modulate its AIEE features, which restricts its application a lot (Zhang et al. 2017a, b; Tang et al. 2017; Guo et al. 2015). Qu et al. (2018) found that fluorescent amino-modified silicon nanoparticles (Si NPs) with positive surface charges could trigger the aggregation of GSH-Au NCs, which carry negative charge via the electrostatic interaction. They prepared self-assembled nanoarchitecture **53** constituting Si NPs and GSH-Au NCs with dual emissions (Fig. 3.23). Similar to free GSH-Au NCs, abundant carboxylic groups of GSH on the surface of **53** provided the binding sites for heavy metal ions while Si NPs had no effect on the chelation. Upon addition of Zn^{2+} or Cd^{2+}, unique second enhancement of fluorescence from GSH-Au NCs could be observed due to its bridge effect to form larger aggregates while the emission from Si NPs was unchanged acting more like an internal reference. Accordingly, the Si NP-capped GSH-Au NCs could be applied as a ratiometric sensor for sensing Zn^{2+} and Cd^{2+}, which has been validated both in real water samples and living cells (Table 3.5).

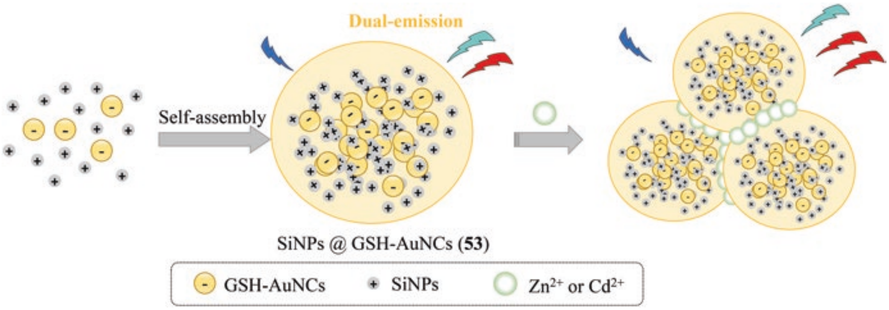


Fig. 3.23 Schematic illustration of the self-assembly of **53** (Si NPs@GSH-Au NCs) and the sensing process of Zn^{2+} or Cd^{2+}. Amino-modified Si NPs were positively surface charged while GSH-Au NCs were negatively charged. Via the electrostatic interaction, Si NPs could trigger the aggregation of GSH-Au NCs to obtain **53** with dual-emission. Upon addition of Zn^{2+} or Cd^{2+}, unique second enhancement of fluorescence from GSH-Au NCs could be observed but the emission from Si NPs was unchanged. Adapted from Qu et al. (2018) with permission from Royal Society of Chemistry

Table 3.5 List of characteristics of nanosensors with AIE properties developed for detection of multiple heavy metals

Nanosensor	Analytes	Emission wavelength	Concentration of sensors	S:A	LOD	Linear range	System	Real water examples	References
49	Cu^{2+}	523 nm	10μM	2:1	212μM	–	Methanol/water (4:1 v/v)	–	Yang et al. (2015)
	Zn^{2+}				71.9 nM		Methanol		
50	Cu^{2+}	424 nm	10μM	1:1	41.3 nM	–	DMF/water (50:50 v/v)	Y	Yin et al. (2019a, b)
	Cr^{3+}				0.94μM	0–8μM			
51	Cu^{2+}	532 nm	20μM	–	1.61μM	–	THF/water (15:85 v/v)	–	Pannipara et al. (2018)
	Hg^{2+}	532/481 nm			–				
52	Cr^{3+}	578/440 nm	10μM	–		–	Ethanol/water (1:1 v/v)	–	Sun and Qian (2016)
	Hg^{2+}								
53	Zn^{2+}	570/450 nm	–	–	0.67μM	1.5–500μM	Water	Y	Qu et al. (2018)
	Cd^{2+}				0.5μM				

S:A stoichiometric ratio

LOD lowest limit of detection, *THF* tetrahydrofuran, *DMF* dimethylformamide; Y means successful practical application in real water samples

3.10 Conclusions and Future Perspectives

For the purpose of guaranteeing environmental and human safety, it is critical and even urgent to develop the sensitive and selective sensors for detecting heavy metals. Nanomaterial-based sensors have achieved high sensitivity due to their large surface-to-volume ratio, high surface activity, and size-dependent property. In this chapter, we have summarized comprehensively and compared various AIE-based nanosensors developed in recent years with a focus on the types of nanomaterials and the related detecting mechanisms. These nanosensors provide stable and strong fluorescence and high sensitivity even at nanomolar concentration of metal ions, which is far below the minimum of environmental needs. Developing nanosensors, including organic nanoparticles, metallic nanoclusters or nanoparticles, metal-organic frameworks, hydrogen-bonded organic frameworks, and carbon dots, has grown noticeably and become a hot research area. Additionally, combining AIE material with other nanomaterials or even utilizing multiple AIE-based nanomaterials to construct a sensing system appears as an outbreak trend for heavy metal ions detection. Meanwhile, sensitivity and selectivity have also been elevated in numerous sensor systems reported. The sensing mechanisms mainly comprise two broad categories, fluorescence enhancement and quenching. Specifically, the addition of heavy metals often causes the sensor molecules to aggregate thereby turning on the fluorescence or disrupts the conjugated system to weaken or quench the fluorescence of the metallic NCs/NPs via metallophilic interaction. As to the AIE nanosensors based on fluorescence enhancement, by contrast, it exhibits lower detection limits and higher accuracy. Furthermore, some fluorescent nanosensors acting in ratiometric behavior can provide higher sensitivity and better selectivity, which makes them promising for real application.

For further design of AIE-based nanosensors for detecting heavy metals, the following trends are proposed: (1) to develop multifunctional sensors for simultaneously detecting multiple heavy metals; (2) to develop *all-in-one* sensors by combing multiple sensing signals to improve accuracy; (3) to develop *theranostic* sensors to achieve efficiently detection and the removal of heavy metals at the same time; and (4) to develop point-of-care testing sensor by integrating the AIE nanosensors into portable devices to provide novel tools in practical applications. We believe that fluorescent AIE-based nanosensors for heavy metal ions will play an increasingly important role in environment science and life of nature.

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Chapter 4
Nanosensors Based on Lipid Films for Environmental Applications

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Contents

Abstract The recent advances in lipid membrane biosensors gave the ability to provide devices to detect trace of environmental pollutants in real samples. Nanotechnology provided sensors with increased selectivity and sensitivity, portability, ease of construction, rapid response times, etc. This chapter reviews recent advances in biosensor technologies for environmental pollutant monitoring. A large number of applications are described herein, clarifying some recent advances in the technology of these devices such as miniaturization, new sensing techniques, and nanotechnology-based transduction schemes. A wide range of environmental toxicants can be monitored and these compounds include toxins, hormones, diox-

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ins, PAHs, etc. As a result, the commercialization capabilities of these biosensors are given in the present chapter.

Keywords Lipid membrane biosensors · Environmental pollutants · Nanobiosensors · Environmental analysis · Nanotechnology

4.1 Introduction

A chemical sensor is a device that changes the concentration data of the convergence of a particular analyte into a scientifically helpful signal. Biosensors comprise of two parts: a chemical component (“receptor”) and a physicochemical transducer. The acknowledgment framework deciphers the compound data (i.e., concentration of the analyte) into a quantifiable physical signal. The physical transducer gives the signal from the yield area of the component into an electrical, optical, or piezoelectric signal. A biosensor is an independent coordinated device that is fit for giving explicit quantitative diagnostic data utilizing an organic component (e.g., catalysts, antibodies, characteristic or fake receptors, and cells), which is held in direct spatial contact with a transduction component. Recent reports have appeared in the literature that describe the nanotechnological advances in biosensors (Pandit et al. 2009).

The early 1960s reconstitution of lipid bilayers has founded the “lipid membrane technology.” The number of biosensors that were based on lipid membrane technology has increased during the last 20 years. During the last 10 years, the construction of stabilized lipid film biosensors was performed and the preparation of biosensors to monitor environmental pollutants in real samples and in the field was successful. These devices have a large number of advantages, which include biocompatibility, fast response times, a high sensitivity and selectivity, and their small size. The new class of stabilized lipid film nanobiosensors has the potentiality to provide analytical instrumentation with high selectivity, sensitivity, and stability.

Lipid film devices reduce the complexity of the surface interaction forces of membranes to well-defined surface chemistry (Fig. 4.1). The mechanism of signal generation still needs more investigations (Gould 2018); the investigations for drug permeability (Ebert et al. 2018) or protein–lipid interaction studies (Vacek et al. 2018) or even to manipulate processes on the lipid films by altering the macroparameters are in a very good stage (Nikoleli et al. 2016). Biological “receptors” (enzymes, antibodies, receptors, ligands, DNA, etc.) can now be deposited on the lipid film surfaces (Mazur et al. 2017) or can be incorporated into the lipid structure (Vacek et al. 2018) by patterning (Raghunathan and Kenworthy 2018) or surface printing (Kalyankar et al. 2006). The lipid membrane represents a biocompatible structure for natural receptors to keep their function. The physical structure of the lipid film provides intrinsic signal transduction and amplification, which fits for biosensing—when the biological element interacts with the target analyte (Siontorou et al. 2017) providing current changes. Figure 4.1 shows the function and

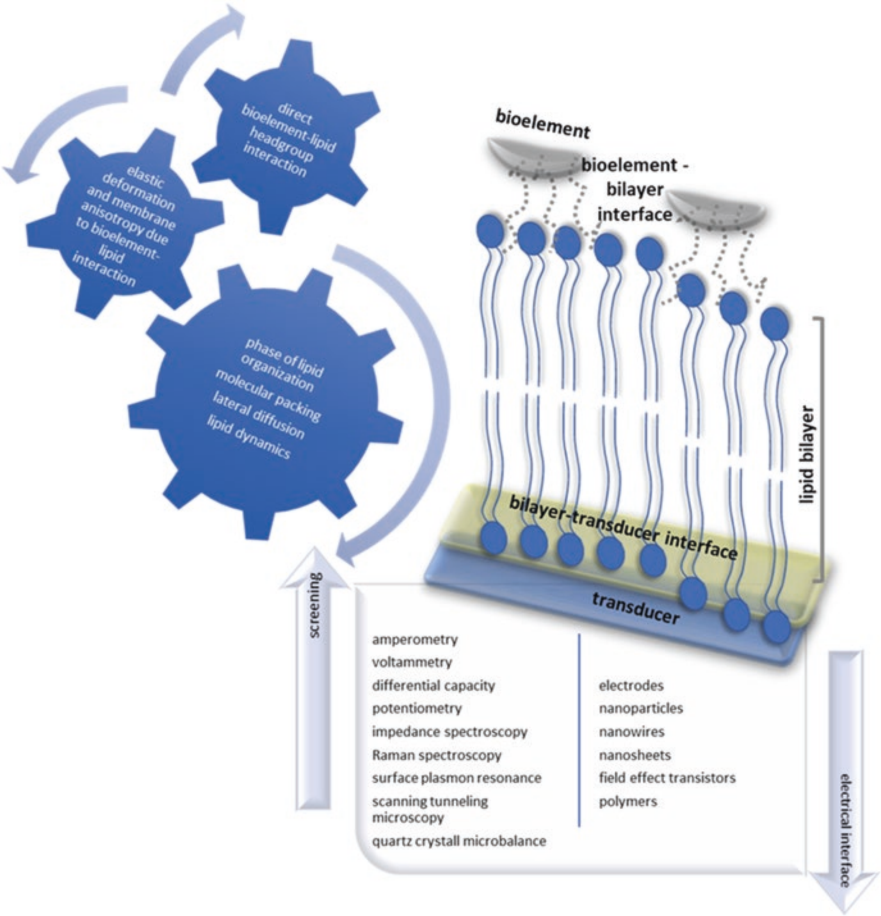

Fig. 4.1 Simplified schematic of the function and composition of a biosensor based on lipid film technology, illustrating, also, the physicochemical mechanism for the signal recovery. (Source: Nikoleli et al. 2018)

composition of a biosensor based on lipid film technology, illustrating, also, the physicochemical mechanism for the transduction and other screening methods employed. A number of recent articles have appeared in the literature that mainly describe recent advances and applications of various platforms of lipid film-based biosensors (Nikoleli et al. 2016, 2018, 2019; Siontorou et al. 2017; Pandit et al. 2016; Aljerf and AlHamwi 2018).

4.2 Methods for Construction of Nanosensors Based on Lipid Membranes

4.2.1 Metal-Supported Lipid Layers

Tien and Salamon have reported in the literature a system for the construction of stabilized bilayer lipid membrane (s-BLM) at the end of Teflon-coated metallic wire that was freshly cut (Tien and Salamon 1989). This technique has been described in the literature in detail (Siontorou et al. 1997a, b; Nikolelis et al. 1996). Also, s-BLMs have been characterized (Siontorou et al. 1997a, b; Nikolelis et al. 1996). The diameter and composition of the wires are important for the time of the bilayer stabilization (Siontorou et al. 1997b; Nikolelis et al. 1996). A schematic setup for the s-BLM experimentation is shown in Fig. 4.2.

4.2.2 Stabilized Lipid Films Formed on a Glass Fiber Filter

The preparation of stabilized electrolyte lipid membranes was reported by Nikolelis' group and these membranes were constructed on GF/F glass microfiber (0.9 cm in diameter and 0.7 μm nominal pore size) filters (Nikolelis et al. 1995; Andreou and Nikolelis 1998).

4.2.3 Polymer-Supported Bilayer Lipid Membranes

The use of a polymer-supported lipid film has been in practice to stabilize lipid membrane-based devices in the air for periods of over 1 month (Nikolelis and Mitrokotsa 2002).

The preparation of stable-in-air lipid membranes was reported by Nikolelis' group (Nikolelis and Mitrokotsa 2002; Nikolelis et al. 2006, 2008a, b). The lipids used were previously described. No receptor was used in these detections. The polymer stable-in-air lipid membranes were constructed as has been described in detail previously (Nikolelis and Mitrokotsa 2002; Nikolelis et al. 2006, 2008a, b).

4.2.4 Polymeric Lipid Membranes Supported on Graphene Microelectrodes

Our group has prepared an electrode that was composed from a lipid film on a copper wire that contained graphene nanosheets (Nikoleli et al. 2012). The experimental setup is shown in Fig. 4.3. These nanobiosensors were utilized for the fast

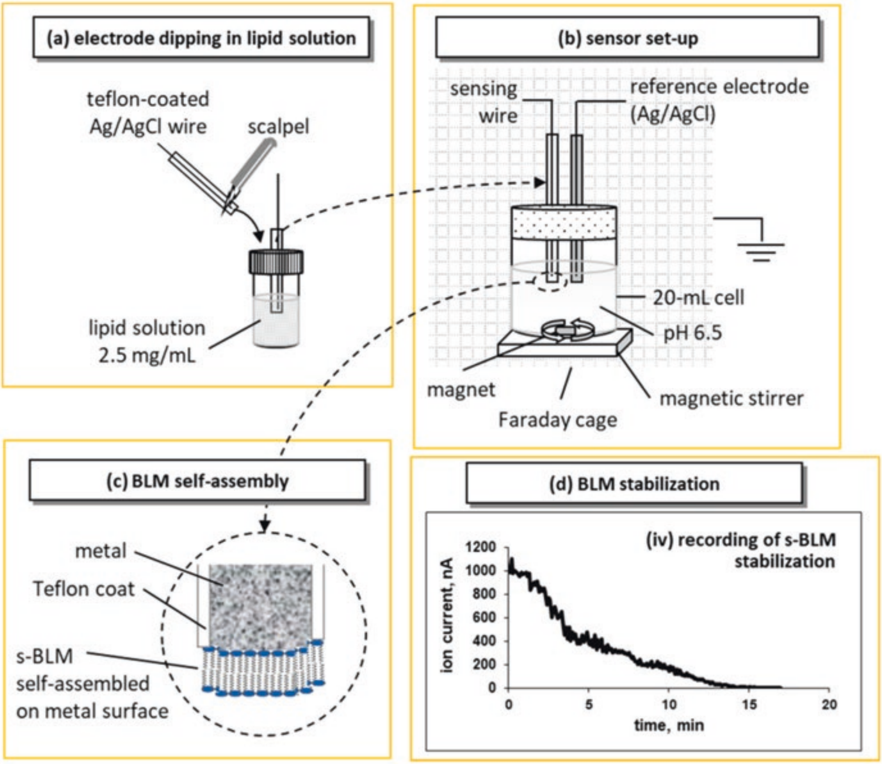

Fig. 4.2 Schematic of the sensor, measurement setup, and lipid self-assembly process (not drawn to scale). (**a**) The sensing electrode is tipped with a scalpel and immediately immersed in lipid solution before being dipped in the electrolyte solution. (**b**) The electrochemical setup consists of a 20-mL cell and a two-electrode configuration, that is, the sensing electrode and a Ag/AgCl reference electrode, placed in a grounded Faraday cage; an external DC potential of 25 mV is applied between the electrodes, and the ionic current through the BLM is measured with a digital electrometer; the cell is stirred using a magnetic stirrer. (**c**) Upon immersion, the lipid droplet attached to the wire is self-assembled into a bilayer that has one layer adsorbed on the metal surface and the other facing the aqueous solution. (**d**) Recording of the ion current decreases during the self-assembly process; recording started at the immersion of the sensing electrode in the electrolyte solution. (Source: Nikoleli et al. 2018)

monitoring of food and environmental toxicants (Nikoleli et al. 2012) such as urea, using the enzyme urease, cholesterol (using cholesterol oxidase), cholera toxin (using its receptor), and saxitoxin (using its receptor). The construction of graphene microelectrodes has been reported in the literature (Nikoleli et al. 2012).

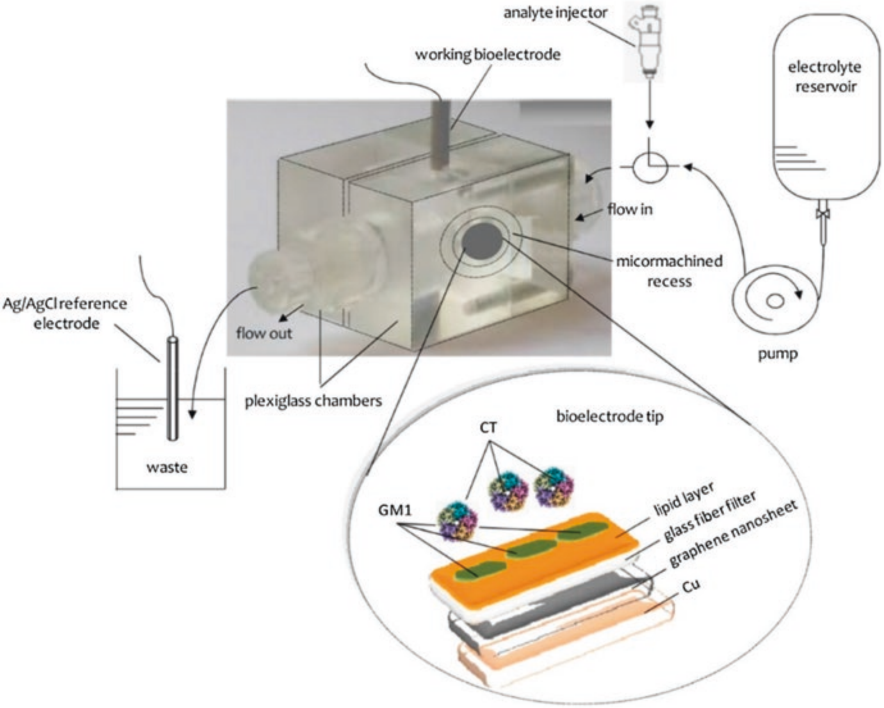

Fig. 4.3 Schematic of the experimental setup; the micromachined chambers are separated by a thin (12.5 μm thick) polyvinylidene chloride wrap and enclose the microfiber disk. (Source: Nikoleli et al. 2018)

4.3 Applications of Lipid-Film-Based Nanosensors for the Rapid Detection of Environmental Pollutants

Potentiometric and amperometric biosensors, which relied on modified gold electrodes, were constructed and used in pesticide analysis (Snejdarkova et al. 2004). Polyamidoamine (PAMAM) dendrimer (generation G4) was incorporated with 1-hexadecanethiol and used for the deposition of the following enzymes: acetylcholinesterase and choline oxidase for the construction of an amperometric device. Polyaniline doped with camphorsulfonic acid was utilized alternatively to have a potentiometric device. Trichlorfon, carbofuran, and eserine decreased the device response due to their inhibitory effects. The detection limits were on the following order: 0.003 and 200 nmol L^{-1} (trichlorfon), 0.04 and 6 nmol L^{-1} (carbofuran), and 0.1 and 700 nmol L^{-1} for amperometric and potentiometric devices, respectively.

A paper was reported in the literature using a synthetic “receptor” immobilized on supported lipid films on glass fiber filters. The supported lipid films were modified by calixarenes and proved adequate for the sensitive and rapid determination of various insecticides in fruit and vegetable samples (Nikolelis et al. 2008b). Other devices similarly developed include a disposable chemosensor for the selective and fast detection of food hormones such as naphthalene acetic acid (NAA) in fruits and vegetables (Nikolelis et al. 2008c) and a sensor for the detection of zinc in water (Nikolelis et al. 2009).

Bilayer lipid membranes (BLMs) were used as devices for the electrochemical detection of monocrotophos and carbofuran (Nikolelis and Krull 1994). Egg phosphatidylcholine (PC) and dipalmitoylphosphatidic acid (DPPA) were the lipids that were the basis of these detectors. A transient current signal of seconds was produced during interaction of these compounds with the lipid films. The sensitivity of the detectors was maximum when dipalmitoylphosphatidic acid was a component of the lipid mixture and by using calcium ions in the electrolyte solution. The peak heights of these transients were correlated to the concentration of monocrotophos or carbofuran in bulk solution with sub-micromolar detection limits.

An electrochemical device/minisensor for the rapid detection of ammonium ions was reported in the literature (Nikolelis et al. 1996), which was based on supported lipid membranes on metal wire. The ionophore that was used was gramicidin, and the lipid films were composed of egg phosphatidylcholine. The mechanical stability and longevity, sensitivity, and response times of this device were adequate, and the reversibility of this biosensor to ammonium ions was investigated and provided good results. The use of semisynthetic platelet-activating factor (PAF; 1-*O*-alkyl-2-acetyl-*sn*-gryceryl-3-phosphorylcholine, AGEPC) provided an increase of the biosensor and decreased the potassium interferences. The response times were rapid (to millisecond speeds) and the selectivity to ammonium ions in the presence of volatile amines was excellent. The analysis of small volumes of samples was possible using this sensor with detection limits on the order of ~1 × 10–6 M. Other advantages of this device were the uses of small volumes and that the sensor was disposable.

A device for the rapid detection of the triazine herbicides simazine, atrazine, and propazine was reported in the literature (Siontorou et al. 1997b). Egg phosphatidylcholine and dipalmitoylphosphatidic acid were the lipids that were used for the construction of the metal-supported lipid membranes. Ellipsometric data were used to explore the mechanism of signal generation. These triazines produced ion current increases within ~10 s after exposure of the lipid films to these compounds. The use of an anionic lipid such as dipalmitoylphosphatidic acid and calcium ions increased the magnitude of sensitivity. These magnitudes were linearly correlated to the insecticide, which could be detected at the nM concentration levels. The characteristics of the detection (i.e., mechanical stability, response times, and reproducibility) were excellent. These herbicides could be monitored in the presence of other insecticides and pesticides and the construction of the sensor could be easily performed and used in the field applications.

A report appeared in the literature that describes the changes in ion current through a lipid membrane with deposited DNA and it is the result of interactions of lipid film biosensors with hydrazines (Siontorou et al. 1998). These devices were based on the deposition of egg phosphatidylcholine on silver metal electrode. The DNAs were single stranded deoxyribonucleic acids: thymidylic acid icosanucleotide that was terminated with a C-16 alkyl chain and deoxyadenylic acid icosanucleotide (dA_{20}). These s-BLMs interact with hydrazines, and give a device to monitor parts per billion concentrations of hydrazines. These hydrazines included methylhydrazine, dimethylhydrazine, and phenylhydrazine.

A biosensor composed of supported polymeric lipid film with incorporated sheep anti-PCB antibody was described in the literature for the fast detection of Aroclor 1242 using flow injection analysis (FIA) (Michaloliakos et al. 2012). This antibody was deposited on the lipid film simultaneously with the lipid. Injections of polycyclic aromatic hydrocarbons (PAHs) were performed in the flowing solutions. A stopped-flow mode was used and the lipids were 15% (w/w) palmitic acid (PA) and 85% dipalmitoylphosphatidylcholine (DPPC); this lipid composition has provided one single signal. The peak height of the ion signal was correlated to the PAH concentration with detection limits at the nM concentration levels. The maximum number of cycles that could be performed was ca. 5.

The same principle was used to construct an electrochemical device for the monitoring of 3,3′,4,4′-tetrachlorobiphenyl (PCB congener 77) (Nikolelis et al. 2013). The polymeric lipid membrane was composed of 85% (w/w) dipalmitoylphosphatidylcholine (DPPC) and 15% (w/w) dipalmitoylphosphatidic acid (DPPA), methacrylic acid, ethylene glycol dimethacrylate, azobisisobutyronitrile (AIBN), and sheep anti-congener 77 antiserum. A single transient signal was obtained and it was proportional to log (congener 77) from 10^{-8} to 10^{-5} M, with a detection limit of ca. 10^{-8} M. The maximum number of cycles that could be performed was ca. 5.

A carbon dioxide minisensor using hemoglobin as an ionophore and s-BLMs was reported in the literature (Siontorou et al. 1997a). The lipids used were egg phosphatidylcholine (egg PC) and dipalmitoylphosphatidic acid (DPPA). The parameters that were investigated included hemoglobin and DPPA concentration in BLMs; other factors exploited were pH of the electrolyte solution. The response times were of the order of 10s and the detection limits were ca. 0.4×10^{-6} M. The presence of semisynthetic platelet-activating factor (PAF; 1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine, AGEPC) in BLMs increased the sensitivity of the device. The device was found that could operate for periods of time of more than 48 h.

Shiratori et al. (2000) have suggested a gas biosensor composed of Langmuir-Blodgett (LB) membranes and fullerenes as spacers. The fullerenes provided a bilayer on a quartz crystal microbalance (QCM) electrode. PAHs were found to permeate more thoroughly through the membranes as molecular weight decreased, which was due to the interactions of the gas with the lipid film.

A biosensor appeared in the literature for the FIA analysis of hydrazine compounds and their mixtures (Siontorou et al. 2000). Filter-supported lipid films with incorporated DNA were used for the construction of this device. Hydrazines or their homologues were injected in the stream of a flowing electrolyte solution and ion current peaks were the result of the interactions of these hydrazines with BLMs. The signals were correlated with the concentration of hydrazines and the time appearance of these signals was different depending on the hydrophobicity of the analyte (i.e., the signal had longer time of appearance on the order of hydrazine, methylhydrazine or dimethylhydrazine, and phenylhydrazine).

Ishimori et al. (2002) suggested an environmental monitoring device that was constructed from lipid films. This device was able to continuously monitor underground water. A BLM device was proposed with an inkjet mechanism. Volatile organic chloride compounds (i.e., cis-1,2-dichloroethylene) could be monitored using this device with a sensitivity of the order of 10 ppb when using monoolein BLMs; these results were evaluated using real samples of underground water.

Novel electrochemical DNA aptasensors were developed on glassy carbon electrode that was altered using neutral red and polycarboxylated macrocyclic ligands polymerized onto the glassy carbon electrode (Evtugyn et al. 2014). The aptamers were deposited on the glassy carbon electrode using covalent immobilization techniques. The analyte was Aflatoxin B1 (AFB1). When AFB1 interacted with the electrode, the cathodic peak current was decreased and measured using cyclic voltametric and electrical impedance spectroscopy techniques. The detection limit was 0.1 nM for the cyclic voltametric method and 0.05 nM for impedance spectroscopy techniques. The aptasensor was used to monitor AFB1 in various samples of nuts, wine, and soy sauce.

A report was described in the literature for miniaturization of an electrochemical potentiometric naphthalene acetic acid (NAA) device on a graphene electrode in which a lipid membrane was deposited along with the auxin-binding protein 1 receptor (Bratakou et al. 2016). This sensor has given a good selectivity and sensitivity, fast response times, and detection limits for the hormone at 10 nM. The device could be easily constructed and has shown excellent reproducibility, reusability, and a slope of ca. 56 mV/decade of hormone concentration. An evaluation/validation of this device was made using real fruit and vegetable samples.

4.4 Conclusions and Future Prospects

The present review describes nanobiosensors that are based on lipid membranes for the fast detection and monitoring of biological compounds and toxicants such as herbicides, toxins, urea, and cholesterol and provides the advantages of lipid membrane devices (i.e., high sensitivity and selectivity, fast response times, and portability). It is of common sense that advances in nanotechnology will further provide biosensors with even improved characteristics.

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Chapter 5
Novel Chemical Sensors Based on Green Composite Materials for Environmental Analysis

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Abstract In this book chapter, we report the recent advances in the development and application of chemical sensors based on green composite materials for environmental analysis. Emphasis is given on the sensor performance in terms of materials employed (including macromolecules from vegetal sources combined with varied nanostructures), structure–property relationships, and device fabrication technology. Specifically, the chapter focuses on green materials obtained from vegetal biomass including cellulose, lignin, starch, alginate, pectin, and vegetal protein, indicating the viability for the construction of non-toxic, recyclable, renewable, and biodegradable devices. Firstly, a brief overview on different types of chemical sensors, including electronic tongues, electrochemical sensors, and chemical optical sensors, is presented. Then, the general aspects of green composites as sensing layers are outlined and discussed with respect to their application in environmental analytical chemistry. Emphasis is placed on results reporting the detection of heavy metals and bacterial contamination in water as wells as hazardous volatile organic compounds. Lastly, a brief perspective on the challenges and upcoming opportunities toward the development of novel sensing devices based on green composites is discussed

Keywords Electronic tongue · Optical chemical sensor · Electrochemical sensor · Cellulose · Green materials · Nanostructures · Two-dimensional materials

5.1 Introduction

In the last decades, an increasing amount of organic and inorganic hazardous compounds, including heavy metal ions, pesticides, and pharmaceuticals, have been released into the environment without proper treatments (Antonacci et al. 2018; Wu et al. 2019; Patel et al. 2019). The identification and quantification of these substances play an important role in pollution monitoring and management, which requires the development of accurate and fast detection technologies (Arduini et al. 2017; Parmar et al. 2018; Zhang et al. 2019). Among these technologies, chemical sensors have been of special interest due to their potential applicability in the detection of a single analyte or simultaneous analytes in a fast and efficient manner, besides other advantages compared to traditional analytical techniques, including easy handling, reduction in cost per analysis, as well as the possibility of automation and miniaturization (Cui et al. 2015; Labib et al. 2016; Maduraiveeran and Jin 2017).

A chemical sensor is a device that combines a sensitive layer (part of the sensor that interacts chemically with the analyte under investigation) and a transducer, which is a component that converts/transforms the chemical information (e.g., composition or concentration) into a useful analytical signal (Hulanicki et al. 1991). Chemical sensors may be classified, based on the transduction principles, as electrical (e.g. impedimetric), electrochemical (e.g. impedimetric, potentiometric, and amperometric), optical (e.g. fluorescent, colorimetric), and gravimetric (e.g. quartz crystal microbalance, magnetoelastic sensors, static and dynamic) sensors (Hulanicki et al. 1991; Correa et al. 2017; Kassal et al. 2018; Paladiya and Kiani 2018; Teodoro et al. 2019b).

A broad range of materials and their combinations have been proposed to be used as sensing layers in sensors, including metals and metal oxides, inorganic crystalline and amorphous materials, and polymers and composite materials (Mercante et al. 2019; Ray 2017). More recently, the number of publications describing the development of sensing layers prepared from ecofriendly solvents and reagents has exponentially increased (Yáñez-Sedeño et al. 2019). Several unique features of natural polymers make them attractive, including biodegradability, relatively low cost, non-toxicity, reactive functional groups, and abundant availability in nature (Maciel et al. 2019). Such features make them suitable for designing devices, including distinct types of sensors that are efficient, durable, inexpensive, simple, easy to prepare, and ecofriendly (La Mantia and Morreale 2011; Tingaut et al. 2012; Golmohammadi et al. 2017; Naveen et al. 2017; Teodoro et al. 2018, 2019a; Wang et al. 2018; Cichosz et al. 2018; Maciel et al. 2019; Andre et al. 2020).

A large variety of natural polymers such as cellulose, chitosan, chitin, and starch, as well as its derivatives, has been applied for the fabrication of ecofriendly sensors. Natural macromolecules as lignin and zein have also been used for this purpose (Sun et al. 2011; Suginta et al. 2013; Rudnitskaya et al. 2013; Saithongdee et al. 2014; Golmohammadi et al. 2017; Anichini et al. 2018; Maciel et al. 2019; Meng et al. 2019). It is well known that natural polymers and macromolecules show electrically insulating nature, which has stimulated researches based on the preparation of hybrid composite sensing layers via the combination with two-dimensional materials (2DMs) (Salavagione et al. 2014; Zhang et al. 2017; Maciel et al. 2019; Teodoro et al. 2019a; Yáñez-Sedeño et al. 2019; Yusoff 2019; Meng et al. 2019). For instance, 2DMs such as graphene, phosphorene, and transition metal dichalcogenides have rapidly emerged as attractive candidates for the fabrication of high-performance chemical sensors due to their remarkable electronic and optical properties combined with their high surface area-to-volume ratios, robustness, and flexibility, improving sensor performance in terms of specificity and sensitivity (Anichini et al. 2018; Meng et al. 2019).

In the next sections, we discuss on distinct types of sensors based on the plethora of green composite materials that can be successfully used in the design of such devices employed for monitoring heavy metals, microorganisms, as well as volatile organic compounds (VOCs).

5.2 Transduction Mechanism in Chemical Sensors: A Brief Introduction

As mentioned before, chemical sensors are devices capable to transform a physical, chemical, or biological stimulus into a measurable analytical signal (Kruse 2018; Vikesland 2018). The use of sensors and biosensors for health and environmental monitoring has been extensively explored in the last decades (Lahcen and Amine 2018; Jayathilaka et al. 2019; Reynoso et al. 2019). Compared to analytical techniques usually employed for these application as atomic absorption spectroscopy (AAS), inductively coupled plasma-mass spectrometry (ICP-MS), mass spectroscopy (MS), and X-ray fluorescence spectroscopy (XPS), chemical sensors offer some advantageous properties for analyte monitoring, which include experimental simplicity, expedite analysis, possibility of miniaturization, portability, and capability for on-site analysis (Wei et al. 2012; Arino et al. 2017; Golmohammadi et al. 2017; Mercante et al. 2017). In the next section we will focus on some types of chemical sensors, including impedimetric e-tongues, electrochemical, and optical chemical sensors.

5.2.1 Impedimetric Sensors (e-Tongues)

Electronic tongues (or e-tongues), as multicomponent analysis, appear as a suitable approach to perform on-site simultaneous evaluation and classification of trial solutions with very similar compositions (Riul-Jr et al. 2010; Karkra et al. 2017; (Kirsanov et al. 2019). Such devices consist of an array of distinct sensing units composed by interdigitated electrodes (IDEs) functionalized with different nanomaterials, and employ the concept of global selectivity and cross-sensitivity (Correa et al. 2014; Di Rosa et al. 2017; Podrazka et al. 2017) as illustrated in Fig. 5.1. Through electrical transduction, the e-tongues collect the sample's fingerprint, which is usually interpreted by varied statistical analysis (Riul-Jr et al. 2010).

The use of impedimetric e-tongues is advantageous for sample analysis once it does not require, in principle, the use of materials that provide specific interactions with the analyte, which is quite attractive for the analysis and classification of liquid samples of complex compositions. Additionally, unlike electrochemical measurements, the sensing array of non-specific electrodes used in impedimetric e-tongues does not require the use of electroactive species neither of reference electrode. The sensor-solution system can be described as an equivalent circuit in such a way that the electrostatic double layer formed at the interface electrode/solution governs the response at low frequencies, the conductance of solution and ultrathin films that coat the electrodes generate the responses at intermediate frequencies, while geometric capacitance is more influential at high frequencies (Taylor and Macdonald 1987; Riul-Jr et al. 2010; Giacometti et al. 2016).

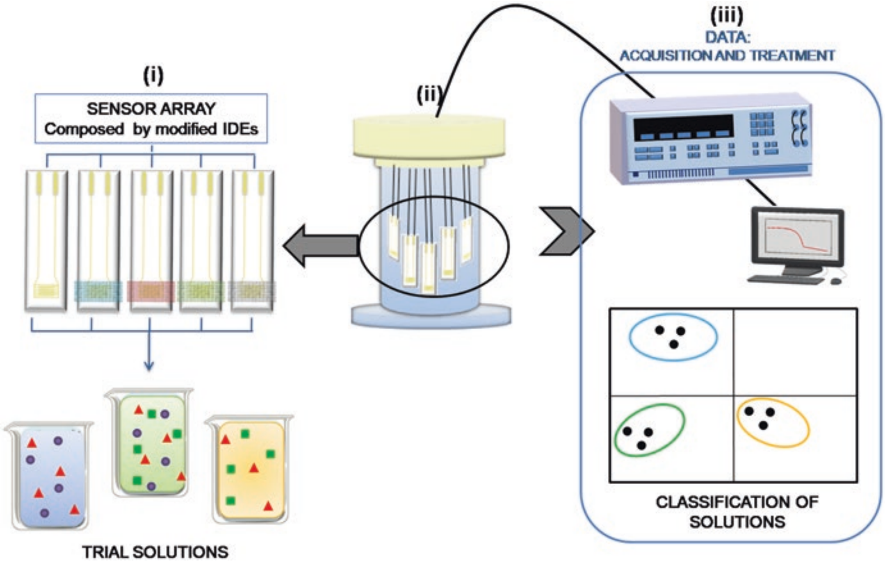

Fig. 5.1 Schematic representation of an experimental setup of a typical e-tongue: **(i)** interdigitated electrodes (IDEs) modified with distinct materials; **(ii)** measurement cell containing the sensor array immersed in the liquid under investigation; **(iii)** data analysis of trial solutions collected using the e-tongue can generate a large amount of data, which can be classified and distinguished using the appropriated statistical analysis

This approach makes use of the impedance concept, once it represents the total opposition to the current in an AC circuit, in which resistance and reactances are provided by resistors, capacitors, and inductors (Bard and Faulkner 2000). In general, it can be assumed that impedance (Z) corresponds to the equivalent resistance of a DC circuit respecting the Ohm's Law. Considering that the impedance study of an AC circuit can be performed using graphical representations of a complex number in the complex plane, impedance spectroscopy can provide a graphical representation of the real and imaginary impedance data (Z and Z^*, respectively) in accordance with the frequency applied. Once an adequate AC voltage is applied to the electrode system, the corresponding response current is measured, and the data can then be collected as resistance, capacitance, or impedance (Bhand and Bacher 2017).

The impedance response is obtained by frequency variation over a wide range (e.g., mHz to MHz), in such a way that the assessment of information from a large amount of data is given. The use of advanced mathematical and statistical methods provides the capacity to distinguish samples with very similar chemical composition, providing useful qualitative and quantitative information. A suitable design of sensing units is a crucial strategy to develop e-tongues capable to discriminate varied analytes at concentrations as low as nanomolar levels (Alonso et al. 2012; Facure et al. 2017; Marques et al. 2017; Teodoro et al. 2019b).

5.2.2 Electrochemical Sensors

Electrochemical sensors constitute a powerful tool for chemical analysis, especially because of the high sensitivity and moderate cost when compared to other analytical techniques. Additionally, electrochemical sensors can provide fast analysis and depending on its design and materials employed, they can also be used as wearable and disposable sensors for in-situ and real-time analysis (Stradiotto et al. 2003; Bandodkar and Wang 2014; Patella et al. 2019). In addition, the versatility of electrochemical techniques also enables customizing and controlling electrode reactions by modifying the electrode–solution interface and potential applied to the electrochemical cell, combined to the ease of automation for the electrical signal measurements (Brett and Brett 1994; Bard and Faulkner 2000).

Electrochemical sensors are generally based on electrochemical cells with two or more electrodes in contact with the electrolyte, as displayed in Fig. 5.2. Such sensors can be classified, according to the mode of operation as amperometric, conductometric, potentiometric, or voltammetric sensors (Stradiotto et al. 2003). The choice of the measurement parameters is made in order to optimize the sensor sensitivity, selectivity, and accuracy, depending on the chemical species to be determined. In this way, the knowledge and limitations of each operational mode are essential in the planning and development of a sensor (Lowinsohn and Bertotti 2006). These types of sensors are usually employed for the evaluation and quantification of chemical or biological compounds, even when they are present at very low concentrations in the medium. The determination of these compounds occurs through redox reactions at the electrode/solution interface, which are later converted into electrical signals (Patella et al. 2019), that is, the output signal is a measurement of current, potential, or electrical resistance, depending on the mode of operation. As the redox reaction occurs at the surface of the working electrode, surface area is an important parameter that can enhance the output signal (Brett and Brett 1994).

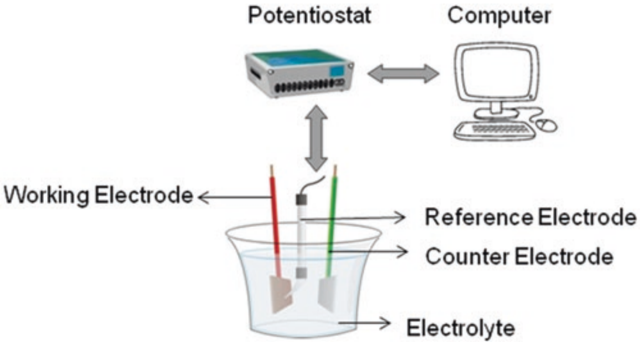

Fig. 5.2 Schematic representation of an experimental setup employed for electrochemical sensor analysis composed of a three-electrode (working electrode, reference electrode, and counter electrode) cell, a potentiostat, and a computer

5.2.3 Optical Chemical Sensors

Optical chemical sensors are a subclass of chemical sensors that employ optical transduction to provide a useful analytical signal (McDonagh et al. 2008). An example of an experimental apparatus used in optical sensors for detection of gaseous analytes is shown in Fig. 5.3. The interaction of the electromagnetic radiation with the analyte of interest can cause significant changes in the optical parameters of the system and the degree of this interaction is related to the concentration of the analyte (Narayanaswamy 1993; Lobnik et al. 2012a; Lobnik et al. 2012b). The transduction can occur by different mechanisms, which include absorbance, scattering, reflection, refraction, and luminescence processes in the electromagnetic spectral region spanning from ultraviolet (UV) to infrared (IR). For the development of optical chemical sensors, the frequent methods of detection are based on the principles of absorption and light emission (luminescence), due to their good sensitivity, experimental simplicity, and sensitivity (Jeronimo et al. 2007; Z. Li et al. 2018).

The process of optical sensing occurs by a direct or indicator-mediated sensing. In the direct sensing, the absorption or emission (luminescence) of analyte is

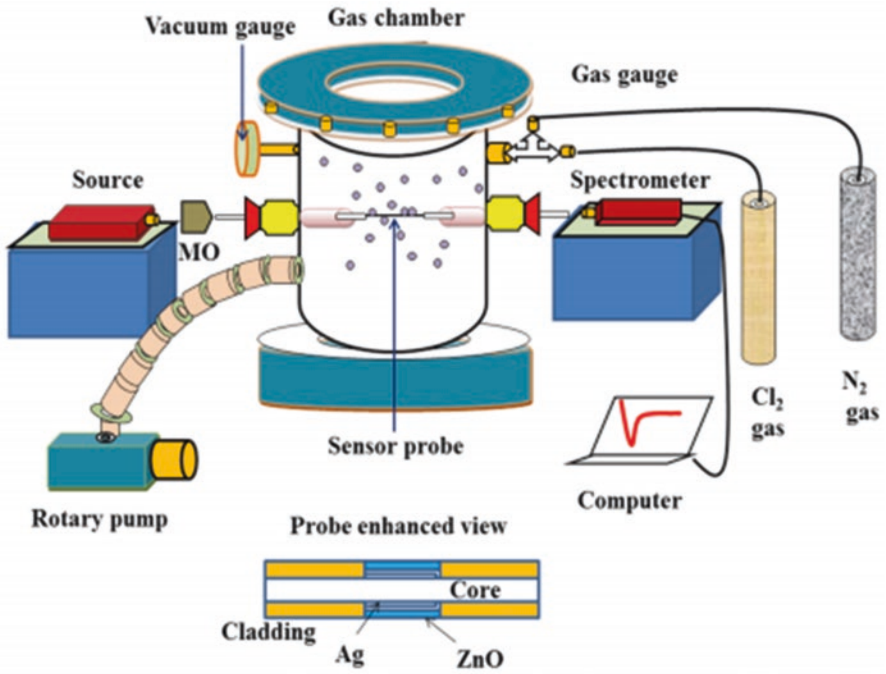

Fig. 5.3 Schematic representation of an experimental setup employed for optical chemical sensor analysis, composed of a spectrophotometric equipment coupled to a hermetically sealed chamber and arranged to enter and exit the gas. Two cylinders are connected to the gas chamber, one filled with the gas being detected and the other filled with nitrogen gas used for the purge. Reprinted with permission from Usha et al. (2015)). Copyright (2015) MDPI

measured directly and quantitatively through a calibration curve. In the indicator-mediated sensing, on the other hand, the use of an intermediate agent is necessary, which acts as an active layer or sensory platform (indicator) interacting with analyte and inducing the response (Hayashi 2015). Such process of optical sensing is interesting because it enables the analysis of a large number of analytes, including those that do not present intrinsic optical properties, the detection of which would be hindered by the direct method. In this case, the optical chemical sensors detect the chemical reactivity between the analyte and the indicator, instead of the physical properties of the analyte. Thus, it is possible to obtain sensors with high sensitivity and discrimination capacity between analytes of similar features in both gas and liquid phases (Lobnik et al. 2012b; Hayashi 2015; Schoolaert et al. 2017; Li et al. 2018).

The indicators usually employed in optical chemical sensors are thin films including those based on polymer owing to the thin film formation capacity at low temperature, adjustable properties, as well as its ability to form composite and hybrid materials with several nanostructures (Sanfelice et al. 2014; Christau et al. 2015; Sanfelice et al. 2017; Andre et al. 2018; Terra et al. 2018; Mahapure et al. 2019; Mao et al. 2019). To be used as a platform in an optical chemical sensor, the polymer material must have optical activity and interact with the analyte investigated. Conjugated polymers exhibit alternating π-bonds throughout the chain, which allows the optical activity of these materials for optical sensors (McQuade et al. 2000; Thomas et al. 2007), such as polypyrrole (PPy; Zhou et al. 2015; Liu et al. 2017b), polyaniline (PANI; Luo et al. 2017; Mohamad Ahad et al. 2018), and polythiophene (PT; Li and Shi 2013; Liu et al. 2017a).

When an optical sensor is based on the use of an indicator, the analyte quantification relies on changes observed in the analytical signal of the indicator. The two most widely employed types of optical chemical sensors are based on colorimetric (Schoolaert et al. 2017; Najarzadekan and Sereshti 2018) and luminescence properties (Najarzadekan and Sereshti 2018; Terra et al. 2018; O'Keeffe et al. 2018). In colorimetric detection, the indicators display color changes in the presence of the analyte of interest, which in many cases can be measured by UV-Vis absorption technique or even detected by naked eyes (Liu et al. 2017a; Maity and Ghosh 2018; Ma et al. 2018). Luminescence sensors usually present a higher sensitivity compared to other optical chemical sensors (Hayashi 2015). Two processes, namely fluorescence and phosphorescence, can explain the luminescence mechanism. Fluorescence occurs through the excitation of an electron to an excited state, and its subsequent radioactive relaxation to the ground state. In phosphorescence, first a forbidden transition occurs to an excited triplet state, and subsequently relaxation to the ground state (Lakowicz 2006). Fluorescence analyses are more commonly used because this technique can take advantage of different parameters to be investigated, such as fluorescence intensity and life time, anisotropy, and quantum yield.

5.3 Applications of Green Composites in Sensors

5.3.1 Green Composite–Based Sensors for Detecting Heavy Metals in Water

A worldwide environmental issue related to water degradation lies in the excessive proportion of heavy metals dumped into water resources, usually related to the inappropriate disposal of industrial wastes (Karkra et al. 2017; Peng et al. 2018). Since these pollutants are non-biodegradable, the occurrence of bio-accumulation in aquatic and terrestrial living organisms and human health triggers serious health disorders (Alkmim-Filho et al. 2014; Liu et al. 2017c; Jose and Ray 2018). Although some of these substances play important role in physiological mechanisms, most of them are poisonous even under low concentrations, resulting in serious diseases, mutation, and even death by intoxication (Tchounwou et al. 2012). Therefore, the development of reliable and expedite techniques capable to detect such hazardous compounds is highly required.

Recent works have shown the interesting synergism between green materials and hazardous heavy metal ions, which has led to the development of innovative strategies for heavy metal sensing detection. For instance, cellulose surface chemical modifications through carboxylation, amination, succinylation, and sulfonation have improved their interactions with varied pollutants (Seely and Hart 1974; Lee and Mooney 2000; Chin et al. 2017); lignin has a large number of active sites that are highly suitable for complexation with heavy metal ions (Garcia-Valls and Hatton 2003); and pectin can coordinate with some heavy metal ions due to electrostatic attraction by carboxyl and hydroxyl groups in its backbone (Kartel and Kupchik 1999; Juan Zhao and Qin Zhou 2015).

Cellulose is the most abundant green material available on Earth and can be tailored to design novel composites for a plethora of applications, including sensing and biosensing. In sensing platforms, cellulose is normally employed as paper substrate, membranes, or thin films. Paper-based platforms, as the one exemplified in Fig. 5.4, encompass features as flexibility, high specific stiffness, porous structure, compatibility with biological samples, printability, biodegradability, and low cost to fabricate disposable sensors (Chaiendoo et al. 2017; Li et al. 2019). Paper has been conveniently applied in order to further reduce the gap between complex laboratory testing and simple point-of-need testing (Cinti 2019). Cellulose can be applied in pristine form (Kuek Lawrence et al. 2014; Ferreira et al. 2015; Cui et al. 2019) or as part of composites (Rashid et al. 2016; Chaiendoo et al. 2017; Sahatiya et al. 2018), as substrate for screen-printed sensors (Fang et al. 2011; de Oliveira et al. 2019; Ruecha et al. 2019) and microfluidic platforms (Moraes et al. 2018; Ilacas et al. 2019; Ruecha et al. 2019). Bacterial cellulose can also be used as nanopaper as novel, flexible, and transparent substrate to optical sensor (Morales-Narváez et al. 2015; Abbasi-Moayed et al. 2018).

Although cellulose shows insulating characteristics, the advances in composite materials field have enabled to extend its application in electrical and

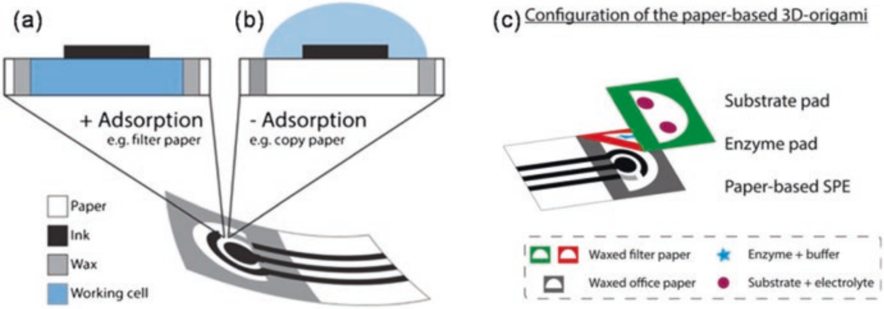

Fig. 5.4 Experimental setup related to electrochemical paper-based devices obtained by application of (**a**) high-adsorption substrates and (**b**) low-adsorption substrates (Cinti 2019). Reprinted with permission from Cinti (2019)). Copyright (2019) Springer Nature. (**c**) Example of paper-based screen-printed electrode proposed by Arduini et al. (2019)), which uses a paper-based device folded as three-dimensional origami combining different enzyme-inhibition biosensors for the detection of different classes of pesticides. Reprinted with permission from Arduini et al. (2019)). Copyright (2019) Elsevier

electrochemical sensors. For instance, Tan and coworkers (2018) studied the use of cellulosic fibers coated with polyaniline (PANI) as working electrode in the electrochemical detection of Pb(II). The composite fabrication required the control of PANI polymerization, in order to achieve a thin layer onto cellulose fibers. Firstly, the aniline monomers were adsorbed onto cellulose surface by H-bonding interactions and then the polymerizing agent was added. Such procedure allowed the formation of a PANI nanolayer of about 50 nm. The physicochemical characterization indicated that the presence of PANI afforded conductive properties for the paper. This disposable sensor responded linearly to Pb in the working range from 0.2 ppm to 1.0 ppm, yielding a limit of detection of 0.348 μM (0.0721 ppm).

Also, potential and recently explored is the use of cellulose nanostructures in sensing platforms. Cellulose nanocrystals, nanofibrils, and nanofilms show distinctive properties that are superior to common paper (Abbasi-Moayed et al. 2018). Application of cellulose nanocrystals as fillers to mechanical reinforcement is very traditional. However, emerging technologies and the necessity of small, biodegradable, lightweight, and strong products have widened the application of this material. In a recent work, Teodoro and coworkers (2019) used a hybrid material based on cellulose nanocrystals and graphene oxide to functionalize fluorine-doped tin oxide (FTO) electrodes for electrochemical determination of Hg(II). Cellulose was explored as a green reducing and stabilizing agent for graphene oxide nanosheets. The combination of this hybrid material with electrospun nanofibers enabled enhancing the charge transfer properties and allowed to detect mercury(II) with a limit of detection of 520 nM. The good performance of this sensor was attributed to a good distribution of graphene onto the platform, as a consequence of synergistic interactions between cellulose nanocrystals and graphene.

Zinoubi et al. (2017) applied nanofibrillated cellulose (NFC) from *Eucalyptus* to modify carbon glass electrodes (CGE) to electrochemically evaluate heavy metal trace in seawater. Nano-sized fibrils were produced by fibrillation of *Eucalyptus* fibers, yielding fibers with 5–10 nm of diameters. The fiber surface was modified using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) reactant, by a procedure called TEMPO-mediated oxidation (Roy et al. 2009), leading to formation of carboxyl groups. The electrode modification was performed by adsorption of nanofibrillated cellulose onto CGE, which were highly adhered due to interactions between the long β-glucans of cellulose and the carbon surface, through hydrogen bonding. The authors also performed a study of accumulation time, once the electrochemical performance could be affected by interactions between NFC matrix and metallic ions. Differential pulse anodic stripping voltammetry (DPASV) was then applied to quantify trace amounts of Cd(II), Cu(II), Pb(II), and Hg(II). As a result, the proposed platform performed reproducible response, high sensitivity, and good stability for all analytes. A low limit of detection of 5 nM was obtained for Cd(II) and Hg(II), and 0.5 nM for Cu(II) and Pb(II). The higher sensitivity and the low limit of detection obtained for these metal ions were attributed to the good affinity with oxidized cellulose nanofibrils.

Chemical modification of cellulose is expanding the sensor fabrication methods and allowing interaction with chromophores, which enables the fabrication of optical heavy metal sensors. Azmi et al. (2018) produced an easy-to-interpret colorimetric platform by impregnation of chromophore dithizone in flat casting films of cellulose acetate. The composite was cut as strips and dipped into mercury(II) aqueous solutions, allowing naked eye detection at 3 ppm Hg(II). Zhang and coworkers (2018a) developed a sensor based on electrospun nanofibrous cellulose acetate/curcumin membranes for colorimetric detection of lead(II). The curcumin is a natural chromophore able to chelate with heavy metal ions to form complexes, which leads to color changes. The sensor demonstrated to be selective, but influenced by pH and membrane thickness.

Starch, another carbohydrate, was used as reducing and capping agent in gold nanoparticle (AuNP) green synthesis performed by Ban et al. (2015). The resultant composite could be applied in the plasmonic sensing determination of Cu(II) and Pb(II) in water. The sensing experiments were performed in aqueous solution, by simply mixing starch-AuNP suspension with known concentration of six different heavy metals: Cu(II), Ni(II), Zn(II), Pb(II), Hg(II), and As(II). The proposed material presented high sensitivity to Pb(II) and Cu(II), which could be seen by color change even under ppm concentrations. The color changed from pink (typically related to AuNP) to dark ruby red in the presence of Pb(II) and to violet due the presence of Cu(II). Simultaneous analysis of other metallic compounds revealed no significant color change, indicating the selectivity for these species. The authors reported that the affinity-based chelating activity of surface stabilizing agents were responsible for sensing the metal ions; therefore, starch might be responsible for the selectivity to Pb(II) and Cu(II). Similar work was performed by these authors using starch-capped silver nanoparticles (AgNPs; Ban and Paul 2018). Very small nanoparticles (2–10 nm) revealed optical (absorption and fluorescence) activity in UV-Vis spectra. The same six heavy metals were evaluated and a selective sensing response for Hg(II) was verified as consequence of the evident color change from yellow to colorless, under a more pronounced surface plasmon resonance (SPR) shift, varying in accordance with the concentration range of 1–10 ppm. The selectivity for Pb(II) and Cu(II) using starch-based optical sensors was also verified by Khachatryan and Khachatryan (2019). In their study, elastic films composed by starch-ZnS quantum dots (QDs) nanocomposites were produced. The sensing experiments showed a decrease in emission intensity when the films were exposed to Pb(II) and Cu(II) ions, which was attributed to the interaction between the cation metal and QDs surface that may reduce the electron-hole recombination.

Narayanan and Han (2017) have applied alginate-stabilized silver nanoparticles to label-free colorimetric sensing of manganese(II) in water. Alginate, a polysaccharide derived from algal biomass, acted in an ecofriendly reduction and stabilization of silver nanoparticles. The proposed nanoplatform showed selectivity and sensitivity for optical detection of Mn(II) in aqueous solution, in the range of 1–10 μM. The mechanism of detection involved the aggregation of silver nanoparticles, which led to color change from pale yellow to brownish yellow, followed by a gradual decrease and broadening of SPR absorbance band at 400 nm. The cross-linking of alginate polymer chains led to reduction in interparticle distance, inducing a very slight aggregation of AgNPs. For comparison, the chelating ability was compared with chelation caused by ethylenediaminetetraacetic acid (EDTA), and the effect caused by the presence of Mn(II) led to a more expressive colorimetric change (Fig. 5.5).

Carbon-based materials from biomass are reported as low-cost and readily available starting materials to the synthesis of interesting novel structures. Among them, lignin has attracted great attention due to its abundance in nature and because it has been applied, for instance, in environmentally friendly Carbon-Dots synthesis (Chen et al. 2016; Yang et al. 2018; Liu et al. 2019). Sources rich in organic compounds such as glucose, cellulose, and phenolic molecules are very applicable for the preparation of Carbon-Dots (Liu et al. 2019). Electrospun carbon-fibers obtained from lignin have also been explored in several applications (Jayawickramage and Ferraris 2019; Roman et al. 2019; Titirici et al. 2019).

Martins and coworkers (2008) performed sensing experiments with lignin extracted from sugarcane bagasse, which was applied in the fabrication of ultrathin Langmuir–Blodgett (LB) films. The sensitivity of lignin-based films to Cu(II) was evaluated by cyclic voltammetry and electrical impedance spectroscopy using an electronic tongue. For the electrochemical study, 21 layers of lignin films were deposited onto indium tin oxide (ITO) electrodes, and for impedimetric study, five layers of lignin films were deposited onto interdigitated gold electrodes. The results showed that the LB film could be used as sensor for detection of low concentrations of Cu (10 mg L^{-1}), the selectivity of which was attributed to the lignin complexation with metallic ions in solution.

Another interesting carbon-based material derived from biomass is the biochar, which has attracted attention in reducing ecological and health risks of hazardous substances, such as heavy metal compounds. Liu et al. (2016) fabricated a low-cost sensor depositing on carbon glass electrodes (CGEs) a thin film based in a biochar prepared from pyrolysis of pine for voltammetric determination of Cd(II). The

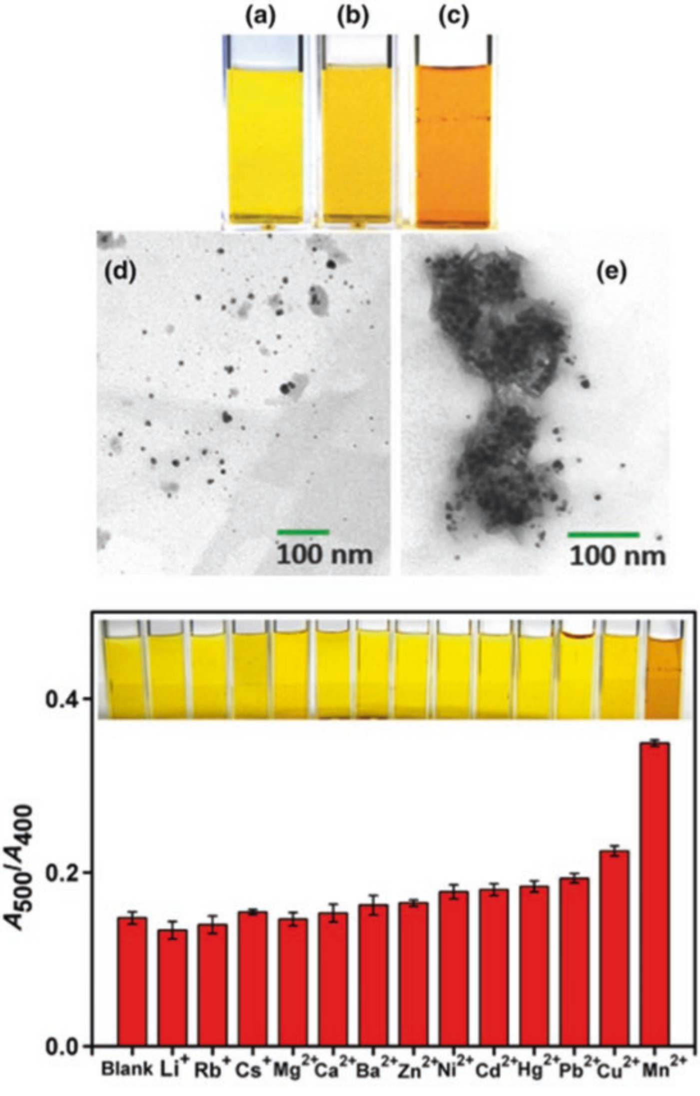

Fig. 5.5 (**a**) Photograph of aqueous suspension of alginate-stabilized AgNP obtained by Narayanan and Han (2017)). (**b**) Color changes caused by EDTA addition and (**c**) Mn(II) addition. (**d**) TEM images of alginate-AgNP and (**e**) alginate-AgNP agglomeration caused by Mn(II). In (**f**) is demonstrated the selectivity for Mn(II) by photographs and plot of A500/A400 for alginate-AgNP suspensions containing different metal ions. Reprinted with permission from Narayanan and Han (2017)). Copyright (2017) Springer Nature

biochar was mixed to montmorillonite for enhancing surface area, ion-exchange ability, dispersive stability, and adsorption capacity, and to carboxymethyl cellulose to improve water-dispersive, film-forming, and adhesive abilities. The as-obtained biochar has flaky aggregates morphology and the film montmorillonite-cellulose-biochar has a large specific surface area. The compositional analysis revealed the presence of several oxygen functional groups such as carboxylic, hydroxyl, phenol, and carbonyl in biochar. Films containing the biochar showed the highest stripping peak, indicating a significant enhanced synergistic effect of different components due to superior adsorption capacity, large specific surface area, and good exchange capacity. The selectivity of the sensor was verified toward other metals—Pb(II), Cu(II), Hg(II), Zn(II), Al(III), and Fe(III)—and the sensitivity was evaluated in linear range of Cd(II) concentration of 2.0 nM to 80 μM, leading to a limit of detection of 6.7 nM.

5.3.2 Green Composites Applied in Sensors for Detecting Pathogens in Water

The monitoring of microorganisms in different environments and conditions is of great relevance nowadays because, in the same extent they play crucial role for the proper functioning of specific natural systems, some microorganisms can also be pathogenic and behave as infectious agents, posing high risks to human and animal health (Leonard et al. 2003; Deisingh and Thompson 2004; Duffy and Moore 2017). Infections with pathological agents can lead to serious illnesses, ultimately causing the death of the infected patient. In addition to health problems, infections caused by live pathogens represent a significant expenditure for the governments and can even threaten global security once they are used as biological weapons (Xu 2012).

A recurring concern in this regard is the quality of water, because infections caused by microbial pathogens can be acquired and transmitted by inadequate and unsafe water supply. Owing to the difficulty in identifying pathogenic microorganisms, combined to the precarious conditions of water in specific regions, waterborne infections are a major cause of concern worldwide (Cabral 2010; Aw and Rose 2012). The need to guarantee a safe water supply leads to the search and the development of ways to detect these pathogens in the water (Leonard et al. 2003). A very used and well-established method for the identification of pathogens is the preparation of a culture medium in which the microbial organisms will multiply and their determination will be carried out. However, these culture-based methods present some drawbacks, such as the long time required for the analysis, the impossibility of being used on-site, and the inability to detect traces of microorganisms. Therefore, accurate and fast methods capable to detect pathogens is crucial for preventing infections and outbreaks (Aw and Rose 2012; Xu 2012). In this way, the development of chemical sensors may represent a viable alternative for the detection of pathogens. The sensors must fulfill some important requirements, though. They should present high sensitivity and low detection limit in order to detect a few cells of the pathogen, which is sufficient to cause health problems. In addition, the sensors must provide rapid results, assisting in the correct treatment choice and restricting the spread of pathogens. It is also desired a high specificity toward target cells and the possibility of performing in-situ detections (Heo and Hua 2009).

Immunosensors are sensors whose transduction mechanism is based on the specific interaction of a very stable complex formed between an antibody and an antigen (Felix and Angnes 2017). The detection is performed through the immobilization of the antibody or the antigen onto a transducer surface, which converts the complex formation into a measurable signal. Antigens can be biological pathogens, such as bacteria, viruses, and fungi, that form a stable complex with a specific antibody. Due to the specificity character, immunosensors present high selectivity and good sensitivity (Moina and Ybarra 2012; Felix and Angnes 2017).

Luo et al. developed an immunosensor for rapid and sensitive detection of the target pathogen *Escherichia coli* (*E. Coli*) O157:H7 and bovine viral diarrhea virus (BVDV) using direct electrical measurements (Luo et al. 2010). The biosensor was made based on electrospun cellulose nitrate (CN) nanofibers. The CN nanofibers were chosen because of their biocompatibility with proteins and the high surface area, which allows occurrence of more biological events, facilitating the assay. The sensor architecture consists of three pads: an application pad, a capture pad, and an absorption pad. The application pad was used to deposit the sample under investigation and to control the flow of the sample in the capture pad, while the absorption pad modulates the capillary action. Conductive magnetic nanoparticles were modified with antibodies and incubated with the sample to conjugate with the target pathogen. Next, a magnetic separation process was used for the sample purification. The CN nanofibers were plasma-treated to enhance the capillary performance and implemented as the capture pad after being immobilized with the specific secondary antibody. Silver electrodes were fabricated using spray deposition of silver paint and recognized the electron transport path through the formation of conductive sandwich complexes between antibodies and pathogen. After achieving capillary flow equilibrium, the direct-charge transfer to the electrode was measured. The amount of *E. coli* O157:H7 or BVDV in the sample was proportional to the captured sandwich complex that generated the electrical signal, leading to a change in the resistance values detected by the electrodes. The detection principle of the immunosensor is shown in the scheme of Fig. 5.6a. The CN nanofiber-based immunosensor showed a linear response for *E. coli* O157:H7 concentration from 0 to 10^4 colony-forming unit per milliliter (CFU mL^{-1}) and a sensitivity of 61 CFU mL^{-1}. For the BVDV sample, the detection limit was estimated to be 10^3 cell culture infectious dose per milliliter (CCDI mL^{-1}).

In a similar work, the detection of two influenza A viruses by a magnetic biosensor using CN membrane and magnetic beads was proposed by Hong et al. (2011)). Viruses were adsorbed to the CN membrane and specific antibodies were coupled to magnetic beads, enabling the formation of antigen–antibody complexes. The complexes were recognized based on the frequency mixing detection through the generation of signals that reflect the concentration of the magnetic beads and

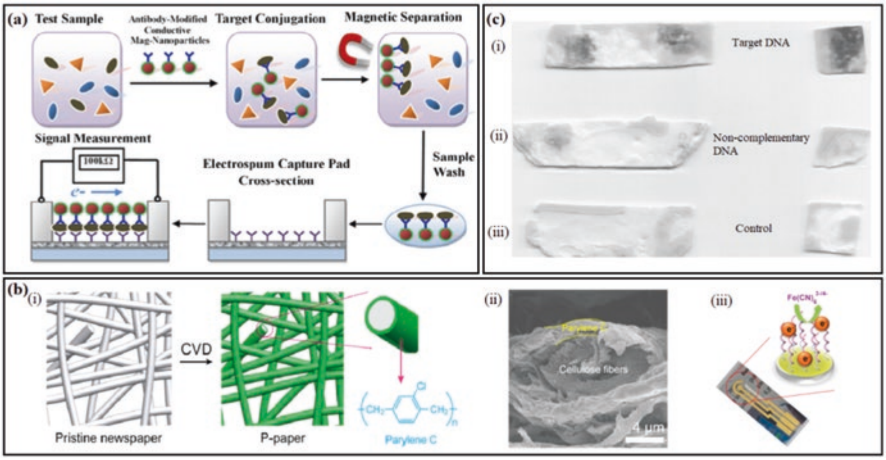

Fig. 5.6 (**a**) Schematic illustration of the principle of detection of the immunosensor based on electrospun functionalized with antibodies. Reprinted with permission from Luo et al. (2010). Copyright (2010) Elsevier. (**b**) (i) Illustration of the process used to obtain the P-paper; (ii) cross-sectional SEM image of the P-paper; and (iii) the fabricated P-paper electrode for electrochemical detection of the pathogen. Adapted and reprinted with permission from Yang et al. (2016)). Copyright (2016) American Chemical Society. (**c**) Digital pictures of the cellulose paper and the distinct coloration developed after hybridization with (i) complementary (target) DNA, (ii) non-complementary DNA, and (iii) the control. Adapted and reprinted with permission from Saikrishnan et al. (2014)). Copyright (2014) Springer

consequently the amount of complex formation. The assay was demonstrated to be superior in some aspects (in terms of reduction of the assay time and robustness) to conventional enzyme-linked immunoflow assay (ELIFA).

Aptasensors have emerged as an interesting alternative for the detection of live pathogens. These biosensors are based on aptamers, that is, single-stranded DNA (ssDNA) or RNA molecules that mimic antibodies' properties. In the detection mechanism of pathogens, aptamers work as artificial antibodies recognizing target molecules through the formation of aptamer–analyte complexes. Aptasensors may present some advantages on immunosensors based on antibodies, namely high specificity, better stability, and ease of synthesis (Luppa et al. 2001; Felix and Angnes 2017). In this context, the selective detection of *Staphylococcus aureus* (*S. aureus*) was performed by an electrochemical aptasensor proposed by Ranjbar and Shahrokhian based on cellulose nanofibers (CNFs), carbon nanoparticles (CNPs), and gold nanoparticles (AuNPs; Ranjbar and Shahrokhian 2018). The desired features of CNFs for the biosensor were combined to the excellent conductivity of CNPs and AuNPs, besides the ability to capture a larger quantity of analytes due to the high surface area of the latter. Electrochemical impedance spectroscopy (EIS) measurements were conducted to perform the detection of *S. aureus*, in which an analytical signal was recorded and the presence of the pathogen caused a change in the charge transfer resistance (R_{ct}). The limit of detection of the aptasensor was found to be 1 CFU mL^{-1} with a wide linear dynamic range, which demonstrated the potential to detect *S. aureus* in human blood serum samples.

Lignin was used by Cerrutti et al. (2015) to fabricate an immunosensor for human immunodeficiency virus (HIV). In their work, an immunosensor based on layer-by-layer (LbL) films of lignin and an antigenic peptide (p-17) was proposed in the recognition of a specific antibody for HIV. The lignin was used due to its biocompatibility and availability and acted by immobilizing the p-17 in the LbL films. The lignin matrix preserved the structure of the peptide, which is essential for molecular recognition. Gold interdigitated electrodes were used in the electrical measurements conducted in phosphate-buffered saline (PBS) solution, and the lowest concentration of the specific antibody used, that is, 0.1 ng mL^{-1}, was comparable to other electrochemical biosensors.

Yang and coworkers used newspaper as a source of cellulose fiber to fabricate a flexible and disposable sensor by coating the fiber with parylene C in order to detect the pathogenic *E. coli* O157:H7 based on DNA hybridization (Yang et al. 2016). The parylene-C-coated paper (P-paper) was obtained by a dry chemical vapor deposition (CVD) method, which enabled an enhancement in the mechanical properties and an increase in the hydrophobicity of the sensor while maintaining its porous structure. Such features allowed its use in electrochemical measurements in aqueous media. The schematic illustration of the fabrication of the P-paper is shown in Fig. 5.6b(i), and the cross-sectional scanning electron microscope (SEM) image of P-paper is presented in Fig. 5.6b(ii). The paper electrodes were obtained via patterning of gold and silver layers on P-paper. To detect the pathogenic *E. coli* O157:H7, the single-stranded DNA (ssDNA) was immobilized onto the gold working electrode (Fig. 5.6c(iii)). The ssDNA is capable of recognizing the target complementary DNA (cDNA) of *E. Coli* O157:H7. EIS was employed and the increase in the R_{ct} values upon increasing target cDNA concentration was evaluated, yielding a detection limit of 0.16 nmol L^{-1}.

Detection of pathogenic bacteria was also conducted by Saikrishnan et al. using a cellulose-paper-based colorimetric bioassay through the detection of the target pathogen DNA (Saikrishnan et al. 2014). The cellulose was tosylated to achieve a very porous surface and then probe of oligonucleotides was immobilized covalently on the tosylated cellulose surface. The principle of detection was based on the manifestation of a blue color derived from the specific hybridization that occurs with a biotin-labeled oligonucleotide and the probe attached to the cellulose surface. A streptavidin-horseradish peroxidase (HRP) acted as a transducer providing the color change that indicated the biorecognition event. The detection of the target DNA resulted in a strong coloration of the cellulose paper, while lower intensities of blue spots were observed with non-complementary DNA and no color change was noticed in a negative control experiment (without DNA oligonucleotide), as can be seen in Fig. 5.6c. Polymerase chain reaction (PCR) was applied to test the biosensor with the pathogen DNA from *Mycobacterium tuberculosis*, and the results showed an expected blue color corresponding to the complementary probe.

Visual detection of pathogenic bacteria was also performed by Tait et al. based on the generation of volatile organic compounds (VOCs) trapped in agarose gel (Tait et al. 2015). The detection was possible because the addition of an enzyme substrate to a bacteria sample generated VOCs, which were trapped in the agarose gel containing color-generating reagents. Agarose is inexpensive and was modified with specific and selective colorimetric reagents in order to show a change of color in the presence of target compounds. *Enterococcus faecium* and *Klebsiella pneumoniae* produce β-glucosidase and, when prepared with 2-nitrophenyl-β-D-glucoside, releasing 2-nitrophenol, generate a yellow color within the agarose gel. Other bacteria that do not have activity toward 2-nitrophenyl-β-D-glucoside showed no change of color. *Pseudomonas aeruginosa*, in turn, is a known β-alanyl aminopeptidase producer and hydrolyzes the trifluoroacetic acid (TFA) salt of 3-amino-*N*-phenylpropanamide, changing the color of the gel to orange. The detection method allowed a simple, low-cost optical discrimination and identification of β-glucosidase producing bacteria and β-alanine aminopeptidase producing species.

5.3.3 Green Composites Applied in Sensors for Detecting Hazardous Volatiles

Concern about emission control and detection of hazardous volatiles, including volatile organic compounds (VOCs), has been increasing in the last years. VOCs are generally colorless (which hinders their direct detection by optical spectroscopy), often have low boiling point and are highly reactive and frequently mixed with interfering gases, which requires the development of sensors with high selectivity (Vaishnav et al. 2005). Some VOCs may be highly toxic and/or carcinogenic and may harm human health and the ecosystem as a whole. The common methods used for detecting hazardous volatiles are gas chromatography and mass spectrometry (De Gouw et al. 2003; Dincer et al. 2006), due to their low limit of detection. However, both apparatuses are expensive and analyses are time-consuming, which restrict their use for in-situ and real-time analysis. For this reason, there is an increasing interest in developing portable gas sensors that display high sensitivity, selectivity, and stability for specific applications (Khanna 2011).

Investigations involving gas sensor analyses have grown considerably in recent years. Approaches based on electrical (Amer et al. 2019), electrochemical (Pang et al. 2018), and optical (Terra et al. 2018) sensors employing different types of materials as active layers, such as polymers, metal nanoparticles, carbon nanotubes (CNTs), semiconductor metal oxides have been proposed (Andre et al. 2018). For instance, Khattab et al. (2019) proposed a solid-state reversible colorimetric sensor for detecting ammonia gas, which can be very harmful and cause serious health problems (Rousidou et al. 2013). In their work, bromocresol was added to a carboxymethylcellulose matrix for developing an easy-to-use and reversible ammonia gas sensor with excellent reversibility and short detection time. The sensor was yellow before ammonia gas exposure, and changed to purple when exposed to ammonia, and the system exhibited a rapid response time and low detection limit of 9.0×10^{-2} ppb for aqueous ammonia.

Zhang et al. (2018b) used graphene/ethylcellulose (EC) nanocomposites to produce a low-cost and flexible VOC gas sensor by depositing a graphene/EC nanocomposite as a thin film onto a flexible polyethylene terephthalate (PET) substrate. The sensorial platform showed no sensitivity to deformation and yielded excellent responses to VOCs at room temperature with detection limits ranging from 37 to 167 ppm. The developed sensor showed potential to be employed in portable electronic products, labels, and intelligent packaging for the monitoring of perishable products.

Although PET and glass microfiber “paper” are known for producing flexible sensing platforms, both are of synthetic origin and display very long life cycle (Andre et al. 2017). Cellulose-based paper, on the other hand, is an ecologically favorable alternative, once it is derived from cellulose, and presents flexibility, versatility, porosity, and low cost, combined to easier degradability. Paper-based platforms used as optoelectronic devices are usually lighter, thinner, and can be easily moldable or cut using scissors, and these features enable their application in colorimetric, electrochemical, and fluorescence sensors (Khansili et al. 2018; Singh et al. 2018; Kanaparthi and Singh 2019). On the other hand, some paper substrates can present high roughness and absorption capacity, factors that can limit its use in flexible electronic devices. This problem can be overcome by treating the paper surface in order to limit its absorption and soften its surface (Bundy and Ishley 1991; Singh et al. 2018). Another possibility is the use of paper composed of cellulosic nanostructures, whose dimensions at the nanoscale exhibit high contact surface area and mechanical resistance (Kim et al. 2015).

Different types of materials can be associated to paper substrates to act as a sensitive layer in gas sensor assays, providing sensitivity and selectivity toward varied analytes. Among the materials employed for this purpose, we can highlight carbon nanotubes (CNTs), conductive polymers, metal oxides, graphene and graphene oxide, and metals. Several gas sensors based on flexible platforms have been reported in the literature, where usually the paper is the sensory platform, while a thin layer of sensitive material is deposited on it, enabling an efficient and economical detection of toxic gases (Moseley 2017). For instance, in the work of Niu et al. (2016), the authors developed an electronic gas sensor that detects ammonia at room temperature by depositing a thin film of polyaniline/reduced graphene oxide (PANI/RGO) on a flexible green paper substrate. The porosity presented by the paper substrate was preserved even after deposition of the thin film, and its roughness is very important for the formation of thin PANI/RGO film coating responsible for the detection.

Maity and Ghosh (2018) reported the development of an inexpensive and disposable paper sensor that can be used at room temperature for ammonia gas sensing. The authors reported that the sensor was able to detect the presence of small amounts of ammonia leading to color changes. For detection, a thin film of perovskite halide $CH_3NH_3PbI_3$ (MAPI) was deposited on the paper, which showed black color when

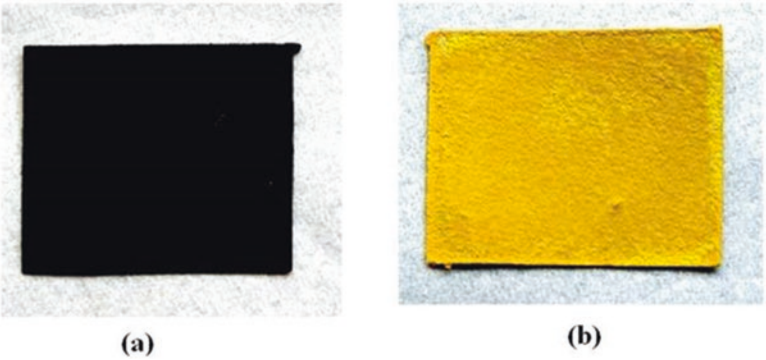

Fig. 5.7 Color change response of the MAPI sensor, where (**a**) represents the original black color of the unexposed film of perovskite halide $CH_3NH_3PbI_3$ (MAPI) and (**b**) represents the yellow color in the presence of ammonia gas. Reprinted with permission from Maity and Ghosh (2018)). Copyright (2018) Nature

in contact with the paper, and yellowish coloring in the presence of the ammonia gas, as can be observed in the images of Fig. 5.7a and b. An important feature of this type of sensor is that there was no need for any extra equipment for its operation, since it is a visual sensor, where the color change could be easily detected with the naked eye.

In addition to being environmentally friendly, gas sensors that use paper as a substrate have become an important emerging class of electronic devices because of their flexibility. Salarbashi et al. (2019) constructed a gas sensor with high sensitivity and flexibility using PbS nanowires processed in solution as the detection material. The device developed demonstrated an excellent detection response after exposure to NO_2 at room temperature, and showed no decrease in performance under different angles of curvature throughout the detection cycles. The results suggested the promising use of paper substrates in flexible devices applied in gas sensor assays.

5.4 Final Remarks

A recent survey of different types of sensors, including electronic tongues and electrochemical and optical chemical sensors, for monitoring distinct substances, using green composite materials was here presented. Specifically, for the sensor design we focused on cellulose and other natural macromolecules combined to carbon-based, metallic, and oxide nanoparticles, to be used as active layers or in some cases as substrates for varied sensors aimed at monitoring heavy metals in water, bacterial contamination, and volatile organic compounds. The green composites produced for this purpose present remarkable properties and can be considered as an alternative to the use of single or isolated materials as active layers in sensors, improving sensor sensitivity, limit of detection, decreasing cost, etc. The use of low-cost and green materials for producing electrical and optical devices, including sensors, that are cheap, portable, and easy to operate appears to be a general approach that will push new developments in the area, including the scaled-up industrial production of such devices.

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Chapter 6
Toxicology and Safety Aspects of Nanosensor on Environment, Food, and Agriculture

Yasmin M. Heikal and Heba M. M. Abdel-Aziz

Contents

Abstract The potential of nanotechnology is for innovation in the agricultural and food industries. Different nanosensors types are being created to satisfy the varying agri/food industry demands, comprising food components, smart packaging, and rapid detection systems. It is necessary to understand the assigned mechanisms or causes for nanoscale toxic impacts, their features and properties both externally and within the biological environment. Several nations around the globe have therefore been concerned in testing the suitability of their legislative outlines to address nanotechnologies. Here we review the latest nanosensor developments and address the most difficult assignments and promising possibilities from chosen latest research in the agri-food sector. The main points are (1) knowledge acquisition and

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development of nanosensor life cycle techniques, risk assessment, toxicity, bioaccumulation, and beneficial and negative impact assessment. (2) The toxicological fundamentals and the exposure risk connected with the usage of nanosensors in agri/food and the environment are also addressed. (3) Regulation and laws are also essential for the regulation of nanosensor production, processing, implementation, and disposal.

Keywords Nanosensors · Toxicology · Agriculture · Food security · Nanotechnology · Environment security · Safety · Regulation · Legislation · Public perception

6.1 Introduction

In view of the growing worldwide population, contemporary technologies such as nanotechnology in the food and agricultural industries must be used to increase agricultural production (Batsmanova et al. 2013). In most developing countries, agriculture is the cornerstone and directly and indirectly offers food for humans. As one of the leading drivers of the economy, agri/food manufacturing is of essential significance. It can also provide paths for value-added plants. Agricultural practices are often in the public eye because the limitations of climate change, power, and resources and the quickly increasing worldwide population place unprecedented pressure on food and water resources (Ghasemzadeh 2012). With restricted land and water resources available, agricultural development can only be accomplished via the use of more efficient fertilizers and pesticides, but also on hygiene by enhancing productivity through excellent agronomy and promoting it with the efficient use of contemporary technology.

Compared to its use in pharmaceuticals and drug delivery, nanotechnology applications in agriculture and food are comparatively recent (Garcia et al. 2010). Nanotechnology relates to the comprehension and control of nanoscale matter where a distinctive phenomenon allows for new applications (Committee on Technology 2014). However, limiting the size of nanotechnology to a range of 1–100 nm excludes countless products and devices, particularly in the agricultural and pharmaceutical areas, and some specialists are cautious against a strict definition based on a sub-100 nm size. Nanotechnology can revolutionize farming and related areas tremendously, comprising fisheries and aquaculture. Nanofarming presently focuses on targeted farming, using nanosized particles with distinctive characteristics to increase crop and livestock productivity (Scott and Chen 2014). Nanotechnology has the ability to safeguard crops, monitor the growth of plant, detect illnesses of plants and animals, boost worldwide food manufacture, improve food quality, and decrease waste for "sustainable intensification" (Gruère et al. 2011; Sonkaria et al. 2012).

Nanosensors are developing as a successful instrument for farming and food production application. Compared to conventional chemical and biological methods, they give important improvements in selectivity, velocity, and sensitivity. Microbes, pollutants, contaminants, and food freshness can be detected by nanosensors (Joyner and Kumar 2015).

Sustainable agro-production relies primarily on several of the securities listed such as land, food, power, and water safety. It should be noted that requests for nanotechnology can be used to attain these prior bonds (Siddiqui et al. 2015; Dubey and Mailapalli 2016; Rai and da Silva 2017). Food and nutrition safety becomes a basic human right and means that all individuals must have access to sufficient, accessible, and safe foods at all socio-economic and geographical levels to satisfy people's nutritional needs and food choices for active and healthy living (FAO 2009).

Research connected with the nanoparticles potential risk to living organisms has attracted interest from academia, business, and government regulatory agencies globally due to the growing amount of nanomaterials and the broad variety of applications. This chapter will therefore concentrate on various nanosensor applications in sustainable agro-food manufacturing. The risk and safety of these nanosensors on the environment, food, and agriculture will also be outlined. The state-of-the-art various legislative policies for nanomaterials in agri/food will be discussed as well as legislation and guidelines for safety evaluation.

6.2 Nanosensors Development in Agri/Food Sector

6.2.1 Nanosensors: Definition, Mechanism, Types, and Classification

The effect of nanosensors on the industrial, food, and environmental industries is anticipated. Portable nanodevices can detect illnesses, pathogens, insects, contaminants, and chemicals quickly and can lead to quicker treatment (Farrell et al. 2012). The entire agri/food industry can be revolutionized by inexpensive sensors, cloud computing, and smart software together. Precise agriculture becomes a possibility thanks to computers, worldwide satellite positions, and remote sensing equipment. The key features of a precise agricultural vision are the monitoring and assessment of environmental factors, the taking of appropriate and prompt decisions, targeted actions based on information gathered to boost crop production using ideal resources for pesticides, fertilizers, and herbicides (Rai and Ingle 2012).

Nanosensors have the structure as ordinary sensors, but their processing is on the nanoscale. The nanosensor therefore can be described as an extremely small device capable of connecting to anything that needs to be detected and transmitting a signal. These minisensors can recognize and react by transmitting this response to a signal or output that can be used by humans in the physicochemical (sensors) and biological (biosensors). Compared with conventional sensors and their limitations, nanosensors have a range of beneficial characteristics: high selectivity and sensitivity, proximity to real time detection, low price, and portability (Lu and Bowles 2013).

Specific nanosensor design methods include molecular self-assembly, lithography from the top down and bottom up-assembly approaches. Current devices for nanosensors can be split into (Liu 2003): nanostructured materials—for example, porous silicon, sensors based on nanoparticles, nanoprobes, nanosensors, nanosystems: nanoelectromechanical systems (NEMS), and cantilevers. Agriculture uses mainly two kinds of nanosensors: (i) electrical-nanosensors and (ii) bio-nanosensors. Biological organisms have significance in defining the environmental condition; the combination of biology and nanoparticles into sensors is capable of improving awareness and could reduce reaction time to feel a prospective problem (Scott and Chen 2014). Nanobiosensor is a modified version of a biosensor that can be defined as a compact analytical unit that includes a sensitized part associated with the transducer (Turner 2000).

6.2.2 *Nanosensors for Food and Agriculture Application*

Numerous nanosensors have been developed to detect threats rapidly in the case of suspected food poisoning for various applications in the agricultural and food industry or to be embedded in the packaging as nanotracers in order to demonstrate the history of the foodstuff and whether its consistency is always appropriate. The use of nanosensors in food packaging, for example, in microorganisms detection and the color change when a threshold is reached, as well as in Internet process control nanosensors, helps track storage conditions so as to prevent toxicity to food (Augustin and Sanguansri 2009). Scientists use gold nanoparticles to coat them with molecules that bind to compounds like pesticides. Farmers could spray these nanoparticles in their areas to detect a chemical such as a pesticide (Rathbun 2013). It is possible to summarize the list of prospective applications of nanosensors in the agri/food industry as shown in Figs. 6.1a and 6.1b.

Field-divided nanosensors can also detect the presence of corn and other plant pathogens and concentrations of soil nutrients (Jones 2006; Brock et al. 2011). Gas sensors and nanosmart dust (using small wireless detectors and transponders) (Mousavi and Rezaei 2011) can rapidly assess levels of environmental pollution. Nanobarcodes and nano-related processing could also be used to monitor agricultural production quality (Li et al. 2005). Hormone regulation based on nanotechnology such as auxin allows scientists to understand how plant roots, especially marginal soils, adapt to their environment (McLamore et al. 2010).

Nanobiosensors can be used efficiently at very minute concentrations to detect a broad range of fertilizers, herbicides, pesticides, insecticides, pathogens, moisture, soil pH, poisonous pollutants, and industrial pollutants (Rai et al. 2012; Sekhon 2014). Nanobiosensors are used in sectors other than food and agriculture. Nevertheless, after considering their significance, several sensors have been recently developed (Sekhon 2014; Jyoti and Tomar 2016). This technology can offer better fertilization management for farmers in the agro-production industry, decrease of inputs and better management of time and climate, as well as control of crop health,

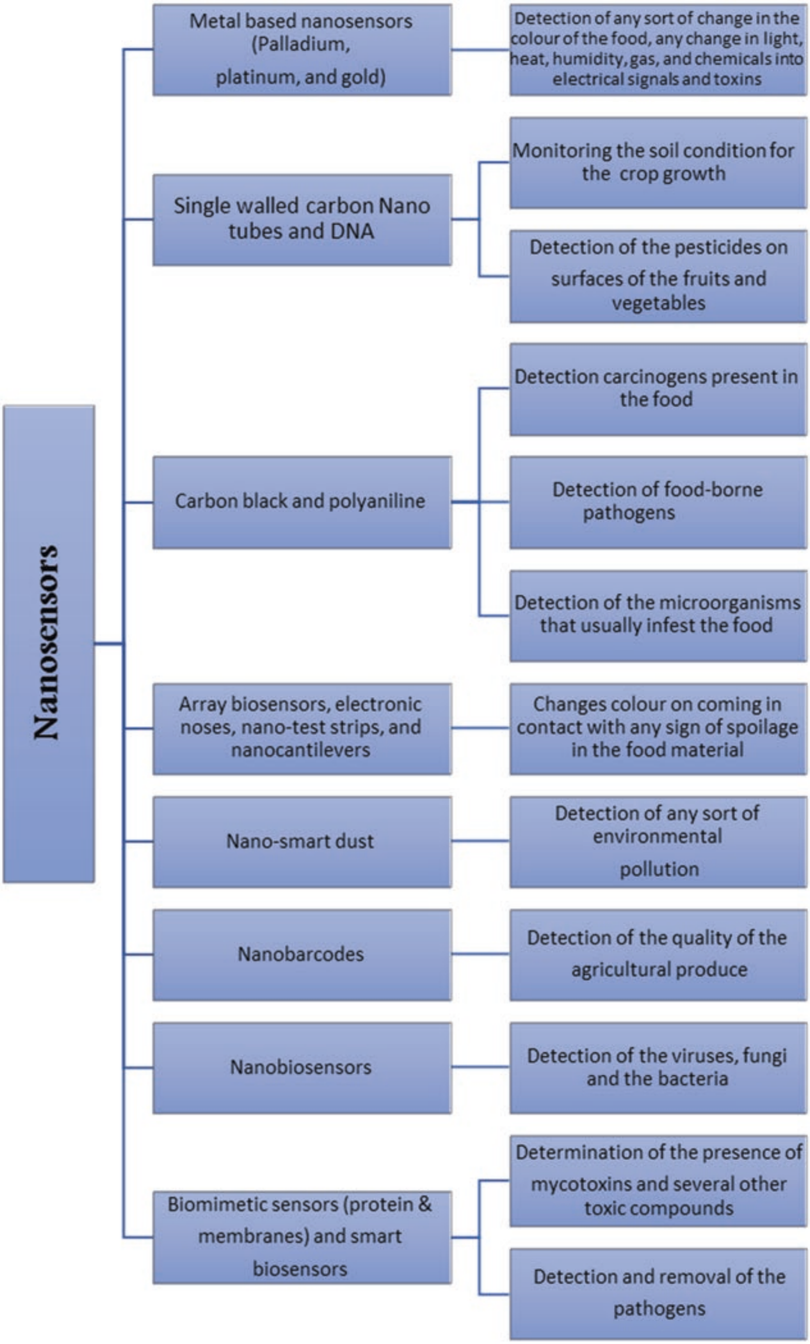

Fig. 6.1a Schematic diagram outlining the nanosensors types: Metal-based nanosensors, single-walled carbon nano tubes and DNA, carbon black and polyaniline, array biosensors, electronic noses, nano-test strips, and nanocantilevers, nano-smart dust, nanobarcodes, nanobiosensors, biomimetic sensors (protein & biomimetic membranes) and smart biosensors and their applications in different agri/food sector

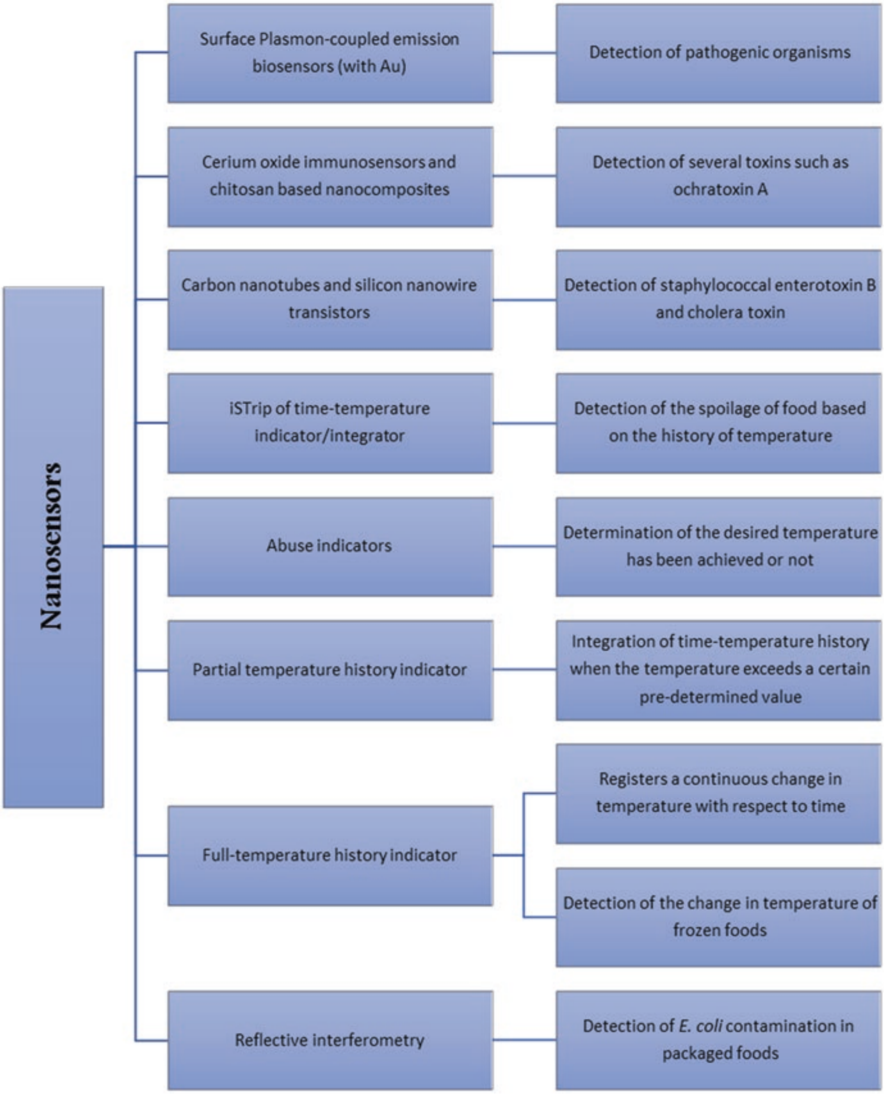

Fig. 6.1b Schematic diagram outlining the nanosensors types: surface plasmon-coupled emission biosensors (with Au); cerium oxide immunosensors and chitosan-based nanocomposites; carbon nanotubes and silicon nanowire transistors; iSTrip of time-temperature indicator/integrator; abuse indicators; partial temperature history indicator; full-temperature history indicator; reflective interferometry and their applications in different agri/food sector

food quality, and security, thus improving agriculture productivity in addition to helping in the effective use of natural resources such as water, chemicals, and nutrients (Farrell et al. 2012; Ansari et al. 2016).

Some researchers use nanosensors to track the biological and ecological health effect of agricultural pollutants (Ansari et al. 2016). These nanosensors can also be used for gases such as nitrogen oxides, sulfur dioxide, ammonia, sulfur hydrogen, and unstable organics and metal oxide nanowire, either metal nanoparticles (palladium, platinum and or gold) or metal oxide nanoparticles and nanotubes. Without altering confirmation and the linkage of the enzyme molecules outside the active enzyme centers, the biosensor development showed excellent compatibility between membranes and proteins (Bäcker et al. 2017). Therefore, the design of sensors/biosensors depends on different interactions resulting in nuclear power spectroscopy (Shuai et al. 2017).

The recent advances have led in near-market nanosensors: nanosensors and nanoscale coatings to substitute thicker, more corrosion-preventing wasteful polymer coatings, nanoscale biopolymers to enhance heavy metal decontamination and recycling, aquatic toxin nanosensors, nanosensors capable of offering quality assurance through the food processing chain by tracking microbes, toxins and contaminants, including the use of data capture for automatic monitoring (Prasad et al. 2014).

Wireless nanosensors provide accurate, time-based information, including food and environmental pesticide detection, quality control, and environmental status. Salicylic acid is a plant-based phenolic phytohormone that promotes plant growth, photosynthesis, and transpiration. It is an essential plant component and it is important to sensitively detect the amount of salicylic acid. Wang et al. (2010) use copper nanoparticles with gold electric nanosensors. Copper nanoparticles detect salicylic acid electro-catalytic oxidation and electrochemical salicylic acid behavior. Nano gold nanoparticle electrode detects properly levels of salicylic acid in oilseed rape infected with the fungal pathogen *Sclerotinia sclerotiorum* (Wang et al. 2010). Electrochemical sensor for the detection of triazophos insecticide with altered carbon nanotube electrode with a gold nanoparticle deposition was used in post-harvest vegetables (Li et al. 2012).

It is essential to highlight multiple micro-nano biosystems that have been established as European Commission projects (2015) and used to implement intelligent agri-food technologies. The development of technology, in particular the Internet of Things (IoT), as more devices connected through the Internet to customers and other devices grows, contributes significantly to the realization of smart agriculture across sustainability, efficiency, quantity and cost-efficacy of agricultural production. Nanotechnology's innovative implementation in IoT generates a fresh paradigm, called the Nano Things Internet (IoNT).

6.3 Environmental Dynamics of Nanosensors, Their Interactions with Target and Non-target Organisms

The need for knowledge and detection of the presence of nanoparticles in the setting, measurement of emissions of nanoparticles, toxicity, life cycle, and effect on the environment and human health are essential to attaining all the advantages that nanotechnologies have to give. The environmental toxicity of nanoparticles relies on their size, type, and load. In addition, nanoparticles impact on the atmosphere also relies on environmental variables (moisture, temperature, wind flow rate, and light nature). However, nanomaterial characteristics, tiny size, and big surface make it simple to disperse and bond with human tissues in the setting (Rai and Ingle 2012).

6.3.1 Nanosensor Life-Cycle Assessment

The requirement that they be biocompatible with the organism or biological tissues and liquids being tested is implicit in any in vitro or in vivo use of nano-bio sensors. They must be nontoxic for in-vivo processes and the materials must not produce a biological reaction that interferes with the experiment. Sensors intended for non-invasive or in vitro use must be consistent with the investigated biological fluids and any reagents, particles, or elements used for measurement purposes. Nanoparticles-mediated sensors such as bio-imaging aids, drug delivery aids, or colorimetric in vitro sensors may have extra problems such as enhanced rates of dissolution, aggregation, and surface adsorption of biological molecules that may reduce their efficacy. The Biocompatibility Assessment Team is structured to provide an early assessment of suggested sensors recognizing and resolving nano-bio interactions that may influence center systems development and marketing. Expertise is also available to assure safety and effectiveness of sensor technology in testing more mature prototypes (CNBS 2016).

6.3.2 Nanoparticles Fate and Agro-Environment

One of the most important environmental issues may be the environmental fate and transportation of nanoparticles. Nanoparticles in various environmental compartments such as soil, air, water, crops, sediments, and animals are parts of this destination and transportation cycle. It is the place to produce our agricultural products for our milk, feed, fibers, and fuel. Thus, nanoparticles movement and translocation in terrestrial environments are a major problem and should be tackled. In addition, this conduct of nanoparticles in agro-ecosystems involves both the beneficial side and the adverse side as shown in Fig. 6.2 (Omara et al. 2019).

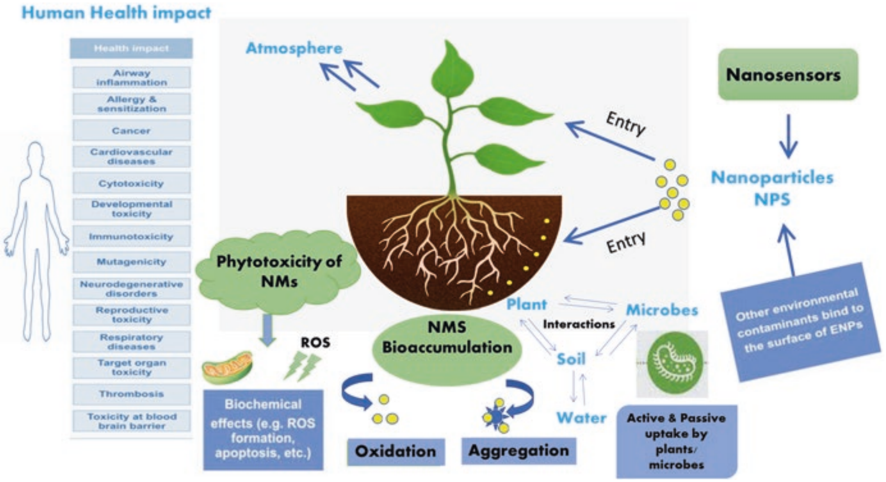

Fig. 6.2 Schematic diagram outlining the possible environmental fate/behavior of nanoparticles (NPs) includes the negative impact as well as the release, transport, and toxicity of nanoparticles in the soil environments, plants, microbes, and human health

Several studies (e.g., Miseljic and Olsen 2014; Soni et al. 2015; Hegde et al. 2016; Tolaymat et al. 2017) have been released on the discharge, transport, and environmental toxicity of nanoparticles. It therefore continues an open question to distribute and transport nanoparticles in distinct environment. Nanoparticles may enter or transport crops and/or other microorganisms from various settings through active or passive uptake into the food chain. Many variables affect this translocation of nanoparticles such as air, soil, water, and sediment and cause severe human and animal changes (Soni et al. 2015; Kwak and An 2016).

One of the most significant agro-environmental researches can be considered by the interaction between nanoparticles under the soil–plant scheme. Agro-environmental studies include relationships between soil–plant nanoparticles (Soni et al. 2015; Zhang et al. 2017) and soil microbial society impacts of nanoparticles (Samarajeewa et al. 2017). Nanoparticles also have the possibility to carry toxic substances (e.g., heavy metals and lipophilic pollutants) due to their large surface area and highly reactive nature (Baun et al. 2008; Gil-Díaz et al. 2017). Additional types of nanoparticles can be entered by roots in pores from 5 to 20 nm in size that allows small particles to pass through the cell walls (Zhang et al. 2017). Thus, nanoparticles of lower sizes can migrate and achieve the plasma membrane than the diameter of the pore. There is also some proof that nanoparticles can enter cells via ion canals and carriers and interfere with normal metabolism, possibly through the manufacture of reactive oxygen species (ROS) (Tolaymat et al. 2017).

6.3.3 Nanosensors Environmental Toxicology Aspects

Nanomaterials only get into the atmosphere and human beings through agricultural production (Rico 2015). Nanomaterials communicate heavily with soils. Improved pesticides and plant products by nanomaterials can spread into soil, water, and atmosphere, bind more heavily to pollutants, and bring them through soil and water. Nanofertilizer and pesticide exposure may lead to risks to health (Sastry 2012). There is also a high risk of nanoparticles migration integrated into human food (Berekaa 2015). Consumers direct exposure to nanomaterials is a major problem for human health. Nanoparticles may enter the human body through the skin, respiratory system, or digestive system. However, the exposure is limited as long as the nanoparticles remain bound. Teow et al. (2011) provided detailed information on the health effect and safety of nanomaterial application.

Modern technologies have shown the potential for various characters of toxic-kinetics and toxic-dynamics of nanomaterials that are more reactive and capable of crossing membrane barriers. Some nanomaterials interact by causing oxidative stress to proteins and enzymes by producing ROS that cause mitochondrial destruction and apoptosis. In recent years, a variety of biological and toxicological interactions in nanomaterials have been documented in vitro and in vivo by experimental structures. A broad variety of endpoints of biochemistry and toxicology have been recorded within each scheme. Most of the inflammatory markers have been targeted, because current health data concerning the environmental effects of nanomaterials have recognized a key role in oxidative stress and inflammation as toxicological action modes for nanoparticles. Consequently, over the last few years, there have been significant advances of the biological and toxicological effects of nanomaterials. Much of this is related to what physical and toxicological characterization data are required for risk assessment and how to get it. In restricted applications of nanomaterials to measure the acute toxicity of these chemical agents, no serious adverse effects were found. Accessible to nanomaterials, such as long-term inhalation research, reproductive or developmental studies, still exist rudimentary toxicological information sets. The fact that nanoparticles can be kept in cells for long periods of time when absorbed into the systemic circulation makes it important to carry out ongoing studies for hazard and nanomaterial risk assessment (Omanović-Mikličanina and Maksimović 2016).

6.4 Regulatory Frameworks for Nanomaterials/Nanosensors Linked to Environmental, Food and Agricultural Hazard, Exposure, and Risk Evaluation

The government is concerned about the toxicity and environmental impact of nanosensors in agriculture and in the food industry, despite the trembling benefits. Long-term negative effects knowledge is very minimal on soil, plant life, and finally on people (Dubey and Mailapalli 2016). The primary elements of nanotechnology are enhanced quality and dietary value in terms of worldwide food and livestock production. Despite prospective advantages in the agri/food industry (livestock feed, food production, packaging and nano-based smart systems), little is known about safety elements of the implementation of nanotechnology in food production and the integration of nanoparticles into food. Furthermore, nanotechnology knowledge is still lacking for customers (Sekhon 2014).

The use of organic nanomaterials in the agriculture and the consumable sector has raised concerns about latent risks associated with the extensive use of nanoparticles on human health. Biotech tools are used for nanoscalable goods such as carbohydrates, fats, and proteins. The main concerns are inadequate knowledge of nanobiosensor factors such as toxicity, bioaccumulation, and exposure risk. The timely behavior of the particles in biological environments and the complexity of locally measured characteristics, such as size, form, and surface chemistry make it difficult to conduct reproducible and precise nanostructure biocompatibility tests. Due to the complexity, risk evaluation should include an early evaluation of anticipated sensors in order for nanobiological interactions to be recognized and fixed that may influence development and marketing center systems. Expertises should be made available to ensure the safety and efficiency of sensor technology during testing of more advanced prototypes. In order to build nanosensors in biological conditions, it is necessary to properly describe and test the nanoparticles and nanoscale materials and assess their toxicity (CNBS 2016). The potential threat to biological organizations has been identified by nanoparticles of significant interest from researchers, business, government ethics committees, and NGOs worldwide.

6.4.1 Current Guidelines for Assessing the Safety of Nanomaterials/Nanosensors

Risk assessment processes are not specific to agri-food nanomaterials, resulting in uncertainty about the nature and magnitude of future risks in most situations. Nanomaterials currently used for food use include the use of nanoparticles and nanomaterials as food ingredients/additives placed directly in food or as food packaging portions (Cushen et al. 2012). During the stage of product development, public views on new technologies in the food business need to be taken into account in order to avoid some of the pit breakdowns encountered by the genetically modified food industry (López-Vázquez et al. 2012). The release of nanoparticles may adversely affect edible crops (Suppan 2013).

The established risk assessment and testing methods are widely seen in nanomaterial (NMs) components but there is a need for further creation of standardized and validated approaches to certain components, including sample preparation, characterizing, dosimetry, exposure, and modeling data (SCENIHR 2007; OECD 2013). The EU Scientific Committee on Emerging and Newly Identified Health

Risks (SCENIHR 2009) proposed a case-by-case technique for risk assessment of NMs. Official bodies have released risk assessment guidelines focusing on the specific features of NMs. In 2011, European Food Safety Authority (EFSA) published a "Risk Assessment Guideline for the Application of Nanoscience and Nanotechnology in the Food and Feed Chain" (EFSA Scientific Committee 2011) that offers a practical approach to assessment of potential threats for nanotechnological and nanoscience applications in food additives, enzymes, flavorings, food contact materials, new food ingredients, feed additives, and pesticides. This provides guidelines on data generation and testing techniques by candidates for the identification and characterization of threats of nanomaterials. In addition, six exposure scenarios and associated testing methods are presented to define and characterize risks resulting from NM's characteristics. These six scenarios are dependent on possible NM transformations before and after food/feed ingestion. The sort of information required to carry out a risk assessment is indicated for each situation.

The guidance provides for reduced information requirements when data indicating no migration from food contact materials or when complete degradation/dissolution is proven without viable NM absorption as such is not verified by NM exposure. The guideline states: the NMs used in food or feed, which are converted into non-nanoforms in a food/feed matrix, may be used as guidance as non-nanoforms before ingestion. For NMs fully transformed in the gastrointestinal tract into non-nanoforms, consideration should be given to local impacts and possible absorption prior to conversion. Existing data should otherwise be used or guidelines should be followed for non-nanoforms. A comparison should show whether, compared to the non-nanoform, the nanoform has increased, less, or comparable risk. In a systematic, staged approach based on a comparison with the non-nano equivalent for food safety evaluations of NMs, an expert group created by the International Life Science Institute (ILSI) (Cockburn et al. 2012) has established a comprehensive approach. The distinction is based on the velocity of dissolution in water or under gastric conditions of the bulk and nano form of the same substance. Although released by EU bodies, these guidelines, like any other guidelines, are not part of EU legislation and therefore not legally binding. EFSA has also created a Food and Feed Nanotechnology Risk Assessment Network (EFSA Nano Network) with general objectives to promote the harmonization of evaluation procedures and methodologies, to improve information and data exchange between EFSA and EU Member States, and to attain synergies in risk assessment operations. In 2012, the EFSA Nano Network applied for an "Inventory of Agricultural, Food and Food Nanotechnology Applications" to obtain more up-to-date data on state-of-the-art nanotechnology apps generated by Rikilt and JRC (2014).

6.4.2 Regulatory Aspects and Legislation of Nanomaterials/Nanosensors

The risk of negative and unintentional effects of nanotechnology and the public opinion about new agro-production techniques during product development stages is crucially important (Zuverza-Mena et al. 2017). The small and large size of nanoparticles allow for fast dispersal without structural obstacles and possible toxicity are causing the risk (Rico et al. 2011). Millions of small-scale farmers in the agro-producing industry can pose a significant health threat by using nanofertilizers and nanopesticides that enable simple soil, water, and atmospheric dispersal (Tripathi et al. 2017). Nanoparticles are permitted into the food chain via nutrients/pesticide systems or food processing (Mattsson and Simkó 2016). Therefore, before NMs usage as agricultural goods, there should be studies of life cycles, particulate plant ingestion, biodistribution, and entry into the food chains (Rico et al. 2011).

In addition, nanobiosensor marketing is also associated with several risk variables such as: (a) original applications "*could act as substitutes for agricultural commodities*" that could be "*disastrous*" on the developing nations economy (Gruère et al. 2011); (b) Secondly, variable import regulations in separate countries could hinder the development of nanoproducts (Gruère and Sengupta 2009; Gruère et al. 2011); (c) Finally, the use of nanotechnology may be "*negative economic effects on the poor by increasing productivity in developed countries,*" which could result in lower commodity prices in developing nations (Gruère et al. 2011). Besides all the related hazards, marketing of any product is dependent on public acceptance of the same, in addition to all the associated risks. Therefore, risk opinions are crucial for future worldwide nanoproduct availability (Gruère et al. 2011). Customers are hitherto more unwilling to use nanofood than other nanotechnology uses (Lyndhurst 2010; Gruère et al. 2011) apparent "*benefits and health risks affect acceptance,*" "*meaning consumers do not perceive all products with the same risk levels*" (Siegrist et al. 2009; Gruère et al. 2011). Strategies for risk communication should be articulated "*attention to the messenger and the target of the message*" (Sylvester et al. 2009; Gruère et al. 2011). Some "*external factors*" could also put an impact in "*shaping future acceptance in the key markets*" that will have a major impact on the global future of nanotechnologies (Gruère et al. 2011). Non-governmental organizations supporting a "*ban on nanotechnology use in food and agriculture*" can be important, approaching condensed international marketing (Lyons 2010; Gruère et al. 2011). This might result in "*technology divide*" (Court et al. 2004; Gruère et al. 2011).

In some developed countries, the probable answer to this problem is appropriate nanoproduct labeling that could lead to legislation and technology consumption in developing countries. The Science and Technology Committee of the UK House of Lords has recommended including a mandatory "*pre-commercialization assessment using the methods supported by a research investment effort in risk assessment and detection methods*" (Gruère et al. 2011). "*The European Food Safety Agency supports the use of conventional risk assessment while addressing the limited* *knowledge on exposure to nanofood applications*" (Harrington 2010; Gruère et al. 2011). Countries should take into account the present institutional capacity while laying down legislation "*Similarities between biotech regulatory systems and nanotech regulatory systems*" should be taken as a benefit (Niosi and Reid, "Biotechnology and Nanotechnology) (Gruère et al. 2011)". Bearing in mind the lessons learned "*from the challenges observed in biosafety issues of biotech regulatory system,*" the "*need of public education, transparency and predictability*" has increased (Falck-Zepeda et al. 2009). "*The lack of risk assessment capacity*" and permeable boundaries should also promote the formation of local organizations by nations (Gruère et al. 2011).

The risk assessment of produced nanomaterials should be evaluated for regulatory and risk management reasons (Mattsson and Simkó 2016). This risk assessment of nanomaterials requires an understanding of exposure time, potential hazards, dosage, and nanomaterial type. This risk assessment of nanomaterials requires an understanding of exposure time, potential hazards, dosage, type and their characteristic changes over time (Priester et al. 2017). Despite accepted advancement in creating nanomaterial risk evaluation (Mattsson and Simkó 2016), there are still open issues about the destiny and conduct of nanomaterials in distinct settings. According to the European Parliament, some agro-producing regulations are as follows. (Lee and Stokes 2016): Legislation on food additives (Regulation: EC no. 1333 /2008, Art 12); Legislation on restrictions on hazardous substances in electrical and electronic equipment (Directive 2011 /65/EU, Recital 16); Legislation on waste electrical and electronic equipment (Directive 2012/19/EU, Art 8 (4); Legislation on food information for consumers (Regulation: EU no. 1169 /2011, e.g., Art 18); Legislation on cosmetic products (Regulation: EC no. 1223 /2009, e.g., Art 13 (1); Legislation on biocidal products (Regulation: EU no. 528/2012, e.g., Art 19 (1) and 7. Legislation on food for infants (Regulation: EU no. 609/2013, Art 9 (2).

Therefore, in the near future, a science-based risk assessment will be able to be carried out for the use of nanoparticles in all manufacturing and government sectors, including farming, medical care, transportation, energy, and machinery.

6.5 Conclusion

It is worth mentioning that the nanotechnology can affect or penetrate nearly all agricultural practices. It is important to explore new opportunities for incorporating nanotechnologies into nanosensors/nanobiosensors, aware of any future risks to the environment or human health. As a result, the use of agro-production has led in many hazards and therefore excellent difficulties have been developed to seek safety strategies for sustainable agro-production. We conclude that nanotechnologies in agriculture can be transformed by concentrated research and development to the goals of sustainable agriculture by government and academia. We discovered that there is still a need for efforts to improve public knowledge and appreciation of the novel nano-enabled food and agricultural products. The intelligent use of nanosensors in a quality and sustainable environment can contribute to achieving food security. A move towards green nanotechnology and green IoT will lead in their comprehensive applications to a whole new globe of safe nanoproducts with low or no health and environmental dangers.

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Chapter 7
Nanosensors for the Detection of Fertilizers and Other Agricultural Applications

Heba M. M. Abdel-Aziz and Yasmin M. Heikal

Contents

Abstract Recently, nanotechnology has started to revolutionize all agricultural practices. Nanotechnology research has improved all aspects of current agriculture. It can enhance the growth of plants by improving uptake of nutrients through engineered nanofertilizers. Also, it plays a pioneer role to monitor plant and soil conditions through nanosensors and detect pathogens and toxins (herbicides, pesticides, and veterinary drugs) residues in the food we eat through bionanosensors. Here we review nanotechnology applications in the form of nanosensors and bionanosensors and how they are used to monitor plant and soil conditions and detect diseases and pathogens in the crops we eat.

Keywords Nanosensors · Bionanosensor · Pathogens · Bacteria · Mycotoxins · Herbicides · Pesticides · Veterinary drugs · Soil · Plant

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7.1 Introduction

The massive increase in population all around the globe leads to the need to produce more food from the same limited farm lands. Previous approaches to improve crop productivity included: the use of biotechnology, genetic engineering, and synthetic chemicals. These approaches caused serious concerns with regard to health and safety of humans. A recent technology has evolved which is nanotechnology (Mura and Dudáš 2013; Chhipa and Joshi 2016).

Nanotechnology deals with synthesis and applications of nanostructures of sizes at the nanometer scale. The word “nano” comes from the Greek word which means “dwarf,” which means one billionth of a meter. Nanoparticles are considered to be atomic or molecular aggregates which have one of their dimensions from 1 to 100 nm (Thakkar et al. 2010; Prasad 2014; Prasad et al. 2016; Kaushal and Wani 2017). Nanoparticles and nanomaterials could be classified into four groups: (1) carbon-based materials, that is, carbon nanotubes; (2) metal oxides such as TiO_2, Al_2O_3, and ZnO; (3) polymer nanoparticles to perform some chemical functions such as dendrimers; and (4) composites which are combinations between two types of nanomaterials or nanomaterials with bulk materials (Lin and Xing 2008; Nair et al. 2010; Kaushal and Wani 2017).

Nanotechnology has reached all aspects of everyday life. Recently, nanotechnology research has started to address agricultural problems in an attempt to find pioneer solutions to enhance productivity of crops and decrease pests, infections, and environmental pollution (He et al. 2019). In a recent application of nanotechnology research, along with nanopesticides, nanoherbicides, and nanofertilizers, nanosensors aroused as new devices set to detect bacteria, mycotoxins, pesticides, herbicides, veterinary drugs, and monitor soil and plant conditions (Chen and Yada 2011; He et al. 2019). Such detection allows better control of pests and pathogens and provides information to improve crop productivity by better uptake of nutrients and improve soil properties. The use of nanosensors in conventional agriculture converts it into precision agriculture (Chhipa and Joshi 2016).

There are two main forms of nanosensors used in agronomy: (1) electrical and (2) bionanosensors (Chhipa and Joshi 2016). A chemical sensor can be defined as a device which measures the concentration of a specific material and transfers it into a useful analytical signal. However, a biosensor is defined as a device which contains an element (biologically active) such as an enzyme or antibody used for the quantitative detection of a specific analyte (Sharma and Rogers 1994; Srivastava et al. 2018). The characteristics of the biological molecule construct the reaction of the biosensor with the measured material which then becomes translated into a measurable signal (Gomes et al. 2015).

Carbon nanomaterials were developed to act as a chemical sensor to detect pesticides accumulation in plants (Sharon and Sharon 2008). For the identification of *Xanthomonas axonopdis*, a plant pathogen causing bacterial spot diseases in Solanaceae plants, a bionanosensor made of silicon nano-probes attached to goat anti-rabbits antibody was used (Yao et al. 2009).

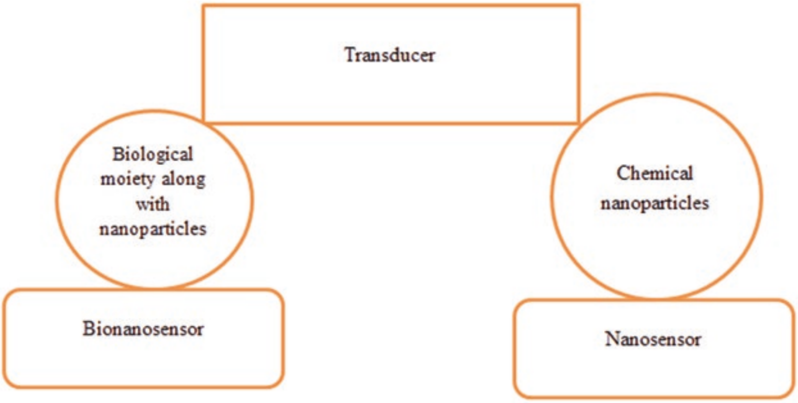

Fig. 7.1 Difference between nanosensor and bionanosensor

In the current work, we reviewed the use of nanotechnology applications: nanosensors and bionanaosensors in agriculture and their effects on crop productivity, diseases detection, and environmental assessment.

7.2 Why We Need Nanosensors?

Recent advances in agricultural practices led to massive use of herbicides, pesticides, veterinary drugs, and synthetic chemical fertilizers. This led to concerns on human health due to the accumulation of these toxic materials in plants and the food we eat. Thus, the need to have devices with precise ability to detect such chemicals and toxins was a priority to research labs all over the globe. Hence, the introduction of sensors at the nano scale was developed (Omanović-Mikličanina and Maksimocic 2016). A nanosensor is a very tiny device that can bind with what needs to be measured and send back a signal. Nanosensors were classified in two main categories: (1) sensors of chemical origin attached to an electrical transducer which give physicochemical signal are defined as electrical nanosensors and (2) sensors which contain a moiety of biological source along with nanoparticles attached to transducer and respond to a biological signal are bionanosensors (Srivastava et al. 2018; He et al. 2019) (Fig. 7.1).

7.3 Types of Nanosensors and Bionanosensors

Nanosensors have their arrangement like normal sensors but their production is at the nanoscale.

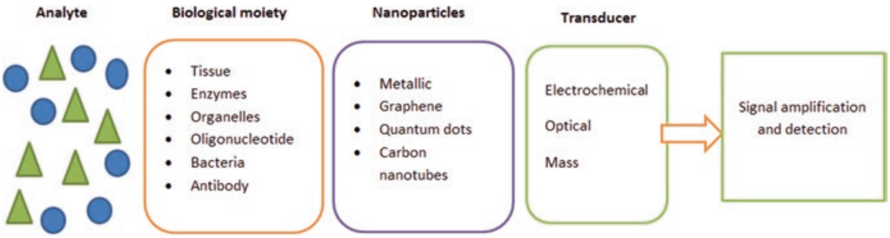

Fig. 7.2 Schematic diagram of a typical bionanosensor

After virtually changing the detection section for upgraded yield with nanostructures, the word nano is included in nanosensors and bionanosensors. The transducer is a sensor composed of nanomaterials such as metallic nanoparticles of gold and iron oxide, quantum dots, graphene oxide, and carbon nanotubes. Increased mechanical, thermal, optical, electrical, and highly specialized surface of the nanomaterial and flexible morphology improve the transfer capabilities in a certain degree (Srivastava et al. 2018). The nanosensors and bionanosensors can be categorized by transduction mechanism for output generation, as nanomaterial-dependent electrochemical nanosensors, and optical nanosensors which are connected to metallic nanoparticle optical properties and quantum dots. Mass nanosensors depend on mechanical and electrical properties of crystals (Srivastava et al. 2018) (Fig. 7.2).

7.4 Applications of Nanosensors in Agriculture

In order to monitor cultivation diseases, development, nutrient effectiveness, and environmental circumstances in the field, nanosensors have been created. In agricultural systems, nanosensors can trace quantities of chemicals such as pesticides, herbicides, and pathogens. This monitoring system provides solutions to prevent crop losses and improve crop productivity together with the aid of other nanostructures (nanofertilizers, nanopesticides, and nanoherbicides). A recent research showed that copper-doped montmorillonite can be used in water (both fresh and salty water) to monitor fungicides with a small detectable threshold of approximately 1 mM (Abbacia et al. 2014; He et al. 2019). Another research has shown that pathogens in wastewater can be detected using nanomaterials such as graphene (Wibowo et al. 2018) and purify it for use as drinking water (Deng et al. 2016), indicating potential application in aquaculture. Many other nanomaterials such as copper nanoparticles (Geszke-Moritz et al. 2012), carbon nanotubes (Esser et al. 2012), gold nanoparticles (Lin et al. 2011), and silver nanoparticles (Jokar et al. 2016) have also been developing as nanosensors for real-time environmental monitoring and crop health and growth (He et al. 2019). Nanosensors were used to measure soil properties (soil moisture, residual pesticides, nutrients, and pH), check for pathogen and determination of nitrogen uptake which helps farmers to maintain crop productivity (Bellingham 2011; Prasad et al. 2017).

The promotion of nanotechnology can be used to monitor cultivation and farm status in real time, such as the level of moisture, soil fertility, temperature, crop nutrient capabilities, and pathogens. The use of nanosensors for accurate soil measurement of soil criteria (soil moisture, residual pesticides, nutrients, and pH), pathogens control, and nitrogen absorbing assessment enables farmers make better use of input and therefore foster sustainable farming (Bellingham 2011; Prasad et al. 2017). These nanosensors are suitable for inspection of water and agrochemical treatments over time and volume based on the need for temporal and spatial macronutrients on plants necessary for the precise agriculture mission. Modern work is being done to design, in the future, accurate irrigation water supply schemes. The key features of this development are storage of water, the ability to hold water in situ, distribution of water near the root, the capacity to consume water for crops, and enclosed water, freed from crops. Microelectromechanical system sensors (MEMS) based on nanotechnology have the capacity to detect and respond to changes in the environment via microelectronic circuits. Wireless nanosensing devices composed of MEMS beams covered with water-sensitive nanopolymers for humidity optimization were created effectively by researchers (Kaushal and Wani 2017).

7.5 Applications of Bionanosensors in Agriculture

7.5.1 Detection of Bacteria

Microorganisms which are food-borne are a major concern to human health, especially in countries where there is no system to monitor food quality (Kumar et al. 2012). Bacteria are the main cause of gastroenteritis, food poisoning, and other illnesses such as *Salmonella* and *Escherichia coli*. Traditional methods to detect pathogen in food are time-consuming and very expensive. The use of bionanosensors all through food production processes from growth in the field till processing and distributing offers a good way to monitor bacterial pathogens and toxins in food that is infected (Mufamadi and Sekhejane 2017).

In a research study by Viswanathan et al. (2006), they developed a bionanosensor from carbon nanotubes and liposomes to detect cholera toxin. The detection limit of such immunosensor was 10–16 g of cholera toxin. A nanoparticle-based quantum dot biosensor for the identification of *Salmonella* species in food products has been created by Kim et al. (2013) in another research study. An electrochemical biosensor for the identification of *Salmonella* was created in a further study led by Afonso et al. (2013). In a recent study by Wang and Alocijia (2015), they developed with the aid of a nano-particle-labeled biosensor a new method for rapid detection of *Escherichia coli* (Mufamadi and Sekhejane 2017) (Table 7.1).

Table 7.1 Types of bionanosensors

Bionanosensor	Type of biological moiety	Nanomaterials	Biological application	References
Detection of Bacteria				
Carbon nanotubes and liposomes	Liposomes	Carbon nanotubes	To detect cholera toxin	Viswanathan et al. (2006)
Silicon nano-probes attached to goat anti-rabbits antibody	Goat anti-rabbits antibody	Silicon nano-probes	Identification of *Xanthomonas axonopdis*	Yao et al. (2009)
Quantum dot biosensor	*Salmonella* antibodies	Quantum dots	To detect *Salmonella*	Kim et al. (2013)
Nano-particle-labeled biosensor	Monoclonal antibodies	Magnetic and gold nanoparticles	Detection of *Escherichia coli*	Wang and Alocijia (2015)
Detection of mycotoxins				
Nanoparticle- based immunosensor	Polythionine	Gold nanoparticles	For determination of aflatoxin B1	Owino et al. (2008)
Electrochemical immunosensor	Anti-primary antibody	Carbon nanoparticles	To examine for the aflatoxin M1	Parker and Tothill (2009)
Optical biological sensor	Antibody	Gold-nanorod	Identification of aflatoxin B1	Xu et al. (2013)
Electrochemical immunosensors	Polyclonal antibodies	Gold nanoparticles	Detection of ochratoxins	Bone et al. (2010)
Biocompatible molecular bionanosensor	Oligo(ethylene glycol) monomethyl ether methacrylate	Magnetic nanoparticles	Detection of ochratoxin A	Turan and Sahin (2016)
Detection of pesticides and herbicides				
Acetylcholinesterase nanobiosensor	Acetylcholinesterase	Gold nanoparticles	Detection of organophosphates	Vimala et al. (2016)
Enzyme bionanosensor	Acetylcholinesterase	Carbon nanotubes	Detection of carbaryl	Zhang et al. (2008)
Acetylcholinesterase biosensors	Acetylcholinesterase	Chitosan nanoparticles	Detection of organophosphates	Guan et al. (2012)
Electrochemical biosensor	Acetylcholinesterase and acetylthiocholine	Gold nanoparticles	Detection of carbamate	Song et al. (2015)
Glyphosate biosensor	Horseradish peroxidase	Gold nanoparticles	To detect the herbicide glufosinate	Songa et al. (2009c)
Enzymatic biosensor	Tyrosinase	ZnO nanoparticles	To detect chlortoluron	Haddaoui and Raouafi (2015)

7.5.2 *Detection of Mycotoxins*

Mycotoxins are toxic chemicals produced by fungi (molds). They are natural contaminants of human food and animal feed especially when the food is stored at humid areas favorable to maintain molds growth (Akbas and Ozdemir 2006). Mycotoxins which are known to be toxic to humans and animals are: ochratoxin, aflatoxins, and zearalenone (Hussein and Brasel 2001; Ventura et al. 2004). Ingestion of these mycotoxins poses a threat to human health as they are labeled as carcinogenic, mutagenic, hepatotoxic, and nephrotoxic (Hussein and Brasel 2001). Hence, many countries regulate the entry of such toxins through food. Because of these concerns, it is highly recommended to have sensors that detect such toxins even at the lowest possible concentrations. That is where bionanosensors become developed to achieve such a target (Mufamadi and Sekhejane 2017). Several nanoparticles (immunosense systems, optical, magnetic, quantum dots, and carbon nanotubes) have been suggested for detection or tracking of mycotoxins in contaminated food (Xu and Han 2004; Adanyi et al. 2007; Owino et al. 2008; Viswanathan and Radecki 2008; Kaushnik et al. 2008; Mufamadi and Sekhejane 2017). With regard to aflatoxin detection, an electrochemical immunosensor has been developed to examine the aflatoxin M1 contaminants in matrix and milk interference (Parker and Tothill 2009). In addition, Xu et al. (2013) have established an optical biological sensor made of gold-nanorod (GNR) conjugated antibody for the identification of aflatoxin B1 in peanut. For the detection of ochratoxins, Bone et al. (2010) have created electrochemical immunosensors made of polyclonal antibodies and gold nanoparticles (Table 7.1).

Recently, Turan and Sahin (2016) have created an additional method for the detection of ochratoxin A with biocompatible molecular magnetic nanoparticles (Mufamadi and Sekhejane 2017) (Table 7.1).

7.5.3 *Detection of Pesticides and Herbicides*

The toxic substances used to control agricultural pests, such as weeds, fungi, and insects, are pesticides. The benefits of pesticides are the protection of crops by killing farm pests and weeds by herbicides. Unfortunately, residues of pesticides in agricultural products concern human health. Thus, it is important to track and detect pesticides and herbicides.

Current methods of detection are hampered because they are time-consuming and very expensive (Mufamadi and Sekhejane 2017). Hence the need to develop bionanosensors to detect pesticides and herbicides is of great importance to human welfare. Several nano-based pesticide biosensors have been developed to identify and track food for pesticides like herbicides, fungicides, insecticides, and other contaminants (McGrath et al. 2012; Zhao et al. 2015; Vimala et al. 2016). Zhang et al. (2008) created a new multiwalled carbon nanotube-based enzyme biosensor for the identification of pesticide residues in food. Acetilcholinesterase biosensors for the detection of residues of dichlorvos pesticides were developed in another study by Guan et al. (2012). In a new study, Song et al. (2015) have developed a simple electrochemical biosensor to measure carbamate pesticide quantitatively in real samples. The new glyphosate biosensor to detect the herbicide glufosinate has been created by Songa et al. (2009a, b, c). A disposable enzymatic nanobiosensor for the identification of chlortoluron herbicides has been developed in another research by Haddaoui and Raouafi (2015) (Table 7.1).

7.5.4 Detection of Veterinary Drugs

Veterinary drugs or antibiotics are used in farming animals to prevent and treat animal diseases. They are also suitable for improving animal growth, animal health, and feed efficiency (McEwen and Fedorka-Cray 2002). However, the use of antibiotics for animals may pose concerns as being found as residues in the meat and milk which are consumed by humans, hence poses human health problems. Thus, there is a great need to monitor the residues of such drugs in the food we eat. From this point, the need to develop bionanosensors to monitor animal drugs was of great importance. In the context of bionanosensors, intelligent analytical devices can be developed to determine the level or track the presence in real time of veterinary drug products (Wu et al. 2014, 2015). It also promises to provide cheaper, extremely sensitive, specific and precise equipment (Huet et al. 2010). Many nano-organic biosensors are specifically created to determine the level and the concentration of various kinds of veterinary antibiotics and drug residue in meat, poultry, milk, and much more. Most current biosensors are electrical biosensors, visual and aptamer. In addition, nanosensors offered an opportunity to detect residues of veterinary drugs in food by means of single or multi-analyte methods (Mungroo and Neethirajan 2014).

7.6 Conclusion

Nanotechnology has revolutionized all agricultural practices at research labs. The use of nanofertilizers, nanopesticides, nanoherbicdes, and eventually nanosensors has led to a new form of agriculture which is precision agriculture. Nanosensors have been used to detect pathogens, pesticides residues in plants and monitor plant and soil conditions. Bionanosensors have been employed to detect bacteria and mycotoxins throughout all agricultural processes till production of food. Also, they were used to detect pesticides, herbicides, and veterinary drugs. The use of nanosensors and bionanosensors is still at research level. Concerns arise as how these monitors can be monitored in a way to protect food and environment from being polluted with nanoparticles. Further work is needed to assess the safety of using nanosensors and bionanosensors on human and animal health.

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Chapter 8
Sensors for the Detection of Food Contaminants

Duygu Çimen, Nilay Bereli, Handan Yavuz, and Adil Denizli

Contents

Abstract Food safety is a public health concern. Food contaminants could be metal ions, residues of pesticides, mycotoxins, drug residues, allergens, preservatives, and contaminants from food processing and packaging. The contamination hazards in the agricultural food chain include residues of agrochemicals and natural toxins. These chemical pollutants have serious effects on human health such as liver, kidney, and neurological syndromes even in the minimum limits. The food contamination with toxins and environmental pollutants occurs during the processing, packaging, preparing, storage, and transportation. Traditionally, food contaminants are detected by conventional analytical techniques. The other approach for detection of food contaminants is sensors. Sensors offer various advantages including simple use, high sensitivity and selectivity, user-friendly, on-site detection, rapid and low-cost operation. This chapter summarizes the different sensor applications in food contaminant detection and analysis.

Keywords Sensor · Food · Contaminants · Detection · Hazards · Application · Residue · Limit of detection · Health · Environment

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8.1 Introduction

Food contaminants are chemical or biological substances. Food contaminants may be present in foods as a result of different stages such as food production, processing, transport, and storage (Aceña et al. 2015; Liang et al. 2015; Rapini and Marrazza 2017). The continuous use of these compounds is a worldwide problem due to the risks for food safety. Some food contaminants can be very harmful to human health even at low concentrations (Sliwinska et al. 2014; Scognamiglio et al. 2014; Vasilescu and Jean-Louis Marty 2016; Farahi et al. 2012). The residue of these substances even at trace levels can be a reason of food contamination. Although most food contaminants exist in detection limits, the bioaccumulation effect and continuous exposure may increase the risks for human and animal health. For this reason, analysis of food contaminants is essential to protect the ecosystem, ensure food quality and safety, and protect human health from potential hazards. Excessive application of food contaminants such as pesticide, metal ions, pathogens, mycotoxins, drug residues, allergens, and bacteria may leave harmful residues, including metabolites and degradation products into the food (Yılmaz et al. 2017; Hüseynli et al. 2019; Kantiani et al. 2010; Yang et al. 2014; Zhang et al. 2018a; Llorent-Martínez et al. 2019; Freire et al. 2016; Suaifan et al. 2017; Castillo et al. 2015). Significant amounts of food contaminant residues are a serious concern for human and animal health. Until today, various techniques have been used for the detection of food contaminants. They are traditionally detected by conventional analytical techniques such as liquid chromatography–tandem mass spectrometry, gas chromatography (GS), high-performance liquid chromatography (HPLC), mass spectrometry (MS), capillary electrophoresis (CEC), and enzyme-linked immunosorbent assays (ELISA) (Fig. 8.1) (He et al. 2007; Lin et al. 2008, 2018; Tao et al. 2012; Aşır et al. 2015).

These existing techniques have strong trace analysis ability, high reproducibility, and sensitivity with low detection limits. These techniques have many disadvantages such as being time consuming and laborious and requiring sophisticated equipment and expensive instruments, and they also require sample preparation and high-skilledlabors. In addition, they do not allow on-site and real-time application, which is especially important in emergency situations. The other approach for the detection of food contaminants is sensors. Sensors offer various advantages including simple use, high sensitivity and selectivity, user-friendly, on-site detection, rapid and low-cost operation (Zhu et al. 2015a; Li et al. 2019; Dai et al. 2013; Silva et al. 2018; Wu et al. 2018; Moises and Schäferling 2009).

8.2 Sensor Applications for Food Contaminants

Food contaminations have potential carcinogenic properties. Therefore, they need to be determined by a simple, fast, precise, and cost-effective method. The analysis of chemical contaminants needs to be determined compliance with regulatory limits and consumer safety. The detection and measurement of contaminants of foods is

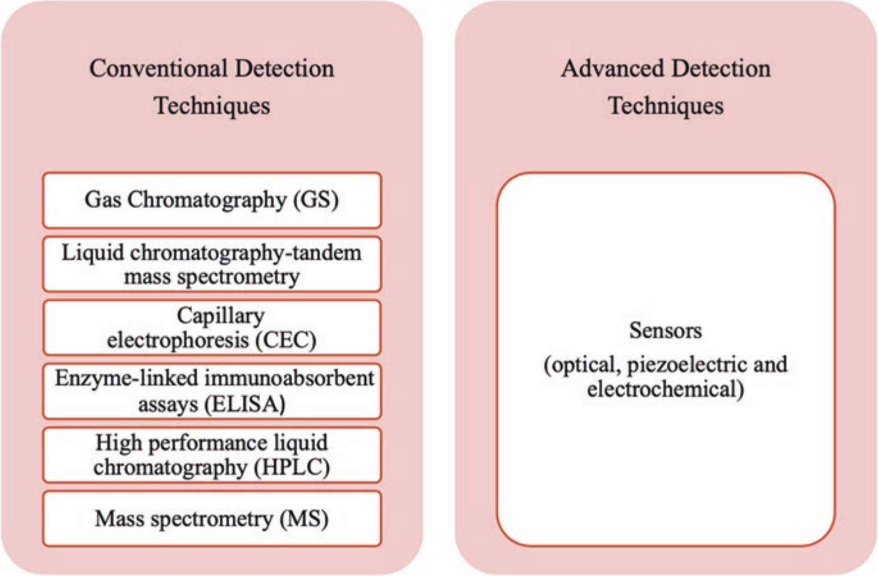

Fig. 8.1 Available techniques for food contaminant detection

generally conducted by purely laboratory-based procedures such as gas chromatography (GC), high performance liquid chromatography (HPLC), and liquid chromatography coupled with mass spectrometry (LC–MS). All of these techniques require laboratories with stringent conditions, and they are expensive and complicated. These are also time-consuming and require trained professionals. In recent years, sensors have several advantages over other analytical methods. Compared with analytical methods, they are more preferable and have attracted increasing attention because of their high sensitivity, low cost, fast response, portability, simple and on-site operation. The use of sensors possesses fast and simple analysis, in situ testing, and additional benefit of low cost. This chapter summarizes different types of sensors developed for the control of food contaminants.

8.2.1 Types of Sensors Based on Transducers

Transducers are based on many physicochemical phenomena like electrochemical, optical, and mass-sensitive sensors, which is a basic classification of sensors.

Electrochemical Sensors

Electrochemical devices need a basic necessity. During recognition event, a measurable change in electrical properties (potential, current, impedance, etc.) must be observed on the sensor surface or in the solution media. These devices need special electrodes to work: working/sensing, counter, and reference electrodes. Electrodes can be made from Ag/AgCl, platinum, gold, graphite, silicon, etc. Electrochemical sensors can be classified into different analytical techniques: amperometric, potentiometric, or conductometric (Yanase et al. 2013).

In potentiometric sensors, the changes in ionic concentrations are determined by use of ion-selective electrodes. Abdel-Ghany et al. (Abdel-Ghany et al. 2017) designed a novel potentiometric sensor for dinotefuran detection in real samples. They prepared four potentiometric sensors using methacrylic acid or acrylamide and carboxylated polyvinyl chloride (PVC) as functional monomer. The performance of the prepared potentiometric membrane sensor was demonstrated in spiked cucumber and soil samples.

Lu et al. (2016) fabricated an electrochemical immunosensor for deoxynivalenol (DON) and fumonisin B1 (FB1) detection. In this study, disposable screen-printed carbon electrode (SPE) with gold nanoparticles (AuNPs) and polypyrrole (PPy)-electrochemically reduced graphene oxide (ErGO) nanocomposite film was prepared for antitoxin antibody immobilization. Electrical conductivity and biocompatibility studies were performed. The limit of detection (LOD) and linear range of FB1 were found as 4.2 ppb, and 0.2 to 4.5 ppm (%RSD: 4.9%), respectively (Table 8.1). The corresponding values for DON were determined as 8.6 ppb, and 0.05 to 1 ppm (%RSD: 5.7%). The prepared immunosensor showed low-matrix interference and high sensitivity when extracts from spiked corn samples were used (Table 8.2).

One of the commonly used food processing contaminants is 3-monochloropropane-1,2-diol (3-MCPD). Fang et al. (2019) prepared a carbon dot-filter paper with a molecularly imprinted polymeric film to extract 3-MCPD from samples. The carbon dots have a high fluorescence intensity and can be easily adapted to sensor systems. The high adsorption capacity for this paper-based sensor was found to be 68.97 mg/g. The limit of detection (LOD) and an excellent selectivity of 3-MCPD were found as 0.6 ng/mL and imprinting factor of 4.5. The recoveries were determined from 97.2% to 105.3% with relative standard deviations <5.6%. These results are correlated linearly when compared to the results of the classical GC–MS method ($R = 0.998$) as shown in Fig. 8.2.

Ochratoxin A (OTA) is the most important mycotoxin known as a pollutant in grain and wine (Armutcu et al. 2018). The detection of OTA with sensitive and rapid detection methods is important for food safety monitoring. Zhang et al. (2018b) developed a lateral flow strip fluorescent aptasensor for one-step determination of OTA in corn samples. In the first experiment step, they immobilized biotin-cDNA on the surface of a nitrocellulose filter. Without OTA and in the presence of OTA, Cy5-labeled aptamer formed a stable double helix. The linear range of OTA was calculated as 1–1000 ng/mL. The limit of detection (LOD) was determined as

Table 8.1 Comparison of the performance of immunosensor (Ab-AuNPs-PPy/ErGO-SPE) and those reported in literature (Lu et al. 2016)

Mycotoxins	Sensor format	Linear range	Limit of detection	References
DON	Ab-AuNPs-PPy/ErGO-SPE	0.05–1 ppm	8.6 ppb	Lu et al. (2016)
FB1		0.2–4.5 ppm	4.2 ppb	
DON	ELIME assay	100–4500 ng/mL	63 ng/mL	Romanazzo et al. (2010)
DON	Label-free inhibition based electrochemical immunosensor	6–30 ng/mL	0.3 μg/mL	Sunday et al. (2015)
DON	96-well SPE plate	2–20 μg/g	1.1 μg/g	Ricci et al. (2009)
DON	AuNPs/*p*-aminothiophenol/folic acid/GC	0.1–20 μg/mL	0.03 μg/mL	Gu et al. (2015)
FB1 + FB2 + FB3	Electrochemical magnetoimmunosensor	–	0.33 μg/L	Jodra et al. (2015)
FB1 + FB2	Direct competitive/amperometry	1–1000 ng/mL	5 ng/mL	Kadir and Tothill (2010)
FB1	Multichannel electrochemical sensor	0–54 μg/L	0.58 μg/L	Ezquerra et al. (2015)
FB1	Electrochemical immunosensor	0.01–1000 ng/mL	0.002 ng/mL	Yang et al. (2015)

Table 8.2 Recovery of FB1 and DON from spiked corn samples (Lu et al. 2016)

Toxins	Spiked (μg/kg)	Measured (μg/kg)	RSD (%)	Recovery (%)
FB1	100	94	8.51	94.1
	500	484.9	3.30	97.0
	2000	1904.2	2.21	95.2
	4000	4141.6	1.71	103.5
DON	100	93.1	9.76	93.1
	500	521.7	4.0	104.3
	1000	982.4	3.26	98.2

0.40 ng/mL. The recovery of OTA in nailed corn samples was between 96.4% and 104.67% (Table 8.3). These experimental results show that it will be used as strip sensors in the practical application for detection of the OTA level in grain samples.

Aflatoxin is one of the most common mycotoxins in food matrices. Aflatoxin B1 (AFB1) is the most toxic contaminant with teratogenic, mutagenic, immunosuppressive, and carcinogenic effects. Yao et al. (2019) investigated a chemiluminescent aptasensor for aflatoxin B1 (AFB1) detection in food samples. In this study, the detection sensitivity of prepared sensor improved by using the hybridization chain reaction (HCR) signal amplification strategy. After determining the optimal experimental conditions, the linear range of AFB1 showed a good linear correlation from 0.5 to 40 ng/mL. The limit of detection (LOD) was determined as 0.2 ng/mL. The practicability of the prepared aptasensor was analyzed with peanuts and milk samples from local market. The different concentrations AFB1 were spiked into peanuts

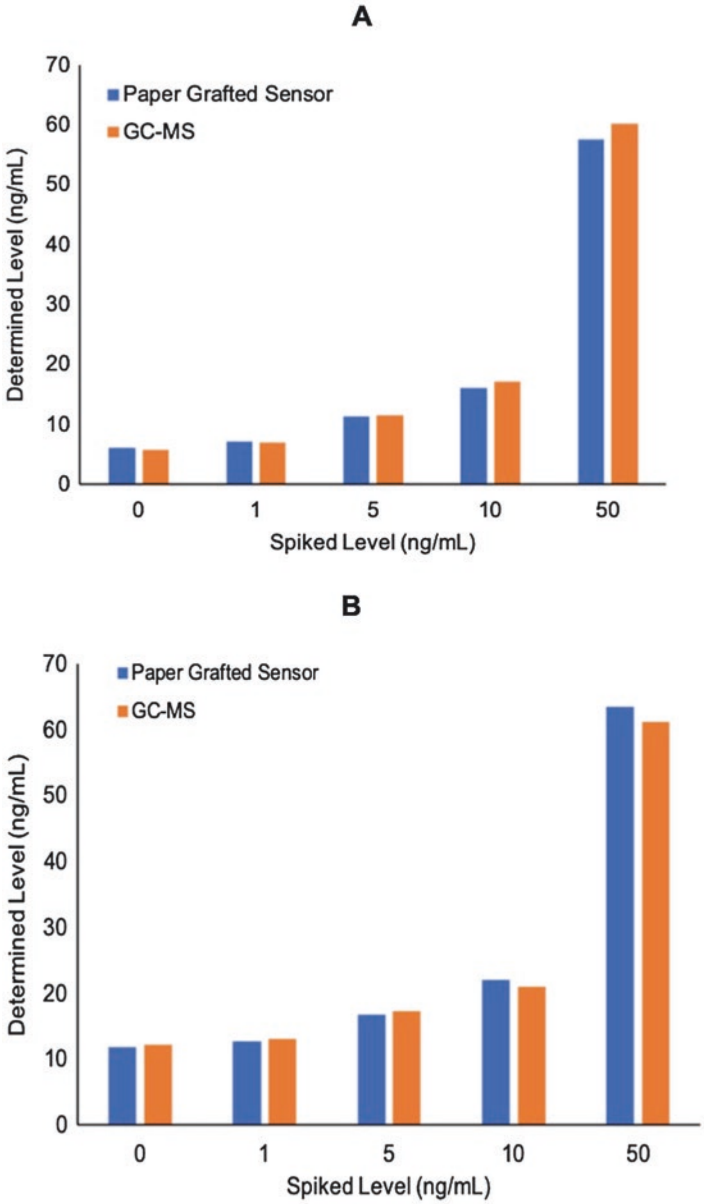

Fig. 8.2 A comparison of paper-grafted sensor and GC–MS methods for 3-MCPD determination in soy sauce 1 (A) and 2 (B) (Fang et al. 2019)

Table 8.3 Detection of the OTA levels in spiked corn samples (*n*:3) (Zhang et al. 2018a, b)

Spiked (ng/mL)	Detected (ng/mL)	Recovery (%)	CV (%)
3.00	3.14 ± 0.47	104.67	6.40
10.00	9.64 ± 1.15	96.40	4.80
30.00	29.17 ± 2.73	97.23	5.10

Table 8.4 Detection of AFB1 in peanuts and milk samples (n:3) (Yao et al. 2019)

Samples	Spiked (ng/mL)	Detected (ng/mL)	Total Found (ng/mL)	Recovery (%)
Peanut 1	10	5.76	16.02	102.6
Peanut 2	10	–	9.74	97.4
Milk 1	10	–	9.82	98.2
Milk 2	20	–	20.88	104.4

and milk sample solutions. The recovery of AFB1 in food samples was observed in the range of 97.4–104.4% (Table 8.4).

Zhang et al. (2015) developed fluorescence-labeled single-stranded DNA-functionalized graphene oxide sensors for the detection of different types of chemical contaminants in food. The designed sensor device was analyzed for multiplex detection of Hg^{2+}, Ag^{+}, and aminoglycoside antibiotic residues in food. Different concentrations of each analyte (0.5 mM, 1 mM, and 2 mM) were spiked into food samples. The recovery ratios (%) were found to be from 87.5% to 116% for Hg^{2+}, 91% to 126% for Ag^{+}, and 95% to 101% for neomycin detection.

Sulfonamides are the synthetic bacteriostatic antibiotics commonly used in many European countries (Şanli et al. 2010). The maximum residue limits (MRL) of antibiotics in foods have been established by the European Union AS (100 μg/L). Adrian et al. (Adrian et al. 2009) prepared an immunosensor for the sensitive detection of sulfonamide antibiotics in milk. The limit of detection (LOD) of sulfonamide with the immunosensor in buffer and in milk was found as 0.2 ± 0.1 and 0.5 ± 0.1 μg/L, respectively. The analysis time for all the experiments was less than 30 min. As a result, the experimental results showed that prepared immunosensors could be succesfully applied for sensitive and easy detection of sulfonamide antibiotics in milk.

Bisphenol A (BPA) is a widely used hormone disrupter. BPA is harmful to human health. BPA is usually found in food and beverage packages (Üzek et al. 2019; Shaikh et al. 2015). Xu et al. (2016) prepared the molecular imprinted nanocomposite and graphene sheets with high conductivity for the detection of bisphenol A. In this study, the chemical functionality and the two-dimensional structure of the graphene increased the sensitivity of the electrochemical sensor. The linear range of BPA was calculated as 3.21×10^{-10} to 2.8×10^{-1} g/L (*R*: 0.995). The limit of detection (LOD) was found to be 9.63×10^{-11} g/L.

Melamine is a cyanamide triazine with an organic-based property and is an important contaminant in food products (Dursun et al. 2016). Rovina and co-workers (Rovina and Siddiquee 2016) developed a fast, novel, simple, and effective electrochemical method for the analysis of melamine in milk products and infant milk. The modified gold electrode was characterized with cyclic voltammetry and differential pulse voltammetry for detection of melamine. Under optimal experimental conditions (pH 7.0 and 0.3 V), the prepared electrochemical sensor indicated an optimal response time, that is, 30 s. The linear range of melamine concentrations was from 9.6×10^{-4} to 9.6×10^{-13} M, and the limit of detection was calculated as 9.6×10^{-14} M.

Optical Sensors

Optical sensors have two basic methods to obtain sensor data from target molecules, which are label-based and label-free methods. Optical devices use special transducers like surface plasmon resonance (SPR), interferometers, gratings, and refractometers. This diversity causes plenty of different constructed optical devices. Optical biosensors are divided into several subclasses such as resonance, dispersion, reflection, refraction, phosphorescence, infrared absorption, Raman scattering, fluorescence, and chemiluminescence. Surface plasmon resonance (SPR)- and quartz crystal microbalance (QCM)-based optical sensors are widely used because of their high sensitivity (Jalilzadeh et al. 2019; Kartal et al. 2019).

Surface plasmon resonance (SPR)-based sensors offer the advantage of rapid, label-free simultaneous monitoring of binding events due to refractive index changes near the sensor surface (Jalilzadeh et al. 2019). SPR sensors can characterize the binding of target molecules to be determined on a sensor chip surface coated with a metal film (gold, 50 nm) directly without any labeling. With SPR sensors, it is possible to study the interactions of biological molecules such as proteins, oligonucleotides, and lipids, from macromolecules to small particles such as phages, viral particles, and cells.

Pesticides applied to a broad range of composition, such as insecticides, herbicides, and fungicides. Use of pesticides is hazardous to humans and environment due to their nonspecific toxicological effects. Saylan et al. reported surface plasmon resonance (SPR) sensors for fast, selective, sensitive, and real-time detection of pesticides, including the most well-known triazine pesticides, atrazine (ATZ), cyanazine (SNZ), and simazine (SMZ). The biomimetic nanofilms on the SPR gold surfaces are prepared, which consist of *N*-methacryloyl-L-phenylalanine methyl ester (MAPA) as a functional monomer, 1-vinyl imidazole (VIM) as a comonomer, and ethylene glycol dimethacrylate (EGDMA) as a crosslinker. The real-time analysis on SPR sensor was performed with a linearity range from 0.10 to 6.64 nM pesticide (Saylan et al. 2017).

Oh et al. (2017) investigated a portable plasmonic biosensor that led to high sensitive and selective detection of *Salmonella typhimurium* in pork meat samples. Under experimental conditions, the limit of detection (LOD) was calculated as 10^4 CFU/mL for *S. typhimurium* in pure culture. All analysis time during the experiments was 30–35 min. The limit of detection of *S. typhimurium* in the spiked pork meat samples was found to be 1.0×10^4 CFU/mL.

Ochratoxin A (OTA) is harmful to human and exists usually in plant origin food. An anti-OTA aptamer immobilized sensor chip was prepared to measure ochratoxin

A (OTA). Zhu and co-worker immobilized the streptavidin as a crosslinker onto the sensor chip. The biotin-aptamer was captured through streptavidin–biotin interaction. A linear range of OTA detection from 0.094 to 100 ng/mL was shown with a lower detection limit of 0.005 ng/mL. The detection of OTA was performed in the surface plasmon resonance (SPR) biosensor using simple liquid–liquid extraction for sample pretreatments in wine and peanut oil. Ochratoxin A recovery from spiked samples were found from 86.9% to 116.5% and coefficients of variation (CVs) were from 0.2% to 6.9%. The designed SPR biosensor method showed good reproducibility, stability, and performances with limits of detection much lower than the maximum residue limit.

Antibiotics such as benzyl-penicillin (PenG) and cephalosporin, amoxicillin are used usually in animal therapy. Maximum residue limits (MRLs) have established to prevent the negative impact of β-lactam and PenG residues present in the milk on human health. Pennacchioet and co-worker proposed an effective alternative to quantify the penicillin G using surface plasmon resonance (SPR) method. The produced antibodies were used as molecular recognition elements for the detection of PenG by SPR experiments. The detection limit was found as 8.0 pM. The results showed that the prepared SPR results could be successfully applied for the accurate and easy detection of PenG (Pennacchio et al. 2015).

Ciprofloxacin (CPX) is the most commonly used synthetic antibiotics. Sari et al. (2018) prepared SPR nanosensor for detection of ciprofloxacin. In this study, ciprofloxacin-imprinted nanoparticles (MIP/NPs) were prepared for sensitive and selective detection of ciprofloxacin and characterized with Fourier transform infrared (FTIR) spectroscopy, zetasizer, and contact angle measurements. The limit of detection (LOD) was found to be 3.21 and 7.1 ppb in ultrapure water and synthetic wastewater (SWW) for detection of CPX, respectively. The selectivity studies were used as competitor agents: tetracycline and enrofloxacin.

Erythromycin produced by *Saccharopolyspora erythreas* during the fermentation process is a macrolide antibiotic. Sari et al. (2016) developed novel surface plasmon resonance (SPR) nanosensor for detection of erythromycin (ERY). First, erythromycin-imprinted nanoparticles were synthesized and characterized by Fourier transform infrared (FTIR) spectroscopy, zetasizer, and scanning electron microscope (SEM). After, the erythromycin-imprinted nanoparticles were immobilized onto the SPR chip surface for detection of erythromycin. The limit of detection was calculated as 0.29 ppm. The stability of erythromycin-imprinted SPR chip was checked by using of equilibration-binding regeneration for several times.

Staphylococcal enterotoxin B (SEB) is an extracellular toxin produced by *Staphylococcus aureus*, causing food poisoning. Dudak and Boyaci developed a label-free SPR sensor using peptide ligands as recognition molecules. A 24-mer peptide was used for the detection of SEB and immobilized onto the gold-coated surface. Limit of detection was found as 20 μg/mL. The sensor was tested with milk samples spiked with toxin and the signal from this sample was observed to be higher than toxin in buffer (Dudak and Boyaci 2014).

Mass-sensitive sensor devices work based on measuring the changes of properties of piezoelectric or magnetoelastic material via increased mass of biomolecules onto the sensor surface. Mass is a common property of all ions, small molecules, proteins, viruses, cells, etc. These sensors are applicable to all target biological structures without exception. Mass-sensitive sensors can work at both liquid and gas phases. Mass-sensitive devices can use quartz crystal microbalance, microcantilever, or magnetoelastic sensors. Quartz crystal microbalance (QCM) sensors produce signal with the changes in the resonance frequency of piezoelectric crystal upon interaction with analyte and have been used for the detection of food contamination in the last 5 years. However, the application of mass-based sensors for the food contamination detection is less than the electrochemical and optical sensors (Li et al. 2010; Raiteri et al. 2001).

Tobramycin is an aminoglycoside (AG) antibiotic that has ototoxicity and nephrotoxicity effects when used in a high amount. Yola et al. (2014) investigated quartz crystal microbalance (QCM) nanosensor for the detection of tobramycin (TOB). First, tobramycin-imprinted and nonimprinted poly(2-hydroxyethyl methacrylate-methacryloylamidoglutamic acid) films onto the QCM nanosensor surface were synthesized and characterized by using spectroscopy, atomic force microscopy (AFM), Fourier transform infrared (FTIR), and ellipsometry. The linear range of tobramycin concentrations was from 1.7×10^{-11} to 1.5×10^{-10} M. The limit of detection was calculated as 5.7×10^{-12} M. The prepared nanosensors were applied to chicken egg white and milk extract for the determination of TOB. The recovery of TOB in milk and egg samples is between 98.22% and 102.43%.

Formaldehyde is a pungent gas and is considered to be one of the main toxic closed pollutants; it is broadly used as an additive for preventing food spoilage, enhancing the flavor, and brightening the color. Hussain et al. reported the detection of formaldehyde vapors in air streams. QCM sensor coated with a copolymer thin film consisting of styrene, methacrylic acid, and ethylene glycol dimethacrylate provided a detection limit of 500 ppb formaldehyde in dry air (Hussain et al. 2016).

Bisphenol A (BPA), which is broadly employed in diverse consumables and crops, has been generally used as a monomer in fabricating polycarbonate epoxy resins and plastics. It is claimed that it can be leached from plastic products such as food packaging materials and acts as an endocrine disrupting chemical. In this study, Matsumoto et al. prepared bisphenol A (BPA)-imprinted polypeptide gel layers based on cyclodextrin-modified poly(L-lysine) (CD-PLL) on QCM sensor chips (Matsumoto et al. 2016).

8.3 Conclusions and Future Perspectives

Over the past several decades, significant effort has been invested with the aim of developing sensing technologies that will impact the practice of food research. Combination of several new techniques, derived from physical chemistry, molecular biology, biochemistry, thick and thin film physics, materials science, and electronics with the necessary expertise has revealed the promise for development of viable food useful sensor. The use of sensor systems in food technology is presented especially for standardization of raw materials, process development, and detection of batch-to-batch variations and quality control of the final product. Device stability in an industrial environment and the know-how of industrial actors will be a key issue here. However, still a lot of research efforts are needed. Continued development is warranted because the sensors have advantages over more complex analytical techniques such as mass spectrometry and optical techniques. The integration of all analytical processes, from sample collection to analyte detection, on the same device, lab-on-a-chip system, can be sought. Sensor platform able to perform sample collection and analysis on the same device could be designed. These techniques include time-consuming procedures, expensive instruments, and hazardous labels. The development of rapid, easy to use, and cost-effective food contamination detection methods based on different sensor systems has been reported. Sensors are a highly sensitive technique and therefore very convenient for use in food contamination detection. The improvement of new sensors is a growing area and improvement provided in the field of sensitivity (low LOD), speed (fast detection), and easy use (portable devices).

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Chapter 9
Nanotechnology-Based Detection and Remediation of Mycotoxins for Food and Agriculture Applications

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Abstract Mycotoxins are highly toxic secondary metabolites produced by fungi, which may contaminate a large variety of food and feed commodities. Among them, the aflatoxins, deoxynivalenol, zearalenone, fumonisins, and ochratoxins are the most common contaminants posing a serious threat to human and animal health. Given that traditional mycotoxin detection methods have been shown to be laborious and time consuming, interest in developing reliable and rapid mycotoxin detection methods has increased during recent decades. Herein, we review emerging nanotechnology-based methods, including gold nanoparticles, magnetic nanoparticles, and quantum dot-based sensors, which have been developed to reliably and efficiently detecting mycotoxins in food and feed commodities. We also summarize recent technologies used to remove mycotoxins via adsorption and photocatalytic degradation. As our review illustrates, the emerging use of nanotechnology offers a reliable and cost-effective means to prevent mycotoxin contamination in food and feed commodities, which could reduce health risks to consumers.

Keywords Mycotoxins · Food contamination · Nanotechnology · Nanosensors · Gold nanoparticles · Quantum dots · Magnetic nanoparticles · Photocatalytic degradation

9.1 Introduction

Mycotoxins are highly toxic secondary metabolites produced by fungi. They can invade a wide variety of agricultural crops while still on the field or afterwards during their processing in food and feed production chains. The presence of mycotoxins in agricultural commodities is high, with an estimated 25% of the world's crops being contaminated by molds or fungi, especially toxigenic species that belong to the genera Penicillium, Aspergillus, and Fusarium (Alshannaq and Yu 2017). At present, about 175 different mycotoxins have been identified in the food and feed commodities grown in outdoor and indoor environments (Bhat et al. 2010). Given their prevalence, mycotoxins have become a health hazard to both humans and animals worldwide (Fig. 9.1).

Based on possible dietary exposures together with their toxicity, aflatoxins (AFs), citrinin, patulin, ochratoxins A (OTA), zearalenone (ZEA), fumonisins, and trichothecenes are of a high concern due to their known health effects (Santos Pereira et al. 2019; Smith et al. 2016). Typical structures, source of contamination, food products contamination, health effects on mammalian system, and country-wise maximum tolerable levels of a wide range of mycotoxins are represented in Table 9.1. Risk assessments of mycotoxins in food are governed by the Joint Expert Committee of the Food and Agriculture Organization (JECFA) of the United Nations (FAO) and World Health Organization (WHO). The international standards are established by the Codex Alimentarius Commission, which lists maximum levels for various mycotoxins in foods (Jukes 2000; Organization 1999).

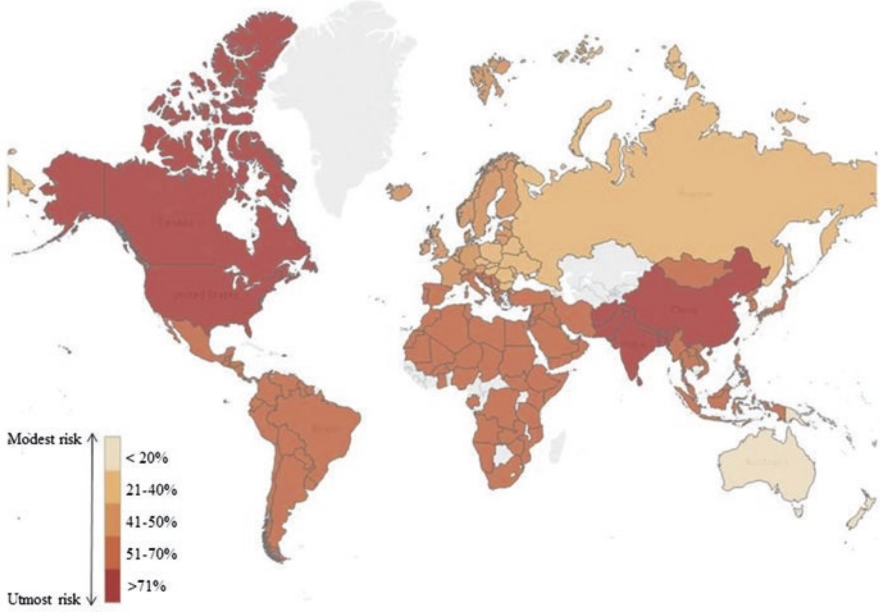
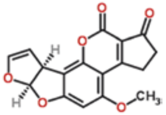
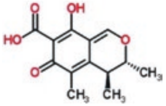
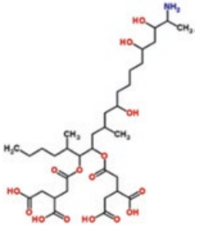


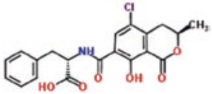
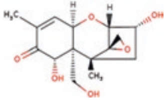
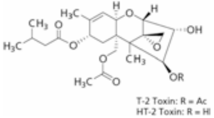
Fig. 9.1 Estimated worldwide health risk caused by mycotoxins during 2018. Data source: World Nutrition Forum/Database (BIOMIN, 2019)

The traditional methods of mycotoxin analysis involve more complex sample preparation and longer detection times combined with the usage of highly sophisticated analytical instruments (Vidal et al. 2013; Zhang et al. 2018a). Nanotechnology has gone through a booming development since 1981. The usage of nanoparticles in sensing applications are accurate with high precision resulting in signal amplification due to their unique characteristics, such as high surface to volume ratio (Tothill 2011). Further the integration of nanomaterials not only enhances the sensitivity in detection of toxins, but they are highly selective, cost effective, and portable and a rapid response can be obtained (Malhotra et al. 2014). A wide-range of nanomaterials comprising gold nanoparticles, silver nanoparticles, quantum dots (QDs), magnetic nanoparticles, graphene oxide, carbon nanohorns, carbon nanotubes (CNTs), and TiO_2 nanoparticles, have been used for the detection of different kinds of mycotoxins.

Till date many reviews have been published in sensing and detection of mycotoxins using nanotechnology (Goud et al. 2018; Horky et al. 2018; Ingle et al. 2020; Zeng et al. 2016). This is a comprehensive review including the various sensing applications with some of extensively used nanoparticles, such as gold, QDs, and magnetic nanoparticles. Here, we review advances from the last 5 years in the use of nanomaterials for the detection of mycotoxins in food and agriculture. This review also summarizes the recent technologies employed for the removal and the photocatalytic degradation and removal of mycotoxins. A literature search for the years

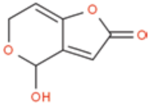
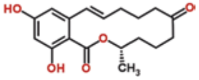
Table 9.1 Mycotoxin sources, occurrence in foods, and health effects

Mycotoxin type/ Typical structure	Source	Food products contaminated	Health effects on mammalian system	Country-wise maximum tolerable levels		Refs.
				Country	Tolerable levels (µg kg^{-1})	
Aflatoxins (B1, B2, M1, M2, G1, and G2) 	*Aspergillus flavus*, *Aspergillus nominus*, *Aspergillus parasiticus*	Maize, oil seeds, nuts, dried fruits, cereals, spices, milk, and milk products including infant food	Carcinogenic, acute hepatitis, impaired immune system	Australia, Canada, Europe	14–15	chuan Li et al. (2011), Wang et al. (2011) and Ye et al. (2010)
				Nigeria, New Zealand		
				South Africa		
				USA, Brazil	20	
				India	30	
Citrinin 	*Aspergillus carneus, Aspergillus niveus, Aspergillus terreus, Penicillium citrinum, Penicillium verrucosum, Penicillium expansum*	Oats, rice, corn, beans, fruits, fruit and vegetable juices, herbs, and spices	Nephrotoxicity, hepatotoxicity, embryotoxicity, cytotoxicity, immunotoxicity, carcinogenicity			(Arévalo et al. (2011) and Flajs and Peraica (2009)
Fumonisins (B1, and B2) 	*Aspergillus alternaria, Fusarium anthophilum, Fusarium dlamini, Fusarium moniliforme, Fusarium naphiformel, Fusarium nygama, Fusarium proliferatum, Fusarium verticillioides*	Maize, rice, sorghum, cereals, green gram	Carcinogenic, nephrotoxic, hepatotoxic, teratogenic	Europe, Turkey, Norway, Switzerland	800–4000	Abdul Kadir and Tothill (2010) and Ghali et al. (2009)
				USA	2000–4000	
				Brazil	2000–5000	

OTA 	*Aspergillus alliaceus, Aspergillus auricomus, Aspergillus carbonarius, Aspergillus glaucus, Aspergillus melleus, Aspergillus niger, Aspergillus ochraceus, Penicillium cyclopium, Penicillium verrucosum, Penicillium viridicatum*	Maize, rice, rye, cereals, dry fruits, coffee, wine, beer, grape, juice, spices, licorice	Mild liver damage, nephrotoxicity, and immune suppression	Brazil	20–30	Heurich et al. (2011), Pfohl-Leszkowicz et al. (2015), Barthelmebs et al. (2011) and Wu et al. (2011)
				China, Kenya	5	
				Europe, Egypt	2–10	
				India	20	
				Nigeria, Russia	5	
				Uruguay	50	
Trichothecenes DON, 3- or 15-Ac-DON, NIV (type B) 	*Fusarium graminearum, Fusarium sporotrichioides, Fusarium poae, Fusarium equiseti*	Cereals, bakery products	Weight loss, diarrhea, vomiting, gastrointestinal hemorrhaging, immune-depressants, dermal necrosis mutagenic, neurotoxic	Europe	500–1750a	Chehri and Godini (2017), Li et al. (2018b) and Maragos (2012)
				Brazil	750–3000a	
				Russia	700–1000	
				Canada, China, India, Japan, USA	1000	
Trichothecenes T-2, HT-2 (type A) 	*F. sporotrichioides*	Corn, wheat, barley, oats, rice, rye	Weight loss, diarrhea, vomiting, gastrointestinal hemorrhaging, immune-depressants, dermal necrosis mutagenic, neurotoxic	Europe	Not permitted	Authority et al. (2017) and Pleadin et al. (2018)
				Russia	50–100a	

(continued)

Table 9.1 (continued)

Mycotoxin type/ Typical structure	Source	Food products contaminated	Health effects on mammalian system	Country-wise maximum tolerable levels		Refs.
				Country	Tolerable levels (μg kg^{-1})	
Patulin 	*Aspergillus clavatus, Aspergillus longivesica, Aspergillus terreus, Penicillium expansum, Penicillium griseofulvum, Byssochlamys sp.*	Apple juice and solid apple products	Genotoxicity, teratogenicity, cancer	Brazil, China, Europe, India, Japan, Kenya, Nigeria, Russia, South Africa, USA	50	Erdoğan et al. (2018) and Zhong et al. (2018)
Zearalenone 	*Fusarium culmorum, Fusarium crookwellense, F. equiseti, F. graminearum, F. sporotrichioides*	Corn, wheat, wheat flour, bread, cereals, noodles, rice, barley, oats, sorghum, walnuts, milk, corn beer, meat, animal feed products	Estrogenic activity (infertility, vulval edema, vaginal prolapse, mammary hypertrophy in females, feminization of males	Europe	75–400a	Panini et al. (2010)
				Brazil	200–1000a	
				China, Russia, Chile	200,000	

from 2014 to 2019 was conducted in the PubMed (https://www.ncbi.nlm.nih.gov) and Scopus (https://www.scopus.com) databases using the keywords "nanoparticles, mycotoxin detection." Additionally, three categories of nanomaterials were searched specifically: "gold nanoparticles," "magnetic nanoparticles," and "quantum dots."

9.2 Nano-sensors for the Detection of Mycotoxins

At present, there is an increasing attention on nanotechnology since it has generated novel advantages across the range of areas comprising the food industry. Accordingly, nanotechnology has revealed new tasks for novelty in food production at a quick rate. Quality and safety of foods are a key component of public health, and with growing public awareness, customers are now demanding foodstuffs that are devoid of any contaminants (Hamad et al. 2018; Pal 2017; Pathakoti et al. 2019; Pradhan et al. 2015).

Due to their staggeringly small size, nanomaterials show specific physical and chemical features. Nanosensors are described as any chemical, biological, or surgical sensory point utilized to expose the nanoparticles to the microscopic world (Yu et al. 2018). Nanosensors utilize several nanomaterials that can identify toxins in sustenance at precise low levels, in the midst of handling or processing of foods (Sonawane et al. 2014; Willner and Vikesland 2018). Thus, in nanosensors, nanomaterials are employed in an analytical device, which is an improved version of a chemical sensor or biosensor. A biosensor works on two basic principles, biological recognition, and sensing. In general, nanosensors or nanobiosensors enhance at the activity by the integration of nanostructures in the sensing component for enhanced output. The basic structure of nanosensor and working principal is schematically shown in Fig. 9.2. These nanostructures enhance the activity both at bioreceptor level and the transducer level. Moreover, the transducer aids in fabrications of sensor with the use of various nanoparticles, such as metal oxide nanoparticles, quantum dots, magnetic nanoparticles, and carbon nanoparticles. Due to their staggeringly small size, nanomaterials show specific physical and chemical features, such as superior optical, electrical, thermal properties, and high surface area, which improves the transducing capability to a large extent. Based on signal production, that is, based on transducer type, nanosensors can be three major types: (1) optical: as optical (colorimetry, fluorescence, luminescence, surface-enhanced Raman scattering (SERS), surface plasmon resonance (SPR) and others), (2) electrochemical (amperometry, conductimetry, potentiometry, and voltammetry), and (3) Piezoelectric (quartz crystal microbalance).

9.2.1 Gold Nanoparticles for the Detection of Mycotoxins

A variety of biochemical and electrochemical assays based on Au nanoparticles have been described for the detection of mycotoxins. The most important and advantageous properties of gold nanoparticles for their usage in designing the

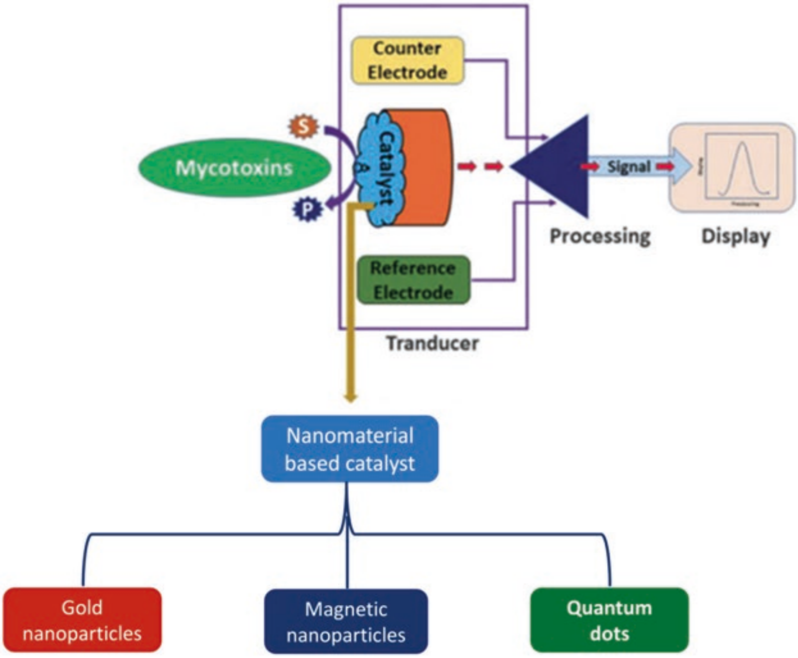


Fig. 9.2 Schematic representation of nanosensor and its working. modified from Goud et al. (2018), Copyright (2018) Elsevier

sensors to detect toxins include localized surface plasmon resonance (SPR) bands and enhanced scattering properties (Lara and Perez-Potti 2018). SPR imaging (SPRi) is an evolving label free semi-quantitative method for the sensitive detection of mycotoxins, which is highly reliable (Joshi 2017). Hossain and Maragos Hossain and Maragos (2018) described a gold nanoparticle based SPRi for the detection of Fusarium toxins such as DON, ZEA, and T-2 in wheat samples. This biosensor was amplified more than 12–90-fold with use of secondary antibody Ab2 with Au nanoparticles. Further, these antigen coated biochips are highly durable with short analysis time, are cost effective, and can be used for at least 46 cycles. In another study, Kong et al. (2016) have developed an Au nanoparticle-based immunochromatographic strip system for the detection of 20 different types of mycotoxins including ZEAs, DONs, T-2 toxins, AFs, and fumonisins (Fig. 9.3).

Similarly, AFs including B1, B2, M1, G1, and G2 in sustenance were identified depending upon a lateral flow strip (Santos et al. 2017). A monoclonal antibody (mB6 mAb), which has high specificity to AFs, was created to develop an immunochromatographic strip test, where the gold nanoparticles were coated with this antibody for detection. This strip consists of a control and test line, where the control line is coated with goat antimouse IgG and the test line containing AFB1 bovine serum albumin. In the strip, red gold nanoparticles form 1–2 pigmented lines on the

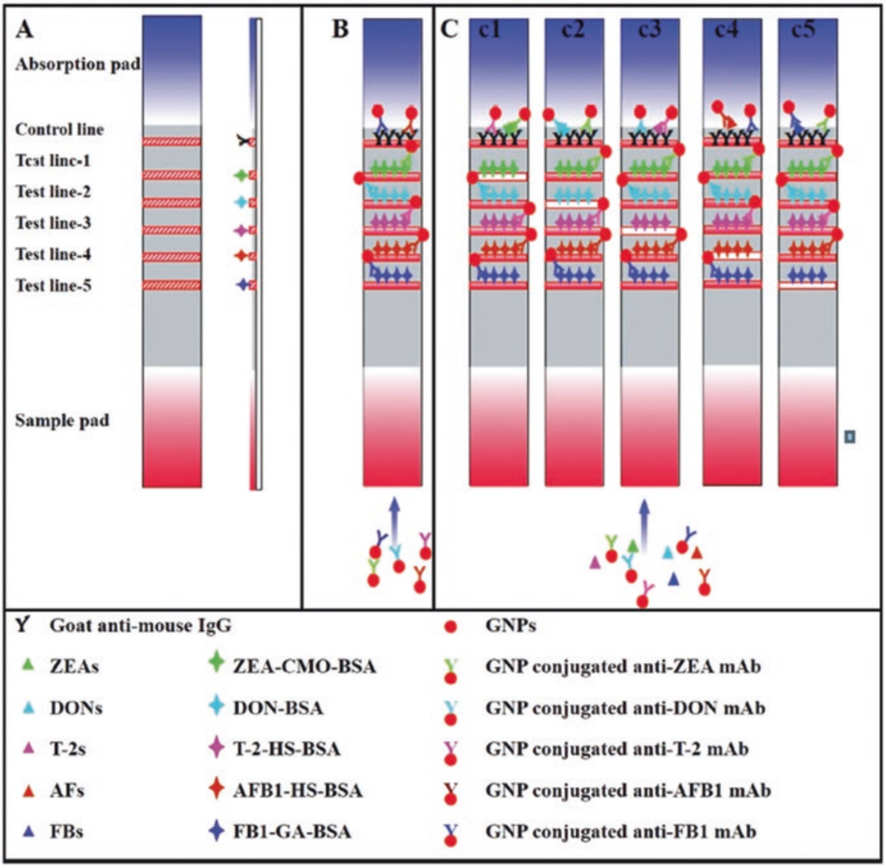


Fig. 9.3 (A) Immunochromatographic strip structure (B) Negative sample (C) Positive sample; c1: ZEAs; c2: DONs; c3: T-2s Toxin; c4: Aflatoxins; c5: Fumonisin B. Copyright (2016) Elsevier, (Kong et al. 2016)

membrane and the nanoparticles coated with anti-AFB1 as the signaling reagent for basic identification of AFB1.

A surface-enhanced Raman scattering (SERS) aptamer-based sensor was developed by using the gold@gold-silver nanostructures for the selective detection of OTA (Fig. 9.4). Magnetic nanoparticles (Fe_3O_4) were used for separation of toxin from solution, which is reusable. After magnetic separation, Raman signals were collected and this SERS probe can be used for the real time detection of OTA (Shao et al. 2018). Table 9.2 represents a wide range of methodology for sensor development using gold nanomaterials for the detection of different types of mycotoxins.

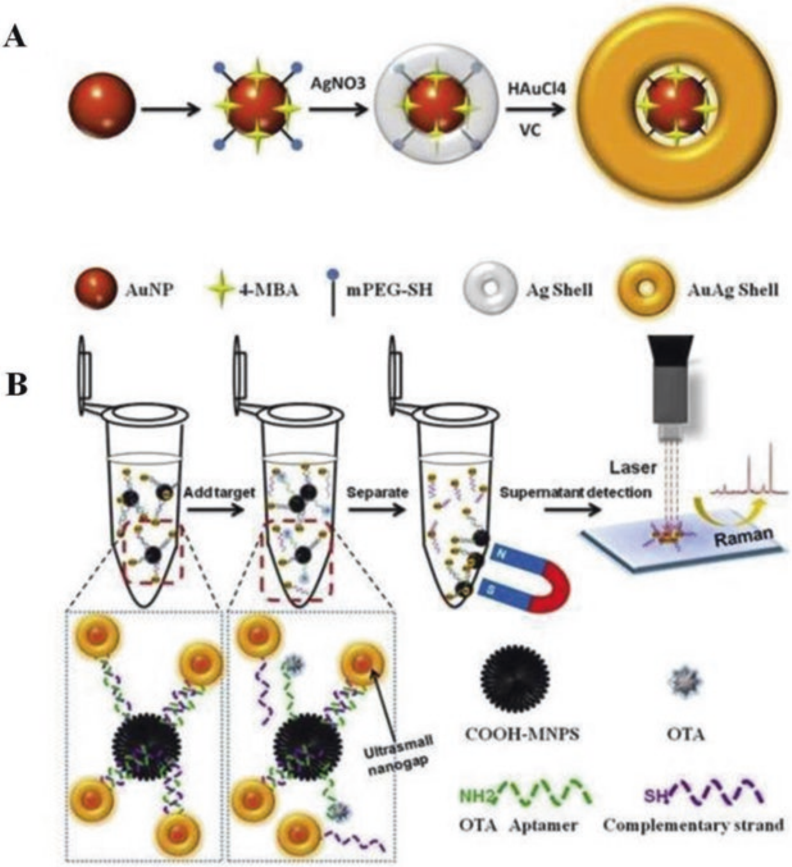


Fig. 9.4 Synthesis of Au@AuAg NNSs (A). Schematic illustration of SERS aptsensor-based on Au@AuAg NNSs-magnetic nanoparticles for OTA detection. Copyright (2018) Elsevier (Shao et al. 2018)

9.2.2 *Magnetic Nanoparticles for the Detection of Mycotoxins*

Superparamagnetism is one of the most important properties of magnetic nanoparticles. The superparamagnetic nanoparticles can be easily dispersed in aqueous solution, remain stable when coated with an appropriate layer, and are able to form ferrofluid. Wide ranges of applications of superparamagnetic nanoparticles are reported. Various methods of detection of mycotoxins by employing magnetic nanoparticles as sensors are represented in Table 9.3. A study by Gan et al. (2013) described the electrochemiluminescent immunoassay for the detection of mycotoxin, aflatoxin-M1 in milk samples. In their study, magnetic nanocomposites were prepared initially by immobilization of Fe_3O_4 nanoparticles onto graphene oxide, which is used as an adsorbent. Later on, aflatoxin-M1 antibody was attached to

Table 9.2 Detection of mycotoxins by using gold nanoparticles as sensors

Mycotoxin	Electrode/sensor	LOD or recovery (%)	Sample or matrix	Refs.
Patulin	Molecular imprinted polymer-SERS technique	96–108%	Fruit samples	Wu et al. (2019)
Ochratoxin A	AuNP@Cu-Co Purssian blue analogue-based electrochemical conductivity assay	5.2 fg mL^{-1}	Spiked watermelon juice	Gu et al. (2019)
Patulin	AuNP-Black phosphorus nanosheets-electrochemical aptasensing	0.03 nM	Apple juice samples	Xu et al. (2019)
Fuminosin B1 and DON	Indium Tin oxide@ Polydimethylsiloxane electrodes functionalized with Au nanoparticles and anti-FB1 and anti-DON antibodies	0.3–140 ppb 0.2–60 ppb	Ground corn extract	Lu and Gunasekaran (2019)
ZEA	Calorimetric assay: use of an aptamer and Au nanoparticles with peroxidase like activity	10 ng mL	Corn and corn oil	Sun et al. (2018)
AFB1	Optical waveguide light mode spectroscopy (OWLS): signal enhancement by increasing the sensor surface through immobilization of Au nanoparticles on OWLS immunosensor chip	0.01–10 ng mL^{-1}	Hungarian paprika samples	Adányi et al. (2018)
Fuminosin B1 and B2	Fluorescence quenching immunoassay based on Au nanoparticles and a recombinant epitope-mimicking fusion protein	1.1 ng mL^{-1}	Wheat samples	Peltomaa et al. (2018)
Fuminosin B1, B2, and B3	Indirect competitive enzyme-linked immunosorbent assay: Au nanoparticles–mercaptoundecanoic acid@ horseradish peroxidase—goat anti-mouse IgA	0.078μg mL^{-1}	Maize	Li et al. (2018c)
AFB$_1$	L-arginine- 6-aza-2-thiothymine—Au nanocluster-based photoluminescence enzyme immunoassay	3.2 pg mL^{-1}	Peanut	Wang et al. (2018)
OTA	Detection based on signal amplification by Exonuclease III (Exo III) and fluorescence quenching by Au nanoparticles	4.82 nM	Spiked red wine	Zhao et al. (2018)
Fuminosins	Lateral flow immunoassay: CdSe/ZnS QD-BSA-FMB1@AuNP-Ab	1 ng mL^{-1}	Maize flour samples	Anfossi et al. (2018)
DON; ZEA; T2/HT2-toxin	Multiplex lateral flow immunoassay: monoclonal antibodies (mAb) conjugated with CdSeS/ZnS QDs or colloidal Au nanoparticles	80–1000μg kg^{-1}	Wheat samples	Foubert et al. (2017)

(continued)

Table 9.2 (continued)

Mycotoxin	Electrode/sensor	LOD or recovery (%)	Sample or matrix	Refs.
AFB1	Label-free electrochemical	8 pg mL^{-1}	Corn flakes	Chauhan et al. (2016)
	Quartz crystal microbalance			
	Based immunoassay: α-AFB1/cysteamine/Au nanoparticles/hexanedithiol (HDT)/Au immunosensor			
ZEA	Immunochromatographic assay: antibody immobilization on ablative Au nanoparticles	0.1 ng mL^{-1}	Standard ZEA	Urusov et al. (2015)
OTA	Label-free aptamer-based assay: cationic polymer poly diallyldimethylammonium chloride@Au nanoparticles	0.009 ng mL^{-1}	Liquor samples with OTA	Luan et al. (2015a)
OTA	SERS labels embedded Ag@Au core–shell nanoparticles	0.006 ng mL^{-1}	Spiked mycotoxins on negative maize meal	Zhao et al. (2015)
AFB1		0.03 ng mL^{-1}		
DON	Electrochemiluminescence electrodes based on nanoporous Cobalt/Co_3O_4 – Au/RuSi@Ru(bpy)$_3^{2+}$	1 pg mL^{-1}	Wheat flour	Lv et al. (2015)
AFB1	AFB1-BSA conjugate modified magnetic beads were employed as capture probe and *anti*-AFB1 antibody-coated gold colloids were used as detection probe for the immunological recognition	7 pg mL^{-1}	AFB1 standard solutions	Wang et al. (2016b)
AFB1	SERS-based immunoassay using silica-encapsulated hollow Au nanoparticles and magnetic beads	0.1 ng mL^{-1}	AFB1 standard solutions	Ko et al. (2015)
DON	The electrochemical impedance spectroscopy of tris(bipyridine) ruthenium (II) chloride was used as a marker enhanced with Au nanoparticles-dotted 4-nitrophenylazo functionalized graphene nanocatalyst mediated in Nafion on a glassy carbon electrode	0.3μg mL^{-1}	Certified corn, wheat, and roasted coffee	Sunday et al. (2015)
AFB1	Label-free aptasensor using un-modified Au nanoparticles	0.025 ng mL^{-1}	AFB1 standard solutions	Luan et al. (2015b)
AFB2	NaCl-induced aggregation of aptamer-modified Au nanoparticles	25 pg mL^{-1}	AFB2 standard solutions	Luan et al. (2015a)

(continued)

Table 9.2 (continued)

Mycotoxin	Electrode/sensor	LOD or recovery (%)	Sample or matrix	Refs.
OTA	Immunochromatographic assay: OTA monoclonal antibody conjugated Au nanoparticles	0.25 ng mL^{-1}	Maize, wheat, soybean, and rice	Majdinasab et al. (2015)
AFB1	SPRi: antibody-conjugated Au nanoparticles on poly[oligo(ethylene glycol) methacrylate-co-glycidyl methacrylate]@modified SPRi chip	8 pg mL^{-1}	Spiked peanut samples	Hu et al. (2014)
OTA		30 pg mL^{-1}		
ZEA		15 pg mL^{-1}		
Fumonisin B1	Electrochemiluminescence aptosensor: Au NP–Iridium complex as nanoprobe	0.27 ng mL^{-1}	Spiked wheat flour	Zhao et al. (2014)

*LOD: Limit of detection

cadmium telluride quantum dots, which can be used as a signal tag. Finally, magnetic nanocomposites were used for the separation of aflatoxin-M1 from milk samples and detected using an immunoassay using an electrochemiluminescent signal. Further, this immunosensor is stable and can be regenerated after storing for two weeks at 4°C and its accuracy was about 95%.

9.2.3 *Quantum Dots for the Detection of Mycotoxins*

Physicochemical properties including enhanced fluorescence, narrow emission peaks, and high photostability of QDs are advantageous in developing the sensors for highly sensitive detection of mycotoxins. Some of the recent applications of quantum dots for mycotoxin detection are presented in Table 9.4. Fang et al. (2014) developed a novel molecularly imprinted optosensing material for selective detection of mycotoxin, ZON in cereal samples. The molecular imprinted polymer is based on ionic liquid stabilized cadmium selenium/ZnS QDs and the mechanism is based on fluorescence quenching.

A highly sensitive aptasensor for the detection of ochratoxin was developed with a combination of nanocomposites consisting of gold nanoparticles functionalized with silica coated Fe_3O_4 magnetic nanoparticles and CdTe QDs modified with graphene/gold nanoparticles. This novel aptasensor is ultrasensitive with detection limit at sub-picomolar level (Hao et al. 2016).

Zhang et al. (2017a) developed an optical sensor based on molecular imprinted polymer capped Mn-doped ZnS QD for detection of the mycotoxin, patulin, from apple juice. This nanosensor is based on a phosphorescence method, for determination of patulin from aqueous solutions, including the intended matrix, apple juice. Recently, Duan et al. (2019) developed multicolor CdSe/ZnS QD nanobeads with yellow, orange, and red luminescence for concurrent recognition of numerous

Table 9.3 Detection of mycotoxins by using magnetic nanoparticles as sensors

Mycotoxin	Electrode/sensor	LOD or recovery (%)	Sample or matrix	Refs.
OTA	SERS: Au@AuAg-magnetic nanoparticle	0.004 ng mL^{-1}	Red-wine samples	Shao et al. (2018)
ZEA	Aptamer-functionalized MNP @ fluorescence NaYF4: Ce/Tb nanoparticles	0.21 pg mL^{-1}	Maize and wheat	Niazi et al. (2018)
AFB1	Magnetic nanoparticle-filled amino-modified multi-walled carbon nanotubes (Fe_3O_4-MWCNTs-NH_2)	0.15 and 0.24 ng g^{-1}	Wheat flour samples	Li et al. (2018a)
ZEA				
Fumonisin B1	Magnetic reduced graphene oxide/nickel/platinum nanoparticles	0.70 ng mL^{-1}	Beer and wine	Molinero-Fernández et al. (2018)
ZEA; α-Zearalanol	Core–shell polydopamine coated magnetic nanoparticle	0.55–11.8μg L^{-1}	Cow, goat, sheep, and human milk	Socas-Rodríguez et al. (2018)
α-Zearalenol;				
β-Zearalanol				
β-Zearalenol;				
β-Zearalanol-10,10,11,12,12-d5				
AFB1	SERS based aptasensor: the amino-terminal aptamer conjugated magnetic-bead and the gold nanotriangles-DTNB@Ag-DTNB nanotriangles	0.54 pg mL^{-1}	Peanut oil samples	Yang et al. (2017)
AFB1	Magnetic microspheres encoded with fluorescent nanocrystals	9 pg mL^{-1}	Spiked corn samples	Zhang et al. (2017b)
ZEA,	Core–shell poly(dopamine) magnetic nanoparticles	0.2–4.8μg L^{-1}	Milk Yogurt	González-Sálamo et al. (2017)
α-zearalanol,				
β-zearalanol,				
α-zearalenol,				
β-zearalenol zearalanone				
OTA	Fluorescence resonance energy transfer: quantum dot-labeled antibody to rhodamine-coated magnetic silica nanoparticles	0.8 pg mL^{-1}	Spiked human serum	Mahdi et al. (2016)
ZEA	Magnetic nanoparticles and chemiluminescent detection	0.04 ng mL^{-1}	Wheat	Hendrickson et al. (2016)
OTA	Chemiluminescence immunoassay: magnetic nanoparticles with targeted inhibition	1.39 pg mL^{-1}	Rice	Kim and Lim (2015)

(continued)

Table 9.3 (continued)

Mycotoxin	Electrode/sensor	LOD or recovery (%)	Sample or matrix	Refs.
AFB1	FRET-based fluorescence immunoassay: magnetic/silica core–shell as a signal intensifier	2×10^{-12} M	Spiked human serum	Kalarestaghi et al. (2015)
AFB1	Immunoenzyme assay: antibody immobilization on the surface of magnetic nanoparticles	20 pg mL^{-1}	Barley and maize extracts	Urusov et al. (2014)

mycotoxins such as ZEA, OTA, and fumonisin B1 from a corn matrix (Fig. 9.5). This is a qualitative method based on an immunochromatographic assay for visual detection of mycotoxins, which can be inferred with the naked eye under UV light with color differentiation.

9.2.4 *Miscellaneous Nanomaterials Employed in Developing Sensors for the Detection of Mycotoxins*

Zinc oxide nanoparticles are recognized for applications in immunosensing, due to their distinct characteristics, such as a high isoelectric point and higher binding energy and moreover being cost-effective and biocompatible (Ansari et al. 2010). For OTA detection, ZnO nanofilm was immobilized with rabbit immunoglobulin antibodies placed onto glass plate made of Indium tin oxide and bovine serum albumin for blocking nonspecific binding of OTA. This nanozinc immunoelectrode has amplified electrochemical signal and has an application for OTA and other mycotoxins (Ansari et al. 2010).

Similar to ZnO nanoparticles, nanostructured CeO_2 is biocompatible due to its non-toxicity and has attracted interest in development of biosensors. In addition, nano-CeO_2 has high chemical stability and mechanical strength. Kaushik et al. (2009a) described the fabrication of chitosan-nano-CeO_2 nanocomposites film deposited on indium tin oxide-coated glass substrate for the immobilization of r-IgGs and BSA. This immunoelectrode has a large surface, including greater electron transport and potential application for OTA detection and other mycotoxins such as AFB1 and citrining.

Likewise, a study by Kaushik et al. (2009b) reported the detection of OTA by integrating nanosilicon-chitosan nanocomposites film for r-IgGs loading, and this immunoelectrode has enhanced sensing properties. This could be due to the presence of chitosan-nano-SiO_2 composites due to greater surface area and higher electrochemical behavior. Similarly, a chitosan-TiO_2-nanoparticle-based immunosensor was developed for the recognition of OTA from *Aspergillus ochraceus* (Khan and Dhayal 2008). Electrochemical impedance spectroscopy (EIS) was used to determine the electroactivity of the bioactive electrode. This matrix has several advantages in biosensor application. Chitosan is cost-effective and has higher mechanical

Table 9.4 Detection of mycotoxins by using quantum dots

Mycotoxin	Electrode/sensor	LOD	Sample or matrix	Refs.
ZEA	Electrochemiluminescence aptasensor: Nitrogen doped graphene QDs on amine functionalized Ru(bpy)3 2+-doped silica nanoparticles surface	1 fg mL^{-1}	Corn flour	Luo et al. (2019)
Fumonisin B1	Fluorescence Enzyme linked immunoassay: mercaptopropionic acid–modified CdTe QDs	0.33 ng mL^{-1}	Corn	Lu et al. (2018)
DON	Fluorescent-labeled immunosorbent assay: monoclonal antibody+amino functionalized multishell QDs	12.2µg kg^{-1}	Maize	Zhang et al. (2018b)
AFB1	Glycine-enhanced photoluminescence assay: 3-mercaptopropionic acid and thiol-terminated methoxy polyethylene Glycol functionalized QDs	0.17–0.35 ng mL^{-1}	Chinese medicinal herbs	Zhang et al. (2018a)
OTA	Fluorescence resonance energy transfer: cerium oxide nanoparticles and graphene QDs aptosensor	2.5 pg mL^{-1}	Peanuts	Tian et al. (2018)
OTA	Direct competitive fluorescence linked immunosorbent assay: QD beads	0.028 pg mL^{-1}	Corn Coffee Red wine	Xiong et al. (2017)
OTA,	Electrochemical detection: CdTe or Pbs QDs coated on to silica sphere	10 pg mL^{-1}–10 ng mL^{-1}	Maize	Wang et al. (2017)
Fumonisin B1		50 pg mL^{-1}–50 ng mL^{-1}		
AFM1	Frit based immunoassay: red and green fluorescent CdSe/ZnS core/shell QDs immobilized in liposomes	0.02µg kg^{-1}	Spiked and natural milk samples	Jiang et al. (2017)
Pirlimycin		0.5µg kg^{-1}		
ZEA,	Multiplex immunochemical assay: InP/ZnS QDs encapsulated in silica shells	50 and 500µg kg^{-1}	Maize	Beloglazova et al. (2017)
DON			Wheat	
DON, ZEA, & AFB1	Immunoassay: colloidal QDs enrobed into silica shell	6.1 and 5.3 5.4 and 4.1 2.6 and 1.9	Cereals	Beloglazova et al. (2016)
OTA	Fluorescence enzyme linked immunosorbent assay: glucose oxidase-mediated fluorescence quenching of mercaptopropionic acid-capped CdTe QDs	2.2 pg mL^{-1}	Corn	Liang et al. (2016)
ZEA	Fluorescence enzyme linked immunosorbent assay: hydrogen peroxide-sensitive QDs	4.1 pg mL^{-1}	Corn	Zhan et al. (2016)

(continued)

Table 9.4 (continued)

Mycotoxin	Electrode/sensor	LOD	Sample or matrix	Refs.
AFB1	Photoelectrochemical immunoassay: CdTe QDs-modified photosensitive electrode	3.0 pg mL^{-1}	Spiked peanut samples	Lin et al. (2016)
DON	Immunoassay: silica-coated CdSe/CdS/ZnS core–shell QDs	20 ng mL^{-1}	Food and feed	Goftman et al. (2016)
OTA	Electrochemiluminescence assay: RuSi nanoparticles/CdTe QDs	3.0 fg mL^{-1}	Corn and human serum	Wang et al. (2016a)
OTA	Fluorescence immunoassay: hydrogen peroxide-sensitive CdTe QDs	0.05 pg mL^{-1}	Corn	Huang et al. (2016)
			Wheat	
			Rice	
ZEA	Immunochromatography assay: CdSe/ZnS QDs submicro beads	3.6 mg kg^{-1}	Corn	Duan et al. (2015)
DON, ZEA, AFB1, T2-toxin, Fumonisin B1	Fluorescent immunosorbent assay: QD nanolabels	3.2μg kg^{-1}	Cereals	Beloglazova et al. (2014)
		0.6μg kg^{-1}		
		0.2μg kg^{-1}		
		10μg kg^{-1}		
		0.4μg kg^{-1}		
AFB1	Fluorescent quenching assay: graphene oxide-aptamer-CdTe QDs	1.4 nM	Peanut oil	Lu et al. (2015)

*LOD: Limit of detection

strength and permeability. TiO_2 provides the biocompatibility and thereby provides longer life and improved stability to the electrode. This technique of conjugating chitosan with nanoparticles also provided the fastest response (25 s) with the lowest detection limit.

Recently, Goftman et al. (2016) synthesized the silica coated CdSe quantum dots to detect DON by the microemulsion method. Further, to increase the bioapplicability of QD@SIO_2 nanoparticles, they were modified using three diverse functional groups including amino, carboxyl, and epoxy groups and polyethylene glycol fragments. This developed fluorescence-labeled immunosorbent assay was used for rapid detection of mycotoxins, especially DON.

Carbon nanotubes (CNTs) are allotropes of carbon with a cylindrical nanostructure (Saifuddin et al. 2013). Among them, single-walled CNTs (SWCNTs) due to their exceptional characteristics such as greater surface area, high electrical conductivity, and mechanical strength provide a compatible environment to preserve the enzyme activity, thereby enhancing the electrochemical signal amplification (Guo 2013; Singh et al. 2009). Zhang et al. (2016) fabricated an electrochemical immunosensor for detection of AFB1 from corn flour using the SWCNTs and chitosan composites. As SWCNTs are not water soluble, addition of chitosan enhanced the dispersion of SWCNTs. This immunosensor was centered on an indirect competitive assay using the primary antibody anti-AFB_1 and AFB_1-BSA immobilized on glass carbon electrode.

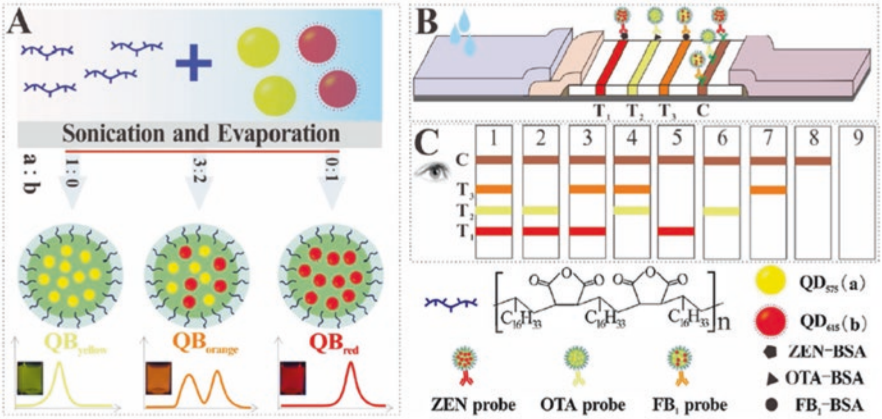


Fig. 9.5 Scheme 1. (**a**) Schematic representation for the synthesis of tricolor QB via using the emulsification evaporation method. (**b**) Schematic illustration of developed tricolor QB-based mICA, in which three T lines of T1, T2, and T3 were designed for the simultaneous detection of ZEN, OTA, and FB1, while one C line was set to indicate the validity of developed mICA, respectively. (C) Schematic presentation for the interpretation of test results. 1, negative; 2, ZEN (−), OTA (−), FB1 (+); 3, ZEN (−), OTA (+), FB1 (−); 4, ZEN (+), OTA (−), FB1 (−); 5, ZEN (−), OTA (+), FB1 (+); 6, ZEN (+), OTA (−), FB1 (+); 7, ZEN (+), OTA (+), FB1 (−); 8, ZEN (+), OTA (+), FB1 (+); 9, invalid. ("+" and "−" indicate the "positive" and "negative," respectively). Copyright from (2019) Elsevier (Duan et al. 2019)

9.3 Remediation of Mycotoxins From Food and Agriculture Using Nanotechnology

9.3.1 Removal of Mycotoxins by Using Adsorption

Traditional enzyme-based decontaminant methods for the removal of mycotoxins from food have several drawbacks, such that the toxin may remain in the food matrix or that it can also result in highly toxic secondary metabolites (Jard et al. 2011; Manubolu et al. 2018). Although nanotechnology has advanced substantially in the detection of mycotoxins, very few studies are available on the elimination or removal of mycotoxins from various food matrices. Among the various immobilization approaches, magnetic nanoparticles are the best solid carriers due to their exclusive high saturation magnetization for facile separation and reusability (Ansari and Husain 2012). Some of the recent applications for removal of mycotoxins from various biological matrices are described in this section (Table 9.5).

Surface active maghemite nanoparticles (SAMNS Fe_2O_3, 11 ± 2 nm) were used for the removal of citrinin in Monascus treated foods, which can be used in the food industry (Magro et al. 2016). The SAMN@citrinin conjugate complex was thoroughly characterized structurally and was magnetically isolated. The offered magnetic separation system was based on the citrinin binding on SAMNS surface and is based on the firm iron chelating keto-enol group on the toxin. In another study, Luo

Table 9.5 Degradation or removal of mycotoxins

Mycotoxin	Nanomaterial	Method	Max. degradation or recovery (%)	Sample matrix	Refs.
Applications for removal					
Citrinin	Surface active maghemite nanoparticles (Fe_2O_3)	Magnetic separation	70% removal	Biological matrixes	Magro et al. (2016)
Patulin	Chitosan-coated Fe_3O_4 nanoparticles	Magnetic adsorbent	99% within 60 min	Fruit juice; water or others	Luo et al. (2017)
Patulin	Magnetic chitosan-Fe_3O_4 nanoparticles coated with *Candida utilis*	Magnetic adsorbent	90%	Orange juice	Ge et al. (2017)
Patulin	Zirconium-based MOF UiO-66(NH_2)@Au-Cys	Adsorption	4.38μg mg^{-1}	Apple juice	Liu et al. (2019)
Patulin	Magnetic multi-walled carbon nanotubes (MWCNT)	Magnetic adsorbent	640.2μg g^{-1}	Aqueous systems	Zhang et al. (2019)
ZEA; fumonisin B1 and B2; DON	Magnetic graphene oxide nanocomposites	Adsorption	37–69%	Animal feed: palm kernel cake	Pirouz et al. (2017)
Applications for degradation					
DON	Graphene/ZnO hybrids	Photocatalytic (UV light)	99% of DON (15 ppm) within 30 min	Aqueous suspension	Bai et al. (2017)
AFB1	Scandium doped $SrTi_{0.7}Fe_{0.3}O_3$	Photocatalytic (visible light)	88% at pH 8 within 120 min	Water	Jamil et al. (2017)
AFB1	CdS/WO_3 composites	Photocatalytic (visible light)	80%	Water	Mao et al. (2019)
AFB1; AFB2	TiO_2, immobilized on a glass support	Photocatalytic (high-pressure UV–vis irradiation)	99% with 4 min	Peanut oil	Magzoub et al. (2019)
AFB1	TiO_2 (P25, Degussa) layer in a closed-loop reactor	Photocatalytic (UV light)	60%	Peanut oil	Xu et al. (2019)
AFB1	Activated carbon supported TiO_2 composites	Photocatalytic (visible light)	98% bare TiO_2 76%	Water	Sun et al. (2019)
DON	Dendritic α-Fe_2O_3	Photocatalytic (visible light)	90%	Aqueous solution	Wang et al. (2019)

et al. (2017) reported the synthesis of chitosan coated Fe_3O_4 nanoparticles as a magnetic adsorbent for the patulin removal from fruit juice. Further, magnetic chitosan Fe_3O_4 nanoparticles coated with deactivated *Candida utilis* cells and used as a new biosorbent for patulin removal from fruit juice (Ge et al. 2017). Similarly, for patulin removal, magnetic multi-walled carbon nanotube (MWCNT) adsorbent was fabricated, which can be regenerated using NaOH solution for recycling usage up to four cycles (Zhang et al. 2019).

9.3.2 Degradation of Mycotoxins Using Nanotechnology

Recently, there has been a growing interest in photocatalytic degradation of many organic pollutants, including mycotoxins. Photocatalytic degradation has numerous advantages, such as being environmentally friendly, low–cost, and requiring mild conditions (Bhatkhande et al. 2002). Various photocatalysts, both under the UV light and visible light irradiation, are presented in Table 9.5. Nevertheless, as UV light accounts for only 4% of the total sunlight, visible light photocatalysts are more beneficial for practical degradation of organic pollutants in natural systems (Pathakoti et al. 2013, 2018).

Bai et al. (2017) reported the synthesis of graphene/ZnO hybrids using a single one-step hydrothermal method for the photodegradation of DON under UV irradiation. As shown in Scheme 1a, the proposed photodegradation mechanism is due to the formation of superoxide radicals at the conduction band. It is recognized that the graphene increases the adsorption capability and the ZnO increases the photocatalytic achievement by graphene hybridization (Fig. 9.6). Additionally, the degradation products of DON were analyzed by using ESI/MS analysis.

Recently, Mao et al. (2019) reported the photocatalytic inactivation of AFB1 at hypertoxic site C8=C9 under visible light treatment using the Z-schematic composite, clew-like WO_3 adorned with CdS nanoparticles, synthesized by the microwave supported hydrothermal and precipitation procedure (Fig. 9.7). The reaction of hydroxyl radical formation with C8=C9 bond of AF for the photocatalytic inactivation was confirmed by radical trapping experiments and ^{18}O isotope labeling. Further, the degraded products were identified by using High Resolution Mass Spectroscopy, and the theoretical calculations using the density functional theory were used to confirm the formation of hydroxyl radicals at the C9 site, thereby forming AFB1-9-hydroxy.

Similarly, another study reported the 10 mole% Scandanium doped $SrTi_{0.7}Fe_{0.3}O_3$ (band gap, 1.58 eV) was synthesized for the photodegradation of afltoxinB1 under visible light irradiation (Jamil et al. 2017). Further, the degraded products were identified using gas chromatography-mass spectrometry (GC-MS), which are nontoxic to *Vibrio fischeri* organism. Hence, it is safe for water treatment, and moreover, both the catalyst and treated water can be reused for up to eight times. The mechanism of oxidation is due to rupture of short chain aliphatic alcohol, which leads to total degradation.

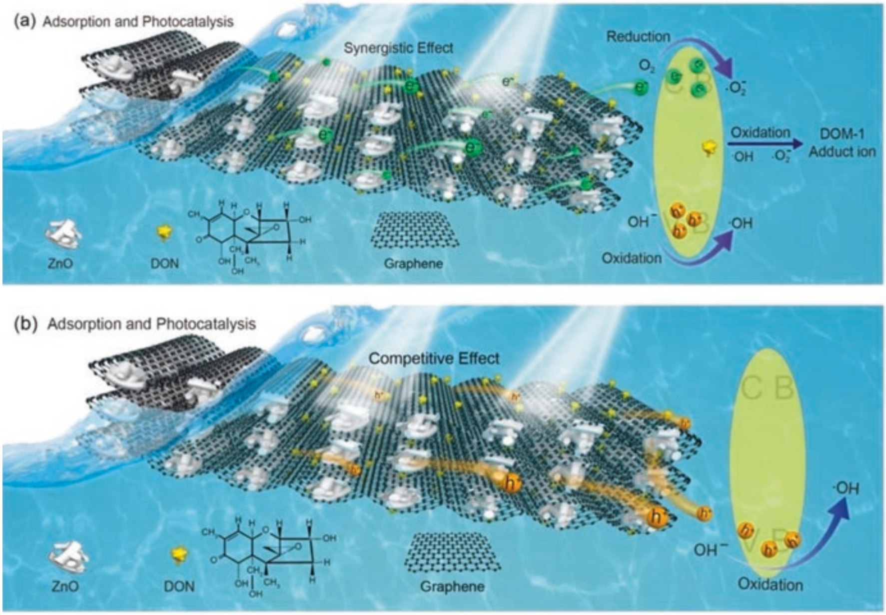


Fig. 9.6 Schematic drawing illustrating synthetic route and the mechanism of charge separation and adsorption-photocatalytic process over graphene/ZnO hybrid photocatalysts under UV light irradiation. Obtained with permission from Elsevier, Ref: (Bai et al. 2017)

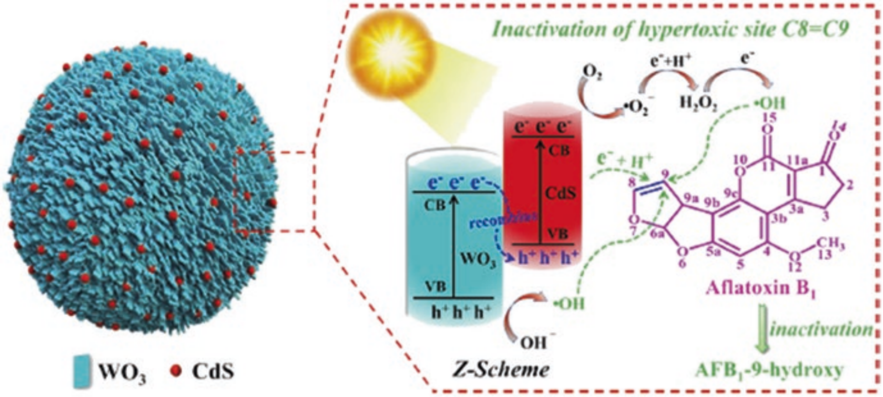


Fig. 9.7 Illustration of the proposed mechanism over CdS/WO_3 composites for inactivating the hypertoxic site [(C8=C9) in AFB1 under visible light irradiation. Obtained with permission from Elsevier, Ref. (Mao et al. 2019)

A study by Magzoub et al. (2019) reported the photocatalytic detoxification of AFB1 and AFB2 from its real sample matrix, peanut oil, using the TiO_2 that was immobilized on a glass support under high pressure UV–vis irradiation. It is noteworthy that the TiO_2 treatment did not alter the physicochemical parameters of the oil, such as iodine value, peroxide value, saponification value, fatty acid composition, and free fatty acids. Furthermore, the photocatalyst can be recycled up to ten cycles without reducing its effectiveness. The proposed mechanism is the formation of hydroxyl radicals and is comparable to previous reports (Jamil et al. 2017; Mao et al. 2019).

Likewise, Xu et al. (2019) reported the closed loop photocatalytic reactor comprising a glass tube holding TiO_2 catalyst for the decontamination of AFB1 from peanut oil. Based on their experimental data on AF detoxification, a theoretical model, a Weibull distribution model, has been proposed, which offers a good depiction for the photocatalytic process kinetics.

A simple hydrothermal method was described by Sun et al. (2019) for the photocatalytic degradation of AFB1 using an activated charcoal/TiO_2 composite under UV–vis irradiation. This newly synthesized composite had higher degradation efficiency when compared to the bare TiO_2 and the catalyst can be regenerated and recycled up to four cycles with 80% degradation efficiency. Formation of hydroxyl radicals plays a vital role in the degradation of AF, whereas superoxide radicals do not have an effect.

Another effective approach is the improvement of the photocatalyst, dendritic-like α-Fe_2O_3, for the DON degradation under visible light irradiation (Wang et al. 2019). A simple hydrothermal has been proposed for dendritic-like α-Fe_2O_3, which has better photocatalytic activity (more than 90% in 2 h) than the commercial α-Fe_2O_3. After degradation the intermediate products formed were identified by high perrformance liquid chromatography-mass spectrophotometry (HPLC-MS) and the major toxicity group, epoxy group at C12 and C13 and hydroxyl groups are destroyed in DON, thereby providing an efficient and green technology for mycotoxin decontamination.

9.4 Summary and Conclusion

The occurrence of mycotoxins in the food chain is a major safety concern around the world. Control of mycotoxins commonly depends on the suitable care taken during pre- and post-harvest conditions. The potential and present uses of nanotechnology in farming and food industries offer various significant benefits to ensure the microbial food quality and safe of nourishment items. The use of gold, QDs, and magnetic nanoparticles has significantly enhanced the biosensor technology for the mycotoxin analyses. All the above discussed nano-based sensors developed for detection and sensing of mycotoxins can be easily applied in the fields and also can be operated by unskilled personnel. Further, the sensitive and early detection of mycotoxins in food will be beneficial in eliminating these toxins to enter into food chain and thereby protects human health. Although QDs have various advantages due to their optical properties in comparison to other nanoparticles in sensing applications, but they are not cost-effective and expensive till date. In order to overcome the overestimation, false positive or underestimation, usage of more than one technique such as multiple sensor devices, which can be facile to fulfill the rapid monitoring and control of mycotoxins is essential.

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Chapter 10
Detection of Toxic Contaminant in the Food Items

Bensu Karahalil

Contents

Abstract Food safety and quality are important issues for public health. It is essential to ensure them. Foods can be contaminated by contaminants, such as pesticides, which have not been intentionally added to it. Veterinary food contaminants can be classified into two main groups: (i) first group consists of four sub-groups (environmental contaminants, pesticide residues, veterinary drug residues, and migrants from packaging materials); (ii) second group consists of three sub-groups (mycotoxins, food processing contaminants, and chemical reactions. Food contaminants are hazardous on human health, and the effects range from minor gastric problems to major health fatalities. For example, toxic metals such as cadmium and lead, which easily enter the food chain, deplete specific nutrients in the body, which leads to declining immunological defenses, and impair psycho-social faculties, and some pesticides cause neural and kidney damage and are carcinogenic. For this reason, many techniques need to be discovered to monitor food contaminants. These techniques should be reliable and cheap and provide high-throughput measurement. Food safety organizations support and encourage using analytical tools to monitor contaminants in foods and establish limits for food contaminants, called maximum residue limits (MRLs), thus providing food standardization. Sensitive sensors are needed for monitoring and controlling food contaminants. Nanotechnology, which is emerging technology, and nanoparticles nanotechnology used have many benefits due to their unique properties. This technology provides to create or discover very sensitive sensors to control food contaminants. In this chapter, it is summarized about food contaminants and their detection and checking of them with nanosensors.

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Nanotechnology and sensor combination provide sensitive and reliable tools in determining and monitoring food contaminants.

Keywords Food contaminants · Metals · Pesticides · Mycotoxins · Veterinary drug residues · Nanotechnology · Food

10.1 Introduction

Food safety is an essential issue because it is directly related to the human health. It needs to improve sensitive, rapid, selective, and reliable methods to detect those food hazards due to some food safety incidents and concerns about synthetic food additives and also chemical residues. Contaminants are chemical substances which are not intentionally added to food or feed. They are present in food in different stages such as production, processing, or transport of foods (European Food Safety Authority [EFSA]). Contaminants are important problems for both animals and humans and have risk to animal and important to human health. When contamination takes places, it generally leads to a negative impact on food quality, therefore it may be a risk to human health (Australian Institute of Food Safety). EFSA carries out risk assessments on various chemicals in food and feed. This work is carried out by EFSA's panel on contaminants in the food chain. EFSA collects data and monitor activities on food contaminants to carry out risk assessment. Following the risk assessment of EFSA, EFSA gives scientific advice to European Union risk managers. Risk managers use this recommendation and decide the safety of these substances for human, animal, and plant health (EFSA).

It is necessary to ensure food safety to protect human health. Sensitive sensors are needed to detect contaminants in foods. Thanks to the conveniences and benefits that nanotechnology brings to our lives, the advantages of nanotechnology are also used in the development of sensors. Nanosensors, sensors developed using nanotechnology, have become rapid, sensitive, and reliable sensors in determining food contaminants. A wide range of nanosensors are being developed to meet the various requirements to provide food safety (Thiruvengadam et al. 2018; Panigrahi et al. 2017). Pathogenic microorganisms, toxins (such as metal toxins) which contaminate, adulterants, fertilizers, pesticides, taste makers, various toxic chemicals or chemical interaction products, vitamins, dyes, and flavor enhancers can be detected by sensors. Time, temperature, and oxygen indicators are used for monitoring food freshness. Furthermore, invisible nanobarcodes are also used for brand protection and product authenticity (Kumar et al. 2017). In this context, nanosensors created using particles with unique properties make superior and successful contributions to the improvement of food quality.

10.2 Food Quality Assurance

Effective national food control systems are imperative to protect the human health and provide the safety for domestic consumers. They are also critical in enabling countries to assure the safety and quality of their foods entering international trade and also to ensure that imported foods conform to national requirements (Food and Agriculture Organization [FAO]). Globalization of food production, concerns about food quality and safety, and increase in food standards bring a new approach when compared to conventional one. There is no more the former end-of-line product inspection (Grunert 2005 and Institute of Physics (IOP); Institute of Physics Conference). In a new inspection approach, food quality assurance is provided from each stage of food production chain to ensure safe food and to show compliance with regulatory and customer needs. New inspection approach gives insurance to the customers by controlling each step of food production (Food and Safety Quality program). For this reason, sensors with improved properties (such as low detection limits, high sensitivity and specificity, simple sample preparation, rapid detection, and miniature tools suitable for portable use) need to be developed (Omanovic-Miklicanin and Maksimovic 2016).

There are public health laboratories to detect the microbiological contamination. Identification of harmful food contaminants and adulterants is provided by carrying out routine, accurate, and reliable testing, which is the only way. Public health laboratories make collaboration with Disease Control and Prevention which is a member of PulseNet. PulseNet is a national laboratory network and monitor foodborne diseases. Without this network, it is very difficult to detect widespread foodborne disease outbreaks. Get the latest information on current foodborne outbreaks on Centers of Disease Control and Prevention’s (CDC) website (Public Health Labs’ Role in Food Safety) (CDC).

There have already been various methods for assessing food safety at laboratory level, such as cell culture, sensitive instrumental analysis; however, these methods have many disadvantages, including long analysis time (hours/days) and needed pretreatment steps. There are various food contaminants and standard analytical techniques are not enough to detect them. These conventional methods are insufficient to detect food contaminants (such as pesticide residues and some pathogens), and improvement of new analytical methods or techniques are needed to overcome these deficits (Li and Sheng 2014). Food safety is an important issue for public health. There are many challenges which lead to risk in food safety due to contaminants, especially chemical contaminants are a major concern. Regulatory agencies responsible for food safety have established strict control programs to avoid contamination through the food chain (Food Regulation and Safety). Thus, we need sensors with a rapid, sensitive, high-throughput, and fast-operating system to be able to measure many samples. Nanotechnology-based method, called nanosensor, is one of the effective detection methods to be used. Nanotechnology is a promising new field and uses nano-sized materials which have unique properties to provide rapid, sensitive products having advantages (Christian et al. 2008). This technology provides new sensors (detection of external and internal conditions in food packaging, carbon nanotubes based electrochemical sensors for detection of cations, anions, and organic compounds in food, various aptamers for detection of pesticides, antibiotics, heavy metals, microbial cells, and toxins) to provide food safety and thereby improving food functionality and quality. Nanosensors have advantage to detect food components in an easy and quick manner compared to conventional methods.

10.3 Classification of Food Contaminants

Scientists or experts in food field classify food contaminants in different manners. For example, Mastovska classified food contaminants as environmental contaminants, food processing contaminants, unapproved adulterants and food additives, and migrants from packaging materials (Mastovska 2013). Other classification for food contaminants which are commonly used is as physical, chemical, biological, and radiological contaminants. The most common physical contaminants in food are metals and plastic, ceramic, and glass pieces which may occur. Physical and radiological contaminants are not commonly encountered and they their hazard potential is more weak. Therefore, they do not lead to public concern. Therefore, these topics will not be included in this chapter. If biological contaminants occur in food, they may affect human health, either by infection or intoxication by pathogens such as bacteria, viruses, parasites, and prions and cause fever, headache, nausea, vomiting, abdominal pain, and diarrhea. Chemical contaminants include mycotoxins, phycotoxins, pesticides residues, fertilizers, antibiotics and veterinary drug residue, allergens, adulterants in food, and heavy metals (physical contaminants). These contaminants are discussed in detail below.

Different types of classification on food contaminants are present; however, generally they are similar and they contain same type of contaminants, of course, only the presentation of classification type of them is different. My classification is also a little different from others. Food/chemical contaminants on food items, especially organic chlorine substances and agrochemicals like pesticides, a large part of chemical contaminants, have been introduced into our life in the last 70–80 years. Other chemical contaminants have been in the food items for thousands of years; however, we are aware of them after analytical methods were developed. Before the 1950s it was measured only at mg levels; nowadays detection limits of chemicals have increased, and even ppt (part per trillion) and ppq (part per quadrillion) levels are measured (Karakaya 2018).

There are more than 1000 food contaminants in different. Food contaminants are divided into two main categories (Fig. 10.1).

A. Food contaminants that originate from developments in the chemical industry on foods due to rapid industrialization in the twentieth century. This category also consists of four sub-groups:

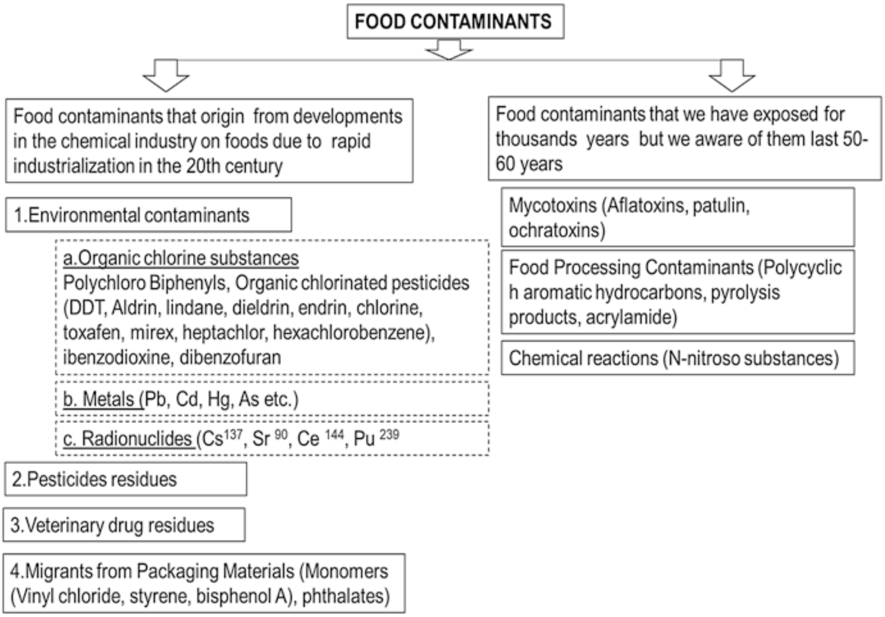

Fig. 10.1 Classification of food contaminants

1. Environmental contaminants
2. Pesticides residues
3. Veterinary drug residues
4. Migrants from packaging materials

B. Food contaminants we have been exposed to for thousands of years but we are aware of them for the last 50–60 years:

1. Mycotoxins (aflatoxins, patulin, ochratoxins)
2. Food processing contaminants (polycyclic aromatic hydrocarbons, pyrolysis products, acrylamide)
3. Chemical reactions (N-nitroso substances)

1. *Environmental contaminants*

a. Organochlorine substances, which are in the first place on the Fig. 10.1, are no longer used today. They are chemicals of global concern due to their persistence in the environment, ability to bio-magnify, and bio-accumulate in the environment. Persistent organic pollutants (POPs) are thus found in organisms at the top of the food chain since they biomagnify throughout the food chain and bioaccumulate in organisms. Consequently, background levels of POPs can be found in the human body (Rather et al. 2017; Goerke et al. 2004; Guo et al. 2019).

Humans are exposed to these chemicals in a variety of ways: mainly through food, air, and at the workplace. The most commonly encountered persistent organic pollutants are organochlorine pesticides (OCP), such as dichlorodiphenyltrichloroethane (DDT), aldrin, lindane, dieldrin, endrin, chlorine, toxaphene, mirex, heptachlor, hexachlorobenzene, industrial chemicals, most notably polychlorinated biphenyls (PCB), as well as unintentional by-products of many industrial processes, especially polychlorinated dibenzo-p-dioxins (PCDD) and dibenzofurans (PCDF), commonly known as “dioxins.”

Since 1976, the World Health Organization (WHO) through its the Global Environment Monitoring System ; GEMS/Food Programme, which is the Global Environment Monitoring System—Food Contamination Monitoring and Assessment Programme, commonly known as GEMS/Food, informs governments and has collected and evaluated information on levels of persistent organic pollutants in foods, including human milk. Three international studies were made to assess the levels and trends of polychlorinated dibenzodioxins, polychlorinated dibenzofurans, and dioxin-like polychlorinated biphenyls on human milk, which is an ideal matrix to generally monitor levels of persistent organic pollutants in the environment. Biomonitoring of human milk data can provide information on the exposure of the mother as well as the infants. This information provides guidance on the need for measures to reduce levels of these substances in food (WHO). Milk is a very important food due to its content of fat, protein, vitamins, and minerals. However, the use of organochlorine pesticides (OCP) for decades has also contaminated the milk since they have contaminated the soil, water, and air. Meanwhile, while mentioning milk, sensitive sensors are used in the determination of melamine used as fertilizer. Melamine, which is a fertilizer and used as adulterant in protein-rich products in infant formulas and cow milk, is detected by gold nanoparticles-based fluorescence sensors. These sensors are very sensitive and are able to detect at picomolar levels of melamine (Vasimalai and John 2013). Although organochlorinated pesticides have been banned since the 1980s, these compounds or their metabolites have still been detected in many samples and even above the maximum allowed levels by the World Health Organization. Milk and other dairy based products are highly consumed worldwide, especially by young children. Various electrochemical sensors have been developed. They assess milk quality for melamine, antibiotics, bisphenol A, DNA bases, and hydrogen peroxide. Hydrogen peroxide activates the inherent lactoperoxidase enzyme system and help to improve the quality of raw dairy products. However, possible adverse health effects from over exposure take place. Hydrogen peroxide is 80 ppm according to Food and Drug Administration. Eggshell membranes (ESMs) have been used as a platform for supporting graphene oxide (GO) for hydrogen peroxide sensitive electrodes. The versatility of electrochemical nanosensors are preferred because of their versatility and especially are used for detecting compounds like sulfite in sugar, grapes, wine and water, staphylococcal enterotoxin B (a possible source of food poisoning), aflatoxin, and durabolin (Baryy and O’Riordan 2016; Mittal et al. 2016).

b. Metals

In the early nineteenth century, foods were stored in glass jars, but it was difficult to use or handle in battlefields because it was easily broken and metal cans/

containers had to be developed (Badilla et al. 2012). Nowadays, metal containers are widely used in packaging besides glass jars. Most people prefer glass jar because they think that they are safer than metallic cans, so they prefer to use them; and they consider that metal migration takes place from can to food content and it is hazardous to human health. Metallic cans are cheaper than glass ones; for these reasons, in some regions, the preference, whether glass or metal, changes according to the socio-economic status of people. Of course, the migration of metal ions from cans is also an issue that should not be ignored. Heavy metals (lead, arsenic, cadmium, mercury, chromium) are hazardous elements. Lead causes memory problems, abdominal pain, constipation, headaches, irritability, inability to have children, and tingling in the hands and feet (Wani et al. 2015). It is reported that Arsenic causes multisystem diseases and encephalopathy and peripheral neuropathy (Ratnaike 2003). Cadmium causes damage to liver and kidney (Satarug 2018). Mercury is neurotoxic (Alexeandrov et al. 2018). When corrosion takes place on metallic cans, metallic ions migrate to food and thus food contamination occurs. To avoid this, the inner side of cans is coated to save from corrosion. Coating materials are epoxy resins. Still in some minor by-products the epoxy resins (cyclo-di-BADGE, bisphenol A, or bisphenol A diglycidyl ether) can migrate to food. These by-products are endocrine disrupters which mimic to estrogens or testosterone or other hormones and change hormonal balance of the body and are hazardous to human health. These metals have been extensively studied and their effects on human health regularly reviewed by international bodies such as the WHO. They can damage and alter the functioning of organs such as the brain, kidney, lungs, liver, and blood (Rather et al. 2017). Heavy metal toxicity can either be acute or chronic effects. Exposure to these heavy metals might be from food, air, or water pollution, as well as medicine, food containers with improper coating, industrial exposure, or lead-based paint. Therefore, sensitive and selective determination of toxic heavy metals with cost-effective and convenient procedures is required. For detection of toxic metal ions such as cadmium ions in foods, multi-walled carbon nanotubes-silica nanocomposite-based potentiometer sensors are used (Bagheri et al. 2013).

Electrochemical sensors are used for detection of heavy metal ions for food samples. For many years, anodic stripping voltammetry (ASV) at the mercury and its modified electrode was commonly used to determine the trace metal ions for the extensive cathodic potential range. However, the improper use of the mercury-containing device (disposal of that devise, incorrect handling, etc.) leaks mercury vapors. It causes health problems for humans and also not good for ecosystem. Therefore, various mercury-free electrodes were developed such as a nanostructured bismuth film electrode (nsBiFE). This nanosensor is used for ASV detection of multiple heavy metals (detection limits of $0.4 \mu g L^{-1}$ and $0.1 \mu g L^{-1}$ for Cd2+ and Pb2, respectively). Bismuth and antimony are used similarly for similar purpose. More and more electrochemical sensors based on screen-printed carbon electrode (SPCE) have been fabricated for detection of heavy metals in food safety (Baryy and O'Riordan 2016).

2. *Pesticide Residues*

Pesticides are widely used to control pests that would otherwise destroy or reduce food. In this area of agriculture, pesticides, especially organophosphate and carbamate, are commonly used worldwide. They are highly toxic since they inhibit acetylcholinesterase which is key enzyme for the nervous system. This inhibition causes respiratory failure, weakness in muscles, miosis, unconsciousness, convulsion, and finally death. For these reasons, pesticide contamination in food is very important issue. It is essential to detect the contamination to protect human health (Judge et al. 2016).

The development of simple, sensitive, user-friendly, and cost-effective sensors using nanotechnology is required. Biosensors have more advantages than the existing techniques such as high-performance liquid chromatography or gas chromatography, because biosensor can provide rapid, sensitive, simple, and low-cost on-field detection. Biosensors (optical, electrochemical, and piezoelectric) have been used and are a powerful alternative for the detection and monitoring of pesticide residues. Biosensors are based on the intimate contact between a biological element (such as receptor, tissue cell, nucleic acid, enzyme, antibody) and a transducer system. The biological component interacts specifically with the target analyte while the transducer transforms the signal. After interaction target analyte to biological element cause a signal thereby, measured and quantified. For organophosphate and carbamate pesticide residues, biosensors based on acetylcholinesterase inhibition form a link with the active site of the enzyme. The electrochemical impedance spectroscopy (EIS) is transduction technology, which detects direct analyte by studying the electrical properties of the sensing device interface. The new label-free impedimetric affinity sensors are also developed based on AChE and detection limit is 2,5 and 10 ug/kg for organophosphate and carbamate (Sciencetrends.com). The detection of some pesticides, such as pesticides in organophosphorus and carbamate groups, in foods is provided by using colorimetric and fluorometric sensors, which are composed of gold (Liu et al. 2012).

3. *Veterinary Drug Residues*

Antibacterial drugs and hormonal growth promoters are the main veterinary drug residues that potentially contaminate foods of animal origin. Consumption of these residues in animal products may cause the development of antibiotic resistance and hypersensitivity reaction. Veterinary drug products and agricultural chemicals used according to label directions should not result in residues at slaughter. However, in some cases, veterinary drug residues are encountered. These situationsare not to follow the recommended label directions or dosage (extra-label usage) not to properly clean equipment and not to prevent animals from reaching the spilled drugs, dosage/measurement errors, the use of contaminated drug due to drug interactions when it is used more than two drugs and to use the improper use of pesticides, etc. The presence of veterinary drug residues in foods is one of the key issues for food safety, and it is a great health concern. It is essential to develop sensor for detecting veterinary drug residues in foods and also needs to be quantified these residues which are less than the maximum residue limits (MRL) on the basis of food safety.

Detection of veterinary residues in meat and dairy products ensures their quality and safety. Using bioreceptors from biological organisms or receptors, biosensors have been employed as a new mean of analytical and chemical analysis. The most frequently used biosensors are those based on antibody/antigen affinity pairs for detection of veterinary drug residues. Electrochemical biosensors composed of nanomaterials have better performance due to their unique electrical and chemical properties. The incorporation of nanomaterials can potentially increase the response speed, selectivity and sensitivity. Biosensors using an aptamer as a recognition element are also commonly used for the detection of antibiotic residues. Electrochemical can be categorized as potentiometric, amperometric, voltammetric, impedimetric and conductivity sensors. An amperometric biosensor measures the current produced, potentiometric devices measure the changes in pH and ion concentration and conductimetric biosensors which is a limited response for the detection of antibiotics due to its poor signal/noise ratio, quantify the electrical conductivity changes in a solution at constant voltage (Majdinasab et al. 2017; Verdian 2018). Enzymatic biosensors are commonly used for the analysis of herbicides contaminants. Enzymatic biosensor for penicillin, cellular biosensors for antibiotic residues such as tetracyclines, beta-lactam antibiotics, quinolones, chloramphenicol and quinolones, and transducer-biosensors for antibiotic residues are developed (Falowo and Akimoladun 2019).

4. *Migrants from Packaging Materials*

Polymer packaging with chemicals are called plastics. These chemicals improve functional properties of plastics. However, these substances might be concern on product safety and quality when amount of these migrating compounds in food exceed their specified limits. Migration means the diffusion of substances from the food-contact layer to the food surface. This process is influenced by food-packaging interactions and temperature (Bhunia et al. 2013). The five polymers most commonly applied in plastic packaging include polyethylene (PE), polypropylene (PP), polyethylene terephthal-ate (PET), polystyrene (PS), and PVC. Manyo ther polymers, including, for example, polycarbonate (PC), polyamides, (PA, nylon), acrylics, polylactic acid (PLA), polyurethanes (PU) and even more specialized polymer types, are also used for specific packaging applications (Groh et al. 2019; Omeroğlu et al. 2017). Phthalates are esters of phthalic acid and are used as plasticizers to increase the flexibility, transparency, durability, and longevity of plastics. Phthalates are used in a large variety of applications, from enteric coatings of pharmaceutical pills to food packaging materials. These compounds are easily released into the environment since they are not covalently bound to the plastics. Phthalates can cause many health problems such as reproductive abnormalities, low birth weight, asthma, endocrine disruption, cancer, autism (Street et al. 2018). Sensitive and reliable methods to rapidly detect the presence of phthalates in food are clearly needed. The selectivity of the sensor is important for complex organic matrices. Phthalates are detected in detection system in complex organic matrices like soups, milk, juice and drinks. Molecular imprinting technique has been used for this purpose and develop sensor (Asif et al. 2015). Gas Chromatography-Mass Spectrometry (GC/MS) and Liquid Chromatography-Mass spectrometry (LC/MS) are currently used and enable to provide sensitive detection of phthalate compounds (Agilent Technologies). Phthalates are known endocrine disrupters which are structurally diverse compounds that interfere with the endocrine system, cause a broad range of adverse effects. Nanosensors developed for endocrine disruptors can also be used for phthalates. A high throughput cell-based nanosensor provides highly sensitive identification of estrogenic agents.

A. Food contaminants that originate from developments in the chemical industry on foods due to rapid industrialization in the twentieth century
B. *Food contaminants that we have been exposed to for thousands of years, but we aware of them for the last 50–60 years*

1. *Mycotoxins*

Mycotoxins are naturally occurring toxins produced by certain molds. Aflatoxins are produced by certain kinds of fungi (Aspergillus: *Aspergillus flavus*, *A parasiticus,* and *A. nomius*) that are found naturally all over the world; they can contaminate food crops and pose a serious health threat to humans and livestock. Long-term or chronic exposure to aflatoxins has several health problems including carcinogenicity, mutagenic in bacteria, genotoxic and causing birth defects, chronic diarrhea, infectious diseases, malnutrition (WHO).

Generally, GC-MS and LC-MS techniques are used for detection of mycotoxins in foods as contaminants due to their selectivity and sensitivity; however, these techniques are time-consuming and not enough rapid assay and also pretreatment steps are needed before detection. Inconsistent results and poor sensitivity are from sample preparation and extraction steps (Daly et al. 2000). Surface plasmon resonance (SPR) has advantages compared to these analytical techniques. SPR is used for molecular interactions. Furthermore, it is also used to elucidate biospecific interaction analysis. The feature of SPR, which makes use of molecular interactions, is adapted for various sensing applications. There is a biorecognition layer on sensor. The action mechanism of SPR is based on to detect the changes in the refractive index of the biorecognition layer. Furthermore, SPR monitors the binding interactions of immuno-components in real time (Wangkam et al. 2009; Choi et al. 2009).

Immunoassays and biosensor are preferred to these conventional techniques for detection of mycotoxins such as aflatoxins due to their advantages. Biosensors based on the use of monoclonal or polyclonal antibodies are used in the mycotoxin's analyses. The immunosensor based on antibody-attached gold nanoparticles provide rapid and effective detection for aflatoxin and detection range of that method for aflatoxin is 10–100 ng/d Land response time is very short (60 s) (Torres-Pacheco 2011). Systems (dip-stick kits, hyperspectral imaging, electronic noses, molecularly imprinted polymers, and aptamer-based biosensors are used for detection of aflatoxins (WHO).

The immunosensor based on competitive fluorescence immunoassay is used for ochratoxin and also aflatoxin B1. The immunosensor is used antigen-modified magnetic nanoparticles as immunosensing probes and antibody-functionalized rare-earth-doped sodium yttrium fluoride up conversion nanoparticles as multicolor signal probes for detection of ochratoxin. Ochratoxin also can detect an immunosensor method based on nanostructured zinc-oxide film, which is deposited onto indium-tin-oxide glass plate for comobilization of rabbit immunoglobulin antibodies and bovine serum albumin. The action mechanism of this method is to bind positively charged nano-zinc oxide with carboxyl groups of r-IgG by electrostatic interaction. Therefore, free amino- terminal sites of r-IgG bind to the carboxylic group of ochratoxin molecules. Aptamers, which use single-walled carbon nanotubes, are also used for detection of ochratoxin as a fluorescent assay (Kuswandi et al. 2017).

2. *Food Processing Contaminants*

Acrylamide naturally forms in starchy food products during high-temperature cooking, including frying, baking, roasting and also industrial processing, at +120 °C and low moisture. Maillard Reaction is the main chemical process is the same reaction that ‘browns’ food. Acrylamide forms from sugars and amino acids (mainly one called asparagine) that are naturally present in many foods such as potato crisps, French fries, bread, biscuits, and coffee (EFSA). Acrylamide can create adducts with hemoglobin which form the reaction between the -NH2 group of N-terminal valine of Hb with acrylamide. Voltammetric sensor based on the reaction of Hb with acrylamide is used for detection. Electrochemical biosensor is also designated for detection. The reversible conversion of Fe^3 to Fe^2 of heme is required for its electroactivity. Electromediators such as carbon nanotubes and gold nanoparticles provide intensification of electron transfer rate between Hb and electrode surface (Krajewska et al. 2009). Fluorescent sensors for detection of acrylamide is preferred to conventional analytical methods (GC-MS and LCMSMS) since fluorescent sensors are rapid and specific to analytes.

Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds with two or more fused aromatic rings. Polycyclic aromatic hydrocarbons. Polycyclic aromatic hydrocarbons (PAHs) are a group of contaminants produced by burning of carbon-based materials. They can get into food either from the environment or during food processing. After the first regulatory limits in food were set in 2006, the European Food Safety Authority (EFSA) published a Scientific Opinion and stated that 16 PAHs in food are a possible health concern. Some PAHs are carcinogenic because they damage DNA. It is therefore important to develop methods which are rapid, reliable, and sensitive for PAHs in food to help reduce their deleterious impacts on human health based on the accurate quantification. A conductometric sensor based on screen-printed interdigital gold electrodes are used for PAH detection. These electrodes are on glass and this glass is coated with molecularly imprinted polyurethane layers. Screen-printed interdigital electrodes are very suitable transducers. The working principle is based on the measurement of changes in resistance of PAH-imprinted layers. The sensor has good selectivity and high sensitivity, for example, detection limit is 1.3 nmol/L for anthracene in water (Latif et al. 2018).

3. *Chemical Reactions*

N-nitroso compounds (NOCs) include two chemical classes, nitrosamines and nitrosamides, which are formed by the reaction of amines and amides, respectively, with nitrosating agents derived from nitrite. Endogenous N-nitroso compound formation is estimated to account for 45–75% of total exposure to N-nitroso compounds. Processed meat is a major dietary source of nitrite, amines, and amides (Dubrow et al. 2010). Nitrosamides do not require metabolic activation and directly make alkylation. There are many ways of exposure, and we could be exposed to them through eating foods containing these compounds, including fish, cheeses, bacon, and other cured meats; breathing air containing tobacco smoke or the air inside cars; and drinking some alcoholic beverages like beer and other malt beverages (https://dhss.delaware.gov). The N-nitroso compounds studied by the Environmental Health Protection (EPA) are classified as probable human carcinogens. For the detection of N-nitroso compounds, the commonly used analytical techniques include gas chromatography-mass spectrometry or tandem mass spectrometry and liquid chromatography-tandem mass spectrometry. They are time-consuming techniques. Rapid and efficient sensors are tried to develop for N-nitroso compounds.

Food safety is an essential public health issue for all countries. We cannot think of food quality separately from food safety. Food quality is also an extremely important issue. There are many factors or agents which affect food safety and food quality. Sustainable food safety is a key element, for this reason detection or quantification of factors affecting food safety and food quality are of major issue. Chemical, biological, and sensors integrated with nanotechnology are used for detection of contaminants. However, as mentioned below, nanosensors are preferred to conventional techniques due to their valuable advantageous. Nanotechnology is relatively new technology. It is providing new products in all industrial sectors (electricity, cosmetics, pharmaceutical industry, etc.) widely all over the World. Products produced by nanotechnology have many advantages since it uses nanoparticles and nanomaterials. Nanoparticles or nanomaterials possess unique physical and chemical properties due to their high surface area and nanoscale size. Their optical properties are dependent on the size, which imparts different colors due to absorption in the visible region. Nanosensors, whether used as online or off-line, can be integrated with wireless technology and used for real-time transmission of contaminant alarm or test results to remote servers, providing rapid screening and reporting. Due to perfect integration of nanotechnology with chemical and biological items, nanosensors provide tremendous benefits to detect various food contaminants. It, therefore, provides superior success in food safety and food quality. Sensors developed using nanotechnology are used both on-line and off-line. In both situations, they are integrated with wireless technology and this provides real-time transmission of contaminant alarm or test results to remote servers. All these above properties provide rapid screening and reporting. Of course, there is a need to develop more sensors in future to control the safety of foods.

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Chapter 11
Utility of Nanobiosensors in Environmental Analysis and Monitoring

Kshitij RB Singh and Ravindra Pratap Singh

Contents

Abstract Nanotechnology has evolved very fast in recent years, and biosensors based on nanomaterials (nanobiosensors) are finding a variety of applications in the environmental, clinical, and agricultural domains just due to the versatile properties of the nanomaterials used for designing nanobiosensors. The major threat to environment is the release of heavy metal ions, pesticides, chemical toxins, etc., into water bodies, food, and the atmosphere. These sources are directly in contact with the living world and these environmental pollutants pose severe global threats to health. Using nanoscale-structured material for improving biosensing technology has brought in a novel and cost-effective technology for environmental analysis and monitoring. Due to the complexity of these pollutants, traditional biosensor methods face some limitations, which are overcome by using nanobiosensors; these types of sensors are very selective and sensitive. In this book chapter, different types of nanobiosensors based on quantum dot, carbon, dendrimers, liposomal, metal and

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metal oxides, and polymeric are elaborated in detail for their application in environmental analysis and monitoring.

Keywords Biosensors · Nanobiosensors · Quantum dot nanobiosensors · Dendrimers nanobiosensors · Metal and metal oxide nanobiosensors · Carbon-based nanobiosensors · Liposomal nanobiosensors · Polymeric nanobiosensors

11.1 Introduction

Nanotechnology and nanoscience deal with the scientific study and applicability of nanoscale structures (1–100 nanometer). Nanotechnology is a science that is based on the engineering, design, synthesis, characterization, and application of materials and its products, which range in the nanometer-scale dimensions (Singh et al. 2010a; Silva 2004). In simple terms, nanotechnology basically deals with the fact that very small assemblies of bulk matter have unique properties and behavior that the bulk matter lacks with the same composition. The development of nanosensors for application in the monitoring and analysis of environment pollutants has evolved very fast; different nanostructures are used for the above applications, namely quantum dots, carbon-based, dendrimers, and liposomal (Singh et al. 2012a; Riu et al. 2006; Singh 2016).

Biosensors are analytical devices used for the detection of analytes of interest; analytes are biological components such as biological structure, biomolecule, and microorganism. They have three main parts: recognition element (bioreceptor), transducer, and amplifier. The bioreceptor is the recognition element that binds with analytes to produce biological signal; this signal is the primary signal produced by any biosensor device. The transducer recognizes the biological signal and converts it to a suitable form that can be analyzed, stored, manipulated, amplified, stored, and displayed. The amplifier just amplifies the converted biological signal to an electrical signal and displays the data on a micro-electronic device, as shown in Fig. 11.1

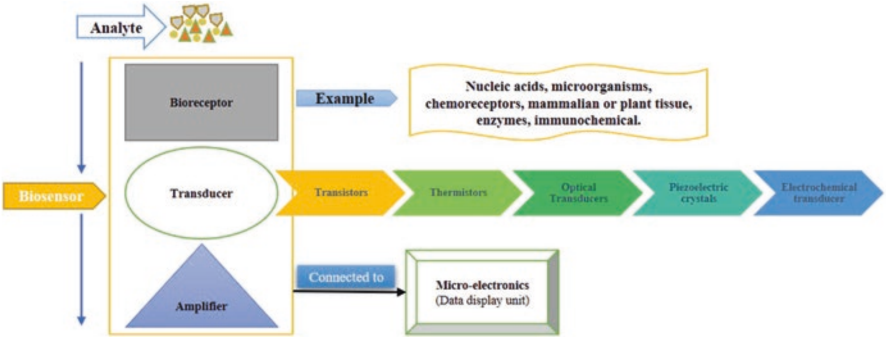

Fig. 11.1 Shows schematic representation of basic biosensors along with examples of different bioreceptors and transducers used in biosensing

(Singh 2011a, 2012; Rasooly and Herold 2006). Biosensors are of various types such as tissue and enzyme based, immunosensors, DNA (Deoxyribonucleic acid), piezoelectric, and thermal. They are used in various fields for environmental monitoring, agriculture, and biomedical diagnostics for the detection of analytes (Singh et al. 2008; Mehrotra 2016). Peptide-nucleic-acid-based biosensors are widely used in the field of biomedical for diagnostic applications (Singh et al. 2010a, 2020), and its application in environmental monitoring and analysis is very less explored.

The heavy metal waste (e.g., Pb, Cd, Hg) from metallurgic industries mostly pollutes the biosphere because of its toxic nature (Yilmaz et al. 2007). Thus, there is a very urgent need to develop real-time monitoring devices, such as biosensors, nanosensors, and nanobiosensors, for the detection of industrial pollutants (Singh and Choi 2010; Singh et al. 2011a). The existing methods, such as atomic absorption spectrometer (AAS), inductively coupled plasma mass spectrometry, atomic emission spectrometers, etc., are very expensive and are not designed for on-site detection (Burlingame et al. 1996; Jackson et al. 1996), but these nanomaterial-based sensors (nanobiosensors) are more powerful analytical tools because of their high sensitivity, portability, selectivity, and on-site detection (Ullah et al. 2018). Much literature suggests that enzyme-based nanobiosensors are very sensitive for heavy metal ion detection, and this type of enzyme-based nanobiosensors use enzyme activity inhibition when the heavy metal ions form conjugates with enzymes thiol groups (Wanekaya et al. 2008).

The use of pesticides in large quantities to enhance the yield of agricultural produce is the main cause of environmental pollution. Residues of pesticides are found in water and food products, which are direct routes of human interaction; these affect human health directly. Thus, there is a very urgent need to develop a device that has the ability to detect these small environmental pollutants in real samples (Singh et al. 2009b; Nsibande and Forbes 2016).

Electrochemical biosensors are most suitable for sensing environmental pollutants as they are sensitive, selective, precise, rapid, and easy to operate (Singh et al. 2009a, 2010b; Badihi-Mossberg et al. 2007). Immunosensors and DNA-based biosensors are effective in the determination of very low concentrations of environmental pollutants at rapid speed. This is because of signal amplification and noise reduction techniques, along with miniaturization, which increases sensitivity (Connelly and Baeumner 2012). The design of biosensors has seen significant changes in recent years, and the use of nanomaterials for biosensor development has reached new heights. Nanomaterial-based sensors (nanobiosensors) are now a hot topic and are attracting enthusiastic researchers for their applicability in the clinical, agricultural, and environmental fields (Singh et al. 2012b, 2012d). This is because of the fact that nanomaterials have unique properties such as better electrical conductivity, piezoelectric, and better shock-bearing ability (Malik et al. 2013).

There is a very urgent need to develop novel methodology for continuous monitoring and analysis of the environment. Thus, in this regard, biosensors have emerged as the best analytical tool for the determination of analytes that pollute the environment (Singh and Pandey 2011; Rodriguez-Mozaz et al. 2006). In this book chapter, we have described in detail the use of quantum-dot-based, carbon-based, dendrimers-based, liposomal-based, metal- and metal-oxides-based, and polymeric-based nanobiosensors in environmental analysis and monitoring (Singh et al. 2012c).

11.2 Quantum-Dot-Based Nanobiosensors

Quantum-dot-based nanobiosensors for environmental analysis and monitoring are gaining more importance and are being developed at a faster pace in recent years. Quantum dots have outstanding optical and electronic properties, and when compared with other fluorophores, they exhibit high-fluorescence quantum yields. Apart from these properties, they also display multifaceted surface functionalization and are highly photostable, which make them unique when compared to organic dyes. There is still a need to develop quantum-dot-based nanobiosensors that can be commercialized and used routinely for the detection and monitoring of environmental pollutants such as pesticides, heavy metals, and chemical toxins. Quantum-dot-based nanobiosensors as a metal sensor for the detection of toxic heavy metal ions, such as cadmium (II)(Cd^{2+}), Hg^{2+}, and Pb^{2+}, are receiving great importance, and many researchers have developed this type of sensors and many are working in this domain because heavy metal contamination of water is the major cause of water pollution (Nsibande and Forbes 2016; Vazquez-Gonzalez and Carrillo-Carrion 2014).

Nanobiosensor systems based on water-soluble quantum dots capped with ligands such as mercaptoacetic acid (MAA), L-cysteine, and N-acetyl-L-cysteine (NAC) for the detection of heavy metal ions are being developed. In this type of systems, ligands are responsible for response to metal ions as well as solubility of quantum dots in aqueous condition. A group of researchers have capped MAA with CdS and CdS/ZnS quantum dots, that resulted in MAA-CdS and MAA-CdS/ZnS quantum dots. The resulting compound is a fluorescent probe that was used for the detection of Hg^{2+} (Mercury (II)). This detection was totally dependent on the fluorescence quenching of quantum dots in the presence of these ions, and the result signifies that this type of sensors show excellent sensitivity and selectivity (Koneswaran and Narayanaswamy 2009, 2012). Further, study by Duan et al. (2011) produced a less toxic sensor based on ZnS quantum dots which was modified by NAC and this modification resulted in NAC-ZnS quantum dots; this nanoparticle-based sensor/nanobiosensor was applied to detect Hg^{2+} traces in water sample.

Wu et al. (2008) reported thioglycolic acid (TGA)-capped CdTe quantum dots for the detection of lead II (Pb^{2+}) in food samples of popcorn and instant noodles. The major principle behind using this method was fluorescence quenching of CdTe quantum dots and the result obtained from this study was almost similar to the results obtained from flame atomic absorption spectrometry. Cai et al. (2012) synthesized highly luminescent l-glutathione (GSH)-capped ZnSe quantum dots in aqueous samples. Further, for the detection of Pb^{2+} in micromolar concentration, Goncalves et al. (2009) also used GHS-capped CdTe quantum dots; to study this system for fluorescence spectra, they carried out PARAFAC (parallel factor) analysis. Zhao et al. (2013) reported an ultrasensitive method for the detection of Pb^{2+} by using dithizone (Dz)-functionalized CdSe/CdS based on enhancement in fluorescence, as conjugates of Dz-quantum dots cause fluorescence quenching. This fluorescent probe was validated on real samples of soil, tap water, and river water for Pb^{2+} detection, and the result of this study showed excellent performance with very good sensitivity and selectivity.

The development of nanobiosensors for heavy metal ion detection or other pollutants are based on changes induced by analytes in quantum dots; these changes are dependent on Forster's theory, and this theory is the major principle behind the fluorescence resonance energy transfer (FRET). In this system, the quantum dots act as donors, and the light energy absorbed by the quantum dots is transferred to other nearby acceptors (example, other nanoparticles and organic fluorophore) (Medintz et al. 2003; Algar et al. 2010). Based on FRET systems using quantum dots, Li et al. in 2008 reported TGA CdTe quantum dots as donors and butyl-rhodamine B, which is an acceptor of light energy in the presence of cetyltrimethylammonium bromide (a surfactant) for the detection of Hg^{2+}. Many researchers have used ZnS QDs and Mn^{2+} quantum dots to make nanobiosensors for the detection of different pesticides such as cyphenothrin (Ren and Chen 2015), pentachlorophenol (Wang et al. 2009; Yang et al. 2012), and acetamiprid (Lin et al. 2016).

11.3 Carbon-Based Nanobiosensors

Carbon-based nanomaterials such as carbon nanotubes (CNTs), graphene, and other allotropes of carbon have been used in the development of nanobiosensors because they are very selective and sensitive in the detection of several analytes. Carbon-based nanomaterial biosensors impart unique electrical and physical properties, which offer them a variety of applications for the detection and monitoring of environmental pollutants such as heavy metal ions, explosives, pathogens, and pesticides. This type of nanobiosensors are simple, cost-effective, and handy (used for on-site detection), and give immediate results (Ramnani et al. 2016).

Aptasensors (DNA-functionalized CNT biosensors) are used widely to study heavy metal ion interaction with DNA because DNA are highly stable at optimum pH condition. Liu and Wei (2008) reported a DNA-single-walled carbon nanotube (DNA-SWCNT)-modified glassy carbon electrode (GCE) for the detection of arsenic (III) (As^{3+}). This type of aptasensors was highly sensitive and selective to As^{3+} with a limit of detection (LOD) of 0.05 μg/L. Li et al. (2009) reported graphene-modified GCE for the detection of Pb^{2+} and Cd^{2+}. Further, Morton et al. (2009) reported a carboxylated CNT-modified GCE for the detection of heavy metal ions Pb^{2+} and Cu^{2+} (Copper (II)). Gong et al. (2013) reported a label-free chemiresistive biosensor for Hg^{2+} heavy metal ion detection based on SWCNTs functionalized with duplex polyT:polyA.

By changing the surface chemistry of the carbon-based nanomaterial using antibodies that are specific to a pathogen which is to be identified, a highly sensitive and selective device for the detection of viruses and bacteria can be developed. Liu et al.

(2013) reported field-effect transistor-reduced graphene oxide nanobiosensors for the detection of the rotavirus (water-borne virus), which causes diarrhea. They have examined real samples and the result showed a LOD of 10^3pfu/ml, which means that this detection method was very sensitive and selective. García-Aljaro et al. (2010) added by reporting SWCNT-chemiresistive biosensors functionalized with antibodies for the detection of E. coli O157:H7 bacteria and T7 bacteriophage virus. There results signify that this type of nanobiosensors for pathogen (bacteria and viruses) detection are very sensitive and selective. Zelada-Guillen et al. (2009) reported a carboxylated CNT-modified GCE for the detection of the Salmonella Typhi bacteria. Further, Huang et al. (2011) designed a graphene-based field-effect transistor for the detection of *E. coli K12. Bacillus anthracis* (gram-positive bacterium) are toxic to humans and are used as an agent for bioterrorism. They produce the lethal toxin anthrax, made up of a protective agent that, on entering the host, causes death in no time (Dixon et al. 1999; Milne et al. 1994). Cella et al. (2010) reported a chemiresistive nanobiosensor with SWCNTs matrix for the detection of protective agent toxin using a single-stranded DNA aptamer (biorecognition molecule).

Lian et al. (2014) reported, DNA-wrapped metallic SWCNTs which was very novel for fabricating the electrochemical nanobiosensor for the detection of Pb^{2+} in water. The working mechanism of this sensor for Pb^{2+} detection is based on the wrapping of Pb^{2+} with negatively charged phosphate groups or to the bases of DNA (Oliveira et al. 2008; Liu et al. 2009). Thus, the testing of real samples from tap water and on-site testing of river water showed similarity with the results of AAS, which proves that these nanobiosensors are reliable and accurate.

Pesticides are widely used in agricultural practices to inhibit the growth of certain plants and animals, which in turn increases the yield of agricultural produces. They are also known as toxic pollutants, which are harmful to human health. The most used toxic substance in pesticides is organophosphates, which cause cholinergic dysfunction in humans and animals. Thus, rapid, cost-effective, and sensitive detection of organophosphate neurotoxins is very much needed to protect food supplies, water resources, etc., from getting contaminated by these toxins. For the detection of organophosphates, there are traditional techniques used in laboratories such as mass spectrometry and chromatography, which consume time and are costly (Sherma 1993). Enzyme-based biosensors using CNTs as transducers for highly selective, sensitive, and rapid detection of pesticides. This enzymatic biosensor can be used for direct detection by using the catalytic activity mechanism of organophosphorus hydrolase (Mulchandani et al. 2001) or by using the inhibitory activity mechanism of different enzymes found in pesticides such as butyrylcholinesterase, tyrosinase, and acetylcholinesterase (AChE) (Andreescu and Marty 2006; Tanimoto and Ferreira 2007). Du et al. (2007) reported a biosensor for rapid detection of triazophos (organophosphorus insecticide) using AChE. They have used multiwalled carbon nanotubes (MWCNTs)-chitosan composite as working electrodes. Joshi et al. (2006) reported highly sensitive and selective carbon nanotube-based amperometric enzyme electrode biosensors for the detection of V-type nerve agents.

11.4 Dendrimers-Based Nanobiosensors

Dendrimers are nanoscale-dimension structures that originate radially from the central core; they are man-made branched polymers and monodispersed macromolecules with star-like structures. In general, dendrimers have three components, namely central core, branches (interior structure), and exterior surface, with functional groups, as shown in Fig. 11.2 (Klajnert and Bryszewska 2001; Singh 2011a, b). Dendrimers have a variety of applications in the biomedical domain for in vitro diagnosis, gene therapy, regenerative medicine, therapeutics, and many more (Dufes et al. 2005; Oliveira et al. 2010; Singh 2007). The use of dendrimer-based nanobiosensors for environmental monitoring and analysis is very less explored and further research in this direction is required.

Castillo et al. (2015) reported a biosensor based on aptamer for the detection of aflatoxin B1 (AFB1); it is a mycotoxin which is a known food contaminant. They used cystamine dendrimer layers and compared with different immobilization platforms such as 11-mercaptoundecanoic acid (MUA), cystamine (Cys), and 11-mercaptoundecanoic acid-dendrimers. After the immobilization, they validated the nanobiosensor for real samples such as peanut extracts and peanut-corn snacks, and the result of the sensing response was very sensitive and selective toward the analyte. Singh et al. (2009) reported a new approach for the fabrication of nanobiosensors based on polyamidoamine (PAMAM) dendrimers (a fourth generation dendrimer) for the detection of explosive molecules like trinitrotoluene, and this type of sensors showed high sensitivity, stability, and reproducibility. Grabchev and Guittonneau (2006) synthesized poly(amidoamine) dendrimers of zero and second generation, which contain fluorescent 4-piperidino-1, 8-naphthalimide units inside their periphery; further, they have investigated these synthesized materials for the

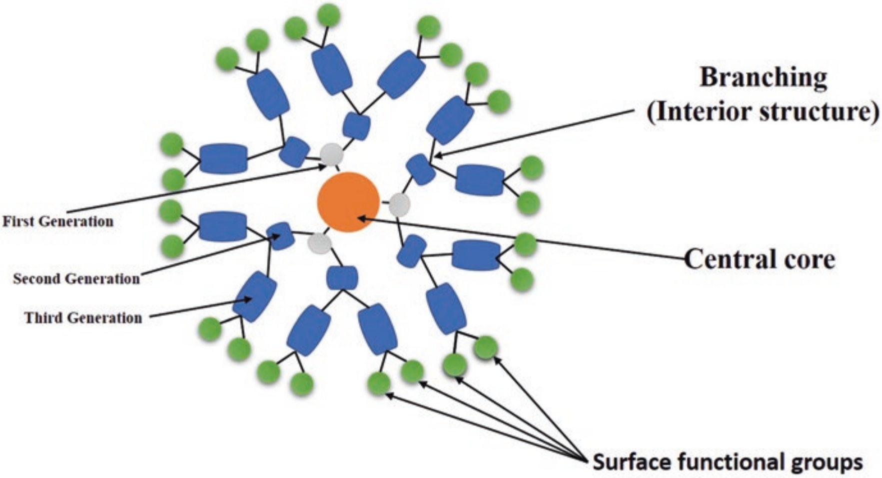

Fig. 11.2 Shows detailed structure of dendrimers

detection of metal cations and protons, and from their studies, they found that these materials are very sensitive and selective in the detection of environment-polluting metal cations and protons such as Zn^{2+}, Ni^{2+}, Ce^{3+}, Ag^{+}, Co^{2+}, and Cu^{2+} cations.

Snejdarkova et al. (2003) reported choline oxidase and AChE immobilized with PAMAM fourth generation dendrimer based biosensors for the detection of dimethyl-2,2-dichlorovinyl- phosphate, carbofuran, and eserine pesticides. From the results of this study, they found that this type of nanobiosensors have very low detection limits compared with the previously reported amperometric and potentiometric nanobiosensors based on AChE. Hence, keeping the above viewpoint dendrimer based nanobiosensors are highly sensitivity and stabel which make them a suitable candidate for the detection of environmental pollutants in real/field samples.

11.5 Liposomal Nanobiosensors

Liposomes are developed to study cell membranes; they are artificial spherical vesicles composed of a phospholipid bilayer surrounded by an aqueous cavity. These cavities can bear different molecules inside them due to which liposomes have unique application in diagnostics, therapeutics, and environmental monitoring. Other molecules can associate with liposomes in different ways such as encapsulation, covalent bonding, partitioning inside the lipid bilayer tails, and by electrostatic interaction. Marker attached on the surface of liposome with antibodies, DNA, or haptens can be used for the detection of environmental pollutants and further after lysing of liposomes, the marker is released (Ahn-Yoon et al. 2003; Edwards and Baeumner 2006).

Triazines are pesticide groups which have a wide range of applicability in the agriculture sector. This herbicide member in their family have many other derivative such as atrazine, terbuthylazine, etc. and is most commonly used in the USA and Europe. These compounds show moderate toxicity but can undergo further transformation and become more toxic, carcinogenic, and mutagenic. These are classified as environmental pollutants and can be found in the human food chain or in drinking water (Jones and de Voogt 1999; Baran et al. 2003). Thus, understanding the need for the detection of such moderately toxic compounds which can in future become more toxic, Baumner and Schmid (1998) reported a liposome-based amperometric sensor for the detection of triazine pesticides in aqueous samples. The developed sensor was disposable and was based on the competition between tagged pollutants and free pollutants.

The *Vibrio cholerae* bacteria secrets cholera toxin, which causes diarrhea, cramps, vomiting, and sometimes leads to death. When the cholera toxin binds to intestinal cells and infects the intestine, it triggers endocytosis of toxins. Hence, for the rapid and sensitive detection of the cholera toxin, Viswanathan et al. (2006) reported liposome carrying potassium ferrocyanide labelled with molecules that are highly specific to the analytes. These type of devices have applications for biomedical diagnostics and environmental monitoring of pollutants; can also be very much useful in controlling epidemic.

11.6 Metal and Metal Oxides–Based Nanobiosensors

Solanki et al. (2011) reported that nanostructured metal oxides (NMOs) are the future materials for the next generation of nano-sized biosensing (nanobiosensing) applications because they provide an effective surface for the immobilization of biomolecules. NMOs exhibit unique electrical, molecular, and optical properties; these properties provide the NMO-based biosensors with unique applications in the clinical, environmental, and agricultural fields (Singh 2019c, d).

Electrode surface adsorption capacity plays a very significant role in electrochemical activities (Wei et al. 2012; Zhao et al. 2012). Ferrite nanoparticles have super paramagnetic properties and high adsorption capacity; therefore, they have attracted a lot of attention (Xu et al. 2013). Iron (Fe^{3+}/Fe^{2+}) exhibits redox coupling that make them relevent for reduction of Arsenic (II) (As^{2+}) (Cepria et al. 2007; Guardia et al. 2012). Arsenic (As) can be removed from water using strong adsorption mechanisms of Fe_3O_4 monodispersed nanocrystals (Yavuz et al. 2006). Thus, ferrite nanoparticles have great potential for the electrochemical detection of heavy metal ions as well as inorganic As (Zhang et al. 2016). Wu et al. (2014)reported a nanobiosensor fabricated by electrodeposition of manganese oxides and gold nanoparticles on the glassy carbon electrode (GCE) for the detection of As (III) in alkaline solution by utilizing the cyclic voltammetry and this reported nanosensor was very selective and sensitive when examined in real samples. Dong et al. (2016) reported metal-organic frameworks (MOFs) based electrochemical sensor that was fabricated by utilizing 1,3,5-benzenetricarboxylic acid copper [$Cu_3(BTC)_2$]) on modified carbon paste electrode for the detection of 2,4-dichlorophenol (2,4-DCP) in real water samples and this type of nanobiosensors gave satisfactory results in the real time sensing of 2,4-DCP.. Thus, MOF-based sensors exhibit promising future applications for routine sensing of environmental contaminants/pollutants (Arora et al. 2006; Shukla et al. 2010; Singh et al. 2011b, c).

For the detection of Pb^{2+} in real samples of water, Zhao et al. (2016) synthesized gold nanoparticles-rGO as surface enhanced Raman scattering (SERS) substrates for sensitive and selective detection. Frost et al. (2015) reported functionalized gold nanoparticles from citrate for the ultrasensitive detection of Pb^{2+} based on SERS in aqueous conditions. Chen et al. (2014) reported SERS nanobiosensors based on Ag nanoparticles functionalized by 4-mercaptopyridine for the detection of Hg^{2+} in aqueous samples with the help of spermine, which binds with Ag nanoparticles by Ag-N bonds that result in Ag nanoparticle aggregation and this, in turn, provides enhanced Raman intensity and helps in the optical sensing of Hg^{2+} metal ions. Li et al. (2013) reported dye-coded Ag nanoparticle nanobiosensors based on SERS for the sensitive and selective detection of Cu^{2+} and Hg^{2+} heavy metal ions, which are major environment polluting agents.

11.7 Polymeric-Based Nanobiosensors

Polymer-based nanoparticles are large molecules ranging between 1 and 1000 nm (sub-micron range). They are colloidal particles with good encapsulation properties; due to this reason, they are excellent pharmaceutical ingredients. Nanotechnology is playing a crucial role in environmental analysis and monitoring (Singh et al. 2014). Polymer-based nanocomposites exhibit unique properties and have received great attention from industries and academia, as the properties of polymers offer the formed composite unique physical and chemical characteristics. The polymer nanocomposites have interesting and never-ending environmental applications for the detection of environmental pollutants (Zhao et al. 2011; Kreuter 2014). Guo and Chen (2005) reported iron oxyhydroxide nanoparticles on cellulose polymer matrix-based biosensors for the detection of As^{3+} and As^{5+} heavy metal ions in groundwater. Zouboulis and Katsoyiannis (2002) reported iron oxides-alginate beads-based biosensors for the detection and removal of arsenic.

Gas sensors are a type of sensors which can detect presence of gases; this type of sensors help in the continuous analysis and monitoring of different types of gases present in the environment, such as carbon monoxide, ethanol, acetone, trimethylamine, carbon dioxide, nitrogen, and methanol (Singh 2019b). Keeping the above viewpoint, Ram et al. (2005) reported an ultrathin conducting matrix of polystyrene (PSS) and polyaniline (PANI) polymers with metal oxide nanoparticles for the detection of carbon monoxide. Further, Geng et al. (2007) reported PANI-SnO_2-based biosensors prepared by using a hydrothermal method for the detection and control of ethanol and acetone fume. Zheng et al. (2008) synthesized titanium dioxide (TiO_2)-PANI using chemical polymerization and the sol-gel method for use as a biosensor for the detection of trimethylamine. Suri et al. (2002) investigated iron oxide-polypyrrole-based biosensors for the detection of Co_2, N_2, and CH_4. Athawale et al. (2006) further reported a biosensor based on Pd-PANI synthesized by using oxidative polymerization for the detection of methanol.

There are many other polymer-based nanobiosensors for the detection of heavy metal ions, humidity changes, industrial wastes, fecal matter (Singh 2017, 2019a). Sugunan et al. (2005) reported a nanobiosensor based on chitosan-Au for the detection of Zn^{2+} and Cu^{2+}. Su and Huang (2007) reported a synthesis of TiO_2-polypyrrole by in-situ photopolymerization for the detection of changes in humidity for proper monitoring and maintenance of environmental pollutants.

11.8 Conclusion

Nanotechnology has evolved very fast in the analysis and monitoring of the environment using nanoparticles, namely liposomes, dendrimers, metal, and metal oxide. These nanoparticles have a wide range of properties that offer them a wide range of applications in the environmental, biomedical, and agricultural fields. Talking

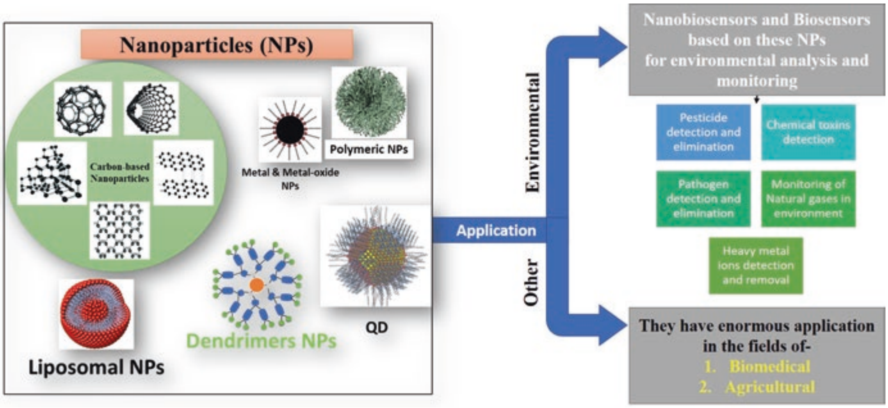

Fig. 11.3 Shows graphical description of the detail work

specifically in this book chapter, we have discussed the application of these nanoparticles in the environmental field for the analysis and monitoring of environmental pollutants, as depicted in Fig. 11.3.

Environmental pollution is the major cause of health issues in humans and animals, and it is also leading to global warming. The major environmental pollutants affect living things by different mediums, namely water, food, and air, as they are directly in contact with these mediums. Biosensors are widely used for the detection of environmental pollutants, which helps to better monitor and control environmental pollutants. But biosensors have evolved rapidly, and now nanoparticle-based biosensors are being used for these applications; these types of biosensors are called nanobiosensors. As nanobiosensors are more precise, sensitive, optimized, selective, rapid, and best suitable for on-site detection of pollutants (single compound/ class of compounds).

Hence, the use of these nanoparticles for making more suitable biosensors for solving the problems related to environmental analysis and monitoring is the future, which can help overcome this global challenge. This book chapter elaborates the current use of these nanoparticles in making nanobiosensors for analysis and monitoring the environment. There are many nanoparticles, namely polymer-based nanocomposites, and dendrimers-based, whose fabrication for the development of nanobiosensors with high selectivity, sensitivity, and cost-effectiveness is the hot topic and needs to be explored by researchers. Studies in this direction for developing a better nanobiosensor for environmental analysis and monitoring for the purpose of commercialization need to be carried out.

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Chapter 12
Nanosensors Based on Lipid Membranes for the Rapid Detection of Food Toxicants

Georgia-Paraskevi Nikoleli, Dimitrios P. Nikolelis, Christina G. Siontorou, Marianna-Thalia Nikolelis, Stephanos Karapetis, and Spyridoula Bratakou

Contents

Abstract The application of lipid film biosensor devices has created the opportunity to reconstitute a considerable part of their functionality to detect traces of food toxicants. Nanotechnology-enabled sensor miniaturization has extended the range of biological moieties that could be immobilized within a lipid bilayer device. This chapter reviews the recent progress in biosensor technologies for food-quality monitoring. A large number of applications are described herein, placing emphasis on size reduction of novel systems of lipid film devices, new sensing techniques, and nanotechnology-based transduction schemes. The range of analytes that can be

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currently detected include insecticides, pesticides, herbicides, toxins, hormones, dioxins, and genetically modified foods. Technology limitations and future prospects are discussed, with a focus on the commercialization capabilities of the proposed sensors.

Keywords Nanosensors · Enzyme-based systems · Antibody-based systems · Receptor-based systems · Food analysis · Nanotechnology

12.1 Introduction

A biosensor is a device that transforms chemical information into an analytically useful signal. Biosensors have two components: a biological recognition element (“receptor”, enzyme, antibody, natural receptor, cell, etc.) and a physical transducer. The recognition system provides the chemical information (i.e., concentration of the analyte) as a physical output signal. The physical transducer transfers the signal to an electrical, optical, or piezoelectric output, among others; the biological recognition element is in direct contact with a transduction element. Biosensors have made a large impact in the area of food applications and provide many advantages as compared to standard analytical techniques (i.e., chromatographic) such as miniaturization, no sample preparation, real-time detection, rapid response times, portability, high sensitivity, and selectivity.

Recent progress in nanotechnology has created the opportunity to mass-produce affordable devices and to integrate these into systems for market applications for the detection and monitoring of food toxicants. These applications include a wide range of food toxicants such as toxins, insecticides, pesticides, herbicides, viruses and other microorganisms, dioxins and polycyclic aromatic hydrocarbons (PAHs), hydrazines, and hormones.

Lipids are amphiphilic molecules, which possess both hydrophilic head groups and hydrophobic chains. Since the discovery of model bilayer lipid membranes (BLM) by Mueller et al. (Mueller et al. 1962), there have been various attempts to use lipid films to construct biosensing devices for applications to detect and monitor food toxicants. However, free-standing BLMs were very fragile and, therefore, not suitable for long-term use. They had low mechanical and electrical stability, which was the main obstacle to their practical application. The recent advances in the construction of stabilized lipid film devices have created the opportunity to prepare devices to detect a large diversion of food toxicants in real samples. Lipid-membrane-based biosensors represent an appropriate biocompatible structure with fast response times (on the order of a few seconds) and high sensitivity (i.e., nanomolar detection limits) and selectivity, small size, and offers many advantages compared with the bulky analytical instrumentation such as liquid chromatographic units. Most of these biosensors are cost efficient, easy to use, fast responding portability, and are good alternative to the expensive, bulky, time-consuming standard analytical methods (i.e., chromatographic techniques). The new generation of lipid membrane nanosensors has improved analytical performance and operational stability.

This work reviews the construction of stabilized lipid film nanosensors that are used to detect food toxicants and facilitate state-of-the-art design and microfabrication of prototype lipid membrane nanosensing devices: for rapid, in-the-field detection of food toxicants and the challenges that lie ahead. It also describes a wide range of applications of lipid-film-based biosensors in food analysis for the rapid detection of urea, cholesterol, glycose, cholera toxin, aflatoxins, naphthalenic acid, dioxins, etc.

12.2 Methods for Construction of Nanosensors Based on Lipid Membranes

A large number of methods were reported in the literature in the last two decades for the construction of stabilized lipid films that are not prone to electrical or mechanical breakage and provide devices that can be used for practical applications. Most of these methods provide lipid membranes with a size less than 1 μm and, therefore, can be considered nanosensors. These biosensors have been used for electrochemical experimentation and belong, therefore, in electrochemical devices. An exception is the development of stabilized polymerized lipid films on a filter paper that switch on and off their fluorescence and therefore belong to optical biosensors. Below we provide the various techniques for the preparation of nanosensors based on lipid membranes.

12.2.1 Metal-Supported Lipid Layers

A simple system for the preparation of a self-assembled lipid bilayer membrane (sBLM) at the freshly cut tip of a Teflon-coated metallic wire was reported by Tien and Salamon (Tien and Salamon 1989). The technique of formation of sBLMs is based on the interaction of an amphiphatic lipid molecule with a nascent metallic surface. One end of a Teflon-coated stainless steel metal wire (with diameter of 0.1–0.5 mm) was immersed in a lipid solution in chloroform and then, while still immersed, the tip is cut off with a miniature guillotine. Then, the fresh tip of the wire becomes coated with the lipid membrane and was placed in the electrolyte (usually 0.1 M KCl), whereupon the lipid film spontaneously thinned, forming a self-assembled lipid bilayer membrane (sBLM). A schematic of the sensor, measurement setup, and lipid self-assembly process is shown in Fig. 12.1.

sBLMs have been fully characterized (Tien and Salamon 1989; Nikolelis et al. 1996; Siontorou et al. 1997a). The diameter and composition of the wires that were used were found to have an important role in the time taken for device stabilization

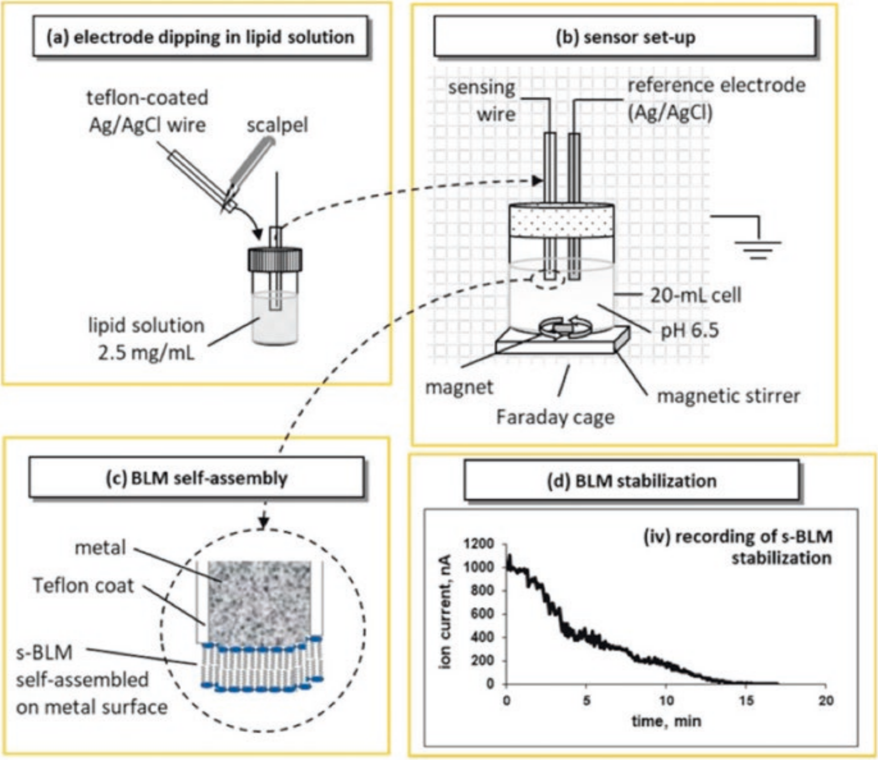

Fig. 12.1 Schematic of the sensor, measurement setup, and lipid self-assembly process (not drawn to scale): (**a**) the sensing electrode is tipped with a scalpel and immediately immersed in the lipid solution before being dipped in the electrolyte solution. (**b**) The electrochemical setup consists of a 20-mL cell and a two-electrode configuration, that is, the sensing electrode and a Ag/AgCl reference electrode, placed in a grounded Faraday cage; an external DC potential of 25 mV is applied between the electrodes and the ionic current through the BLM is measured with a digital electrometer; the cell is stirred using a magnetic stirrer. (**c**) Upon immersion, the lipid droplet attached to the wire is self-assembled into a bilayer that has one layer adsorbed on the metal surface and the other facing the aqueous solution. (**d**) Recording of the ion current decreases during the self-assembly process; recording started at the immersion of the sensing electrode in the electrolyte solution [Reprinted from Nikoleli et al. 2018)

and on the magnitude and noise of the background ion current (Nikolelis et al. 1996; Siontorou et al. 1997a). The use of a wire of 0.25 mm diameter and decane as a solvent should be avoided because the lipid films are so-called “black lipid membrane” and these films do not provide reproducible results. Silver wires of 0.5 and 1.0 mm diameter provide BLMs which were mechanically and electrical stable for more than 48 hours.

12.2.2 Stabilized Lipid Films on a Glass Fiber Filter

The construction of stabilized lipid membranes on ultrafiltration glass fiber filters has been provided in the literature (Nikolelis et al. 1995). These stabilized lipid membranes on glass fiber filters have allowed for their practical application in real samples, for example, for the determination of aflatoxin M_1 in milk and milk preparations (Andreou and Nikolelis 1998). The lipid membrane is formed on a microporous filter glass fiber disk (Nikolelis et al. 1995; Andreou and Nikolelis 1998). The filters and (nominal) pore size used were GF/F glass microfiber, 0.7 μm (Whatman Scientific Ltd., Kent, U.K.).

The experimental setup which is used for the construction of stabilized BLMs consists of two Plexiglas chambers which are separated by a Saran-Wrap partition (thickness of ca. 10 μm) (Nikolelis et al. 1995; Andreou and Nikolelis 1998). This plastic partition was cut to more than twice the size of the contact area of the surfaces of the chambers and was folded in half; then, a hole having a diameter of 0.32 mm was punched through the double layer of the plastic film with a perforation tool. A microporous glass GF/F microfiber disk with a diameter of 0.9 cm and nominal pore size of 0.7 μm is placed between the two plastic layers. The partition containing the ultrafiltration glass fiber was then clamped between the two Plexiglas chambers. One of the chambers consisting an electrochemical cell had a circular shape of diameter 1.0 cm and depth 0.5 cm; this chamber was connected with plastic tubing which was used for the flow of the carrier solution. An Ag/AgCl reference electrode was immersed in the waste of the carrier electrolyte solution. The second chamber was cylindrical and had its longitudinal axis perpendicular to the flow of the carrier solution. The upper hole of this cell was circular with a surface area of about 0.2 cm^2 and the lower was elliptical with diameters 0.5 and 1.4 cm parallel and vertical to the flow of the carrier electrolyte solution, respectively. The lower hole was facing the opposing cell. An Ag/AgCl reference electrode was positioned at the center of the cylindrical cell. An external voltage of 25 mV d.c. is applied between the two reference electrodes. A Keithley digital electrometer is used as a current-to-voltage converter. A peristaltic pump is used for the flow of the carrier electrolyte. Injections of the samples are made with a Hamilton repeating dispenser. The electrochemical cell and electronic equipment were isolated in a grounded Faraday cage. A simple scheme of the apparatus used is presented in Fig. 12.2. The procedure for the formation of the stabilized BLMs is as follows: (Nikolelis et al. 1995; Andreou and Nikolelis 1998): Lipid solution (ca. 10 μL) is put dropwise with a microliter syringe to the water/air interface in the cylindrical cell near the partition. The level of the electrolyte solution is dropped below the 0.32 mm hole and then raised again. The formation of the bilayer structure of the lipid membranes has to be verified by the ion current magnitude and by the electrochemical characterization using gramicidin D. This peptide has the size of a bilayer and is able to cross through only in a layer having the bilayer structure.

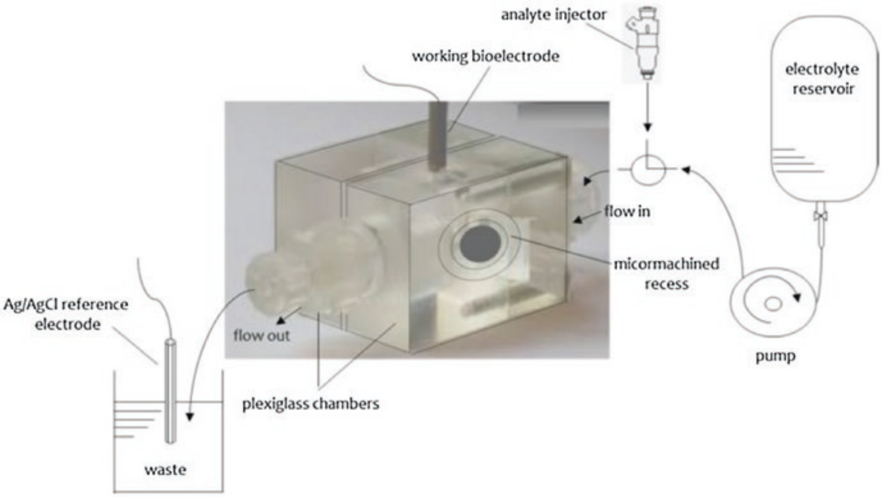

Fig. 12.2 Schematic of the experimental setup; the micromachined chambers are separated by a thin (12.5 μm thick) polyvinylidene chloride wrap and enclose the microfiber disk. For more details, see text (From Nikoleli et al. 2018)

12.2.3 Polymer-Supported Bilayer Lipid Membranes

The preparation of polymer stabilized was recently reported in the literature. These lipid-membrane-based nanosensors were constructed by using UV irradiation instead of heating the lipid mixture to 60 °C (Nikolelis et al. 2006, 2008a) Thus, this process retains the activity of a “receptor” (enzyme, antibody, ion-channel receptor), whereas heating to 60 °C can deactivate an enzyme or antibody or a receptor. The results have shown that the polymerization is completed within 4 hours; physicochemical methods such as DSC, IR, or Raman spectrophotometry were used to exploit the polymerization time. The preparation of these devices makes possible the practical use of biosensors based on lipid membranes for chemical sensing, because it allows for the incorporation of a “receptor” molecule in these lipid films and, more importantly, these devices are stable in the air for more than 48 h.

The preparation of these stabilized lipid films is as follows (Nikolelis et al. 2006, 2008a): Briefly, 0.8 mL of a mixture containing 4% w/v egg phosphatidylcholine (PC) in n-hexane (this solvent evaporates so that these films do not retain the solvent in their structure) were mixed with 0.07 mL of methacrylic acid, 0.8 mL of ethylene glycol dimethacrylate, 8 mg of 2,2′-azobis-(2-methylpropionitrile), and 1.0 mL of acetonitrile. The mixture was sparged with nitrogen for about 1 min and sonicated for 30 min. For the preparation of the stabilized lipid films, 0.15 mL of this mixture was spread on a microfilter (microporous glass GF/F microfiber disk with a diameter of ca. 0.9 cm and nominal pore size of 0.7 μm). The filter with the mixture was then irradiated using a UV deuterium lamp. Raman spectrometry and differential scanning calorimetry (DSC) were used to monitor the kinetics of the polymerization process. The measuring setup was similar to that presented in Fig. 12.2. These membranes were stable in storage in air for repetitive use.

12.2.4 Polymer Lipid Films Supported on Graphene Microelectrodes

Graphene nanomaterials have received tremendous interest in the field of basic research and in technological applications due to their unique physicochemical properties, that is, good sensing ability, and excellent mechanical, thermal and electrical properties; other advantages include large surface-to-volume ratio, excellent biocompatibility, high electron-transfer rates, non-toxicity, and bio-safety. The development of nanosensors based on graphene microelectrodes is an interesting application of this field of nanotechnology. Their implementation in electrochemical biosensing is quite beneficial as it allows for miniaturization, increases the speed of response, decreases the detection limits, and solves the biocompatibility and biofouling problems. Several examples in the development of nanobiosensors by integrating enzymes and antibodies were recently described in literature. Stabilized lipid films were wrapped around a copper wire containing graphene nanosheets (Nikoleli et al. 2012; Bratakou et al. 2015). These nanosensors have been implemented in the rapid detection of food toxicants in real samples, such insecticides (Bratakou et al. 2015), naphthalene acetic acid (Bratakou et al. 2016), cholera toxin (Karapetis et al. 2016), and saxitoxin (Bratakou et al. 2017).

The preparation of graphene microelectrodes was as follows (Nikoleli et al. 2012; Bratakou et al. 2015, 2016, 2017; Karapetis et al. 2016): A homogeneous graphene dispersion (~0.4 mg/mL) has been obtained in *N*-methyl-pyrrolidone (NMP) through mild sonication for 180 hours and centrifugation at 700 rpm for 2 h. This suspension has been poured onto a copper wire ($d = 0.25$ mm) mounted on a glass fiber filter and evaporation of the organic solvent has been carried out using a fan heater. This copper wire has been used to establish the connection for the extraction of voltage signals for the calibration curve. Thus, a simplistic approach of dropwise dispersion of graphene suspended in NMP solution has been used to scatter the graphene nanosheets on the copper wire. The extended sonication time results in a good fraction of monolayer sheets but with smaller lateral sizes.

The procedure of construction of these devices is in brief as follows (Nikoleli et al. 2012; Bratakou et al. 2015, 2016, 2017; Karapetis et al. 2016): Stabilized lipid films were prepared by polymerization with a procedure similar to that previously described (Nikolelis et al. 2006; 2008a). Briefly, 0.15 mL of a mixture containing 5 mg of a mixed lipid powder composed of 35 (w/w) DPPA and 65 (w/w) of DPPC (1.75 mg DPPA and 3.25 mg DPPC) was mixed with 0.070 mL of methacrylic acid, 0.8 mL of ethylene glycol dimethacrylate, 8 mg of 2,2′-azobis-(2-methylpropionitrile), and 1.0 mL of acetonitrile. DPPC is used as lipid and not PC, which can be oxidized by air and does not provide reproducible results. The mixture was spumed with nitrogen for about 1 min and sonicated for 30 min. This mixture could be stored in the refrigerator. For the preparation of the stabilized lipid films, 0.15 mL of this mixture was spread on the glass filer microfilter. The filter with the mixture was then irradiated using a UV deuterium lamp. Raman spectrometry was used to monitor the kinetics of the polymerization process (Nikolelis et al. 2006; Nikolelis et al. 2008a).

The enzyme, antibody or receptor ("receptor") were incorporated in these BLMs before polymerization by spreading 15 μL of the "receptor" suspension with the polymerization mixture (i.e., for the preparation of the stabilized lipid films, 0.15 mL of the polymerization mixture and 15 μL of "receptor" suspension were spread on the microfilter). The preparation of the potentiometric biosensor has been finalized by encapsulating the filter-supported polymerized lipid film onto the copper wire containing graphene nanosheets.

12.3 Applications of Lipid-Film-Based Nanosensors for the Rapid Detection of Food Toxicants

A work was described for the rapid and sensitive electrochemical flow injection monitoring of aflatoxin M1(AFM1) in cheese samples (Andreou and Nikolelis 1998). Stabilized filter-supported bilayer lipid membranes (BLMs) were used as detectors. Single-stranded DNA oligomers terminated with alkyl chains (dT20-C16) were incorporated into the membranes to control surface electrostatic properties. The incorporation of dT20-C16in BLMs lowered the detection limit for the detection of this toxin by one to four orders of magnitude as compared with the detection limit obtained in the absence of DNA. Therefore, it is now possible to continuously monitor this toxin at concentrations that approached those that could be of interest as set by the U.S. Food and Drug Administration and most European countries. The work that was described takes a significant step toward the development of a detector of greater practical potential by demonstrating that the incorporation of C16ssDNA into lipid membranes results in a combination of properties that provides for a much more sensitive and robust detection system. Injections of AFM1 were made into flowing streams of a 0.1 M KC1 electrolyte solution, and a transient current signal with duration of seconds reproducibly appeared in about 12 s after exposure of the detector element to the toxin. The magnitude of this signal was linearly related to the concentration of AFM1 with detection limits at subnanomolar level. The effect of interferents such as proteins and lipids was investigated. It was determined that interferences from proteins could be eliminated by adjustment of the {low rate of the carrier electrolyte solution. The technique was applied for the rapid flow injection determination of aflatoxin MI in cheese samples. AFM1 could be determined in continuous flowing systems with a rate of at least 4 samples min^{-1}. Repetitive cycles of injection of AFM1 have shown no weakning of signal upto 30 cycles of detection.

A work that was reported in the literature describes a technique for the rapid and sensitive electrochemical flow injection monitoring and analysis of mixtures of the artificial sweeteners acesulfame-K, cyclamate, and saccharin using stabilized systems of filter-supported bilayer lipid membranes (BLMs) (Nikolelis and Pantoulias 2001). Injections of artificial sweeteners were made into flowing streams of a carrier electrolyte solution, and a transient current signal with duration of seconds reproducibly appeared in <1 min after exposure of the lipid membranes to the artificial sweeteners. The magnitude of this signal was linearly related to the concentration of artificial sweeteners, which could be determined at micromolar levels. Repetitive cycles of injection of artificial sweeteners have shown no signal degradation during each cycle (30 sequential injections). The time of appearance of the transient response was different for each artificial sweetener and increased in the order of cyclamic acid, acesulfame-K, and saccharin. The difference in time of response has allowed selective detection and analysis of these artificial sweeteners in mixtures. The effect of potent interferences, including a wide range of compounds usually found in foods, proteins, and lipids, was investigated. The results showed no interferences from these constituents of real food samples. The major interference from proteins (most common in lipid-film-based biosensors) can be eliminated by modulation of the carrier solution that does not allow adsorption of these compounds in BLMs. The technique was applied in real food samples, that is, in artificial sweetener tablets, diet soft drinks, wines, and yogurts that contain mixtures of these artificial sweeteners with aspartame and other compounds. A comparison of results using the present method and that of an official method of analysis showed good agreement between the two methods.

A work was reported for the rapid detection of vanillin in alcoholic beverages using stabilized lipid-membrane-based biosensors (Nikolelis and Theoharis 2002). Microporous filters composed of glass fibers (nominal pore sizes 0.7 and 1.0 μm) were used as supports for the polymerization of the lipid film and stabilization of these devices. The lipid film is formed on the filter by polymerization before its use. Methacrylic acid was the functional monomer, ethylene glycol dimethacrylate was the crosslinker, and 2,2′-azobis-(2-methylpropionitrile) was the initiator. The response toward vanillin of the present stabilized lipid membrane biosensors composed of phosphatidylcholine was investigated. The stabilized lipid membranes provided artificial ion-gating events in the form of transient signals and can be used again after storage in air. This has allowed for the practical use of the technique for chemical sensing based on lipid films for the rapid detection of vanillin in wines and alcoholic beverages.

The stabilized supported on glass fiber lipid film nanosensors were used for the flow injection analysis (FIA) of pesticides (Nikolelis et al. 2005). Carbofuran was chosen as a typical pesticide. The determination of this pesticide is based on the degree of inhibition and the reactivation of enzyme by injections of substrate. Carbofuran was determined at concentration levels of 10^{-7} to 10^{-9} M. The investigation of the effect of interferences included compounds usually found in foods, proteins, and lipids. The results have shown no interferences from these compounds. The technique was applied to fruits, vegetables, and dairy samples. The recovery rate ranged between 96 and 106%, which confirms there is no interferences due to matrix effects.

A paper was reported in the literature using a synthetic “receptor” immobilized on supported lipid films on glass fiber filters (Nikolelis et al. 2008b). The supported lipid films were modified by calixarenes and permitted sensitive and rapid determination of insecticides in fruits and vegetables (Nikoleli et al. 2013).

A potentiometric urea lipid-film-based minisensor on graphene nanosheets in which a polymeric lipid membrane was deposited has been recently reported in the literature [10]. The structural characteristics of graphene nanosheets have been studied through atomic force microscopy (AFM) and transmission electron microscopy (TEM) measurements. UV-Vis and Fourier transform IR (FTIR) spectroscopy have been used to study the pre- and postconjugated surfaces of graphene nanosheets. The presented potentiometric urea biosensor shows good reproducibility, reusability, selectivity, fast response times (~4 s), long shelf life, and high sensitivity with a slope of ca. 70 mV/decade over the urea logarithmic concentration range from 1×10^{-6} M to 1×10^{-3} M.

A novel potentiometric cholesterol biosensor has been fabricated by immobilizing the stabilized polymeric lipid membrane onto a graphene electrode (Nikoleli et al. 2013). The stabilized polymeric lipid membrane is composed of a cholesterol oxidase enzyme and polymerization mixture, which holds paramount influence in the properties of the cholesterol biosensor. The presented biosensor reveals appreciable reproducibility, good selectivity, and high sensing capability having a linear slope curve of ~64 mV per decade. The strong biocompatibility among stabilized polymeric lipid membranes and human biofluids offers the possibility to use for real blood samples and other biological applications.

The electrochemical interactions of naphthalene acetic acid (NAA) with stabilized lipid films supported on a methacrylate polymer on a glass fiber filter with incorporated auxin-binding protein 1 receptor were exploited to develop a nanosensor for the rapid determination of NAA in fruits and vegetables (Nikolelis et al. 2008c). An FIA technique was used; NAA was injected into the flowing streams of a carrier electrolyte solution, the flow of the electrolyte solution stops and an ion current transient was obtained, the peak height of which was correlated to the hormone concentration (with μM detection limits). The response times were rapid (on the order of 5 min). The effect of interferences included a wide range of compounds. The results showed no interferences from these compounds in concentration levels usually found in real samples. The method was applied for the determination of NAA in fruits, and vegetables and the reproducibility of the method was satisfactory. Thus, a quantitative method for the detection of NAA in fruits and vegetables that can be complimentary to HPLC methods was attained.

A potentiometric carbofuran minisensor on graphene nanosheets with incorporated lipid membranes has been described in the literature (Bratakou et al. 2015). The graphene electrode was used to develop a selective and sensitive chemical sensor for the detection of carbofuran by incorporating an artificial selective receptor (resorcin[4]arene receptor) on stable lipid films. This chemical nanosensor can detect carbofuran concentrations at nM concentration range, with rapid response times of ca. 20 s, is easy to construct, and exhibits good reproducibility, reusability, selectivity, long shelf life, and a high electrode slope of ca. 59 mV/decade over the carbofuran logarithmic concentration range from 10^{-6} to 10^{-3} M.

A work that describes a method for the rapid and sensitive electrochemical flow injection monitoring (FIA) and analysis of mixtures of the triazine herbicides simazine, atrazine, and propazine using stabilized systems of filter-supported BLMs consisted of egg PC and DPPA has been described in the literature (Nikolelis and Siontorou 1996; Siontorou et al. 1997b). Injections of these herbicides were made into flowing streams of a carrier electrolyte solution, and a transient current signal with a duration of seconds reproducibly appeared in less than 2 min after exposure of the lipid membranes to the herbicides. The magnitude of the peak was linearly related to the concentration of the herbicide, which could be determined at the μM range. Repetitive cycles of injection of herbicides have shown no signal degradation during each cycle. The time of appearance of the transient signal was different for each triazine and increased to the order of simazine, atrazine, and propazine, which has allowed selective detection and analysis of these triazines in mixtures.

A paper appeared in the literature that describes the investigations of electrochemical interactions of cholera toxin with stabilized lipid films on a polymer over a glass fiber Whatman GF/F filter with incorporated ganglioside GM1; this has led to the development of a minisensor for cholera toxin (Karapetis et al. 2016). The analyte was injected into the flowing streams of a carrier electrolyte solution. The flow of the solution stopped for 5 min and an ion current transient was obtained; the peak height of this transient was correlated to the cholera toxin concentration and had detection limits of 0.06 μM.

A potentiometric cholera toxin minisensor on graphene nanosheets with incorporated lipid films has been described in the literature (Nikoleli et al. 2011). Ganglioside GM1 (a natural cholera toxin receptor) was incorporated on stabilized lipid films on graphene electrodes, providing adequate selectivity for the detection of cholera toxin over a wide range of concentrations, rapid response time of ca. 5 min, and detection limits of 1 nM. The proposed sensor is easy to construct and exhibits good reproducibility, reusability, selectivity, long shelf life, and a slope of ca. 60 mV/decade of toxin concentration. The method was evaluated, implemented, and validated in lake water samples. This novel ultrathin film technology is currently adapted to the rapid detection of other toxins and could be used as a weapon against bioterrorism.

A potentiometric saxitoxin minisensor based on graphene nanosheets with incorporated lipid films and immobilized anti-STX (which is the natural saxitoxin receptor) on stabilized lipid films was recently reported in the literature (Bratakou et al. 2017). A good selectivity and sensitivity for the detection of saxitoxin, fast response times of ca. 5–20 min, and detection limits of 1 nM were observed. The proposed minisensor is easy to construct and exhibits good reproducibility, reusability, selectivity, long shelf life, and a slope of ca. 60 mV/decade over saxitoxin concentration. The method was evaluated and validated in lake water and shellfish samples. This novel ultrathin film technology is currently adapted to the rapid detection of other toxins that could be used as weapons against bioterrorism.

12.4 Conclusions and Future Prospects

The present paper describes the various routes for the preparation of nanosensors based on a lipid film technology for environmental analytical applications. Recent technological advances include the construction of stabilized supported lipid films on graphene nanoelectrodes with an incorporated “receptor” (enzyme, antibody, or natural or artificial receptor) stable in air that can be portable for in-the-field applications. These sensors reveal detection limits in the nanomolar range. The most important aspect of the present efforts is to provide a commercial portable unit that can be used for in-field and market applications.

The results have shown that a diversity of lipid film-based nanosensors can be reused after storage in air even after a period of a couple of months, and can be reproducibly fabricated with simplicity and low cost. These nanosensors have rapid response times, are easy to construct, and have a lower cost than those based on chromatographic techniques and can be used as rapid portable detectors complimentary to these methods for in-field and market measurements in food and for environmental monitoring.

Recently advanced lithography will enable the fabrication of nanopores and the insertion of nanoparticles in thin membranes where artificial bilayers can be assembled. This process accommodates a wide range of lipid composition in stable form, with the inclusion of membrane proteins. Therefore, the application of nanotechnology to this field of lipid film technology will allow miniaturization and will result in mass production of sensors. Producing the smaller patterns will enable sensors to respond faster, with a higher degree of sensitivity, and at lower production costs. Development of sensors using the present technologies will offer improved sensitivity for detection with high specificity at the molecular level, with an increment of several order of magnitude over currently available techniques with a large number of applications in environmental monitoring.

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Index

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