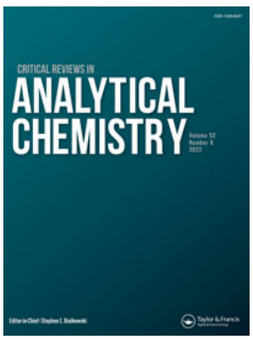

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REVIEW ARTICLE

Progress in Nanomaterials-Based Enzyme and Aptamer Biosensor for the Detection of Organophosphorus Pesticides

Xin Tan, Chundi Yu, Juan Tang, Wei Wu, Qingli Yang, and Xiudan Hou

College of Food Science and Engineering, Qingdao Agricultural University, Qingdao, Shandong Province, China

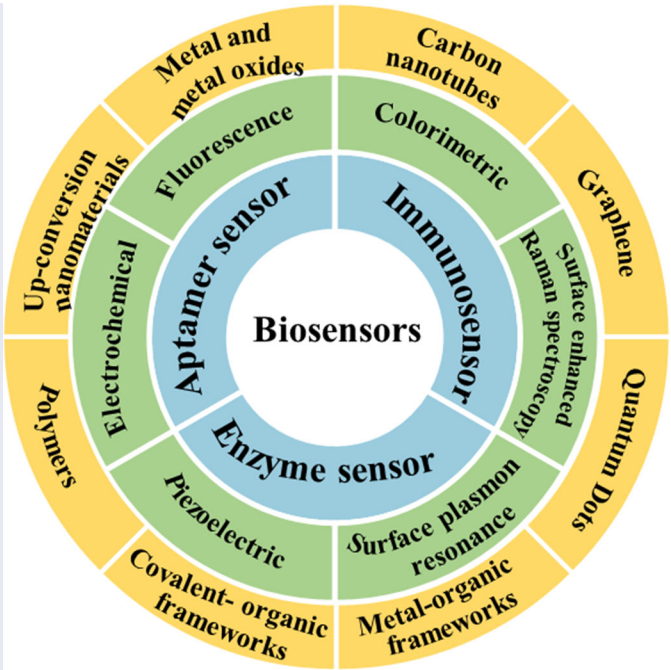
ABSTRACT

With the improvement of people's safety awareness, the requirement of pesticide detection is gradually increasing, and many new detection methods toward Organophosphorus pesticide (OPs) has been further developed and applied. Nanomaterials-based biosensors have played an important role in the trace detection of OPs. This article mainly introduces the detection principle of enzymes and aptamers as the identification element of biosensors. Various nanomaterials (i.e., metals and metal oxides, carbon nanotubes, graphene and graphene oxide, quantum dots, metal organic frameworks, molecular imprinted polymers, etc.) possess their unique properties and play different roles in the enzyme and aptamer-based biosensors toward OPs: (a) to produce the optical or electrochemical signal; (b) as a carrier to load the enzyme or aptamer; (c) to enhance the signal response. Besides, the intelligent portable devices provide the possibility to realize the onsite and real-time detection. The limitations of some nanomaterials and the future development are discussed. Finally, the future of enzyme and aptamer-based biosensors has prospected.

KEYWORDS

Enzyme and aptamer-based biosensors; nanomaterials; organophosphorus pesticides; food safe

GRAPHICAL ABSTRACT



Different types of biosensors for the detection of OPs

1. Introduction

With the development of agricultural industry, the harm of pests and weeds has become increasingly apparent, and thus pesticides are widely used for the prevention. Organophosphate pesticides (OPs), as one of agricultural chemicals with the phosphorus element, are widely used in

CONTACT Xiudan Hou qdxdhou@qau.edu.cn College of Food Science and Engineering, Qingdao Agricultural University, Qingdao, Shandong Province 266109, China;;Qingli Yang rice407@163.com College of Food Science and Engineering, Qingdao Agricultural University, Qingdao, Shandong Province 266109, China

Table 1. Advantages and disadvantages of biosensors on the basis of the signal transduction for OPs detection.

Classification by signal transduction	Biosensors	Advantages	Disadvantages
Optical	Fluorescence	Rapid detection, simple operation	Poor selectivity, high background, quickly chemical degradation
	Colorimetric	Visual inspection, conversion, fast, portable	Low sensitivity and poor stability
	Surface enhanced Raman spectroscopy	Higher selectively, good sensitivity, fast detection	Not portable, high cost, limited practical application
	Surface plasmon resonance	Automatic, high throughput, fast and simple	Expensive equipment, poor recycling and portability
Electrochemical	Electrochemical	Signal stability, simple instrument	Multiple methods are needed, analysis by specially assigned person
Semiconductor	Piezoelectric	Simple, fast, controlled	Long detection time and less practical application

the cultivation of crops.[1,2] They are used to protect crops and plants from plant diseases, pests, grass damage to improve the yield of crops. However, excess OPs would remain in vegetables and fruits to cause the the food safety problem, and also seep into soil and water to cause the environmental pollution. Therefore, more and more attention has been paid on the detection and regulation of OPs. Nowadays, more than 150 kinds of OPs are applied in agriculture, which are generally divided into three categories: (1) extremely toxic OPs, i.e., phorate, parathion, omethoate, methyl parathion, etc.; (2) highly toxic OPs, i.e., dimethylthiophos, dichlorvos, dimethoate etc.; (3) low toxic OPs, i.e., trichlorfon, chlorothion, malathion, etc.[3–5] OPs are an inhibitor of acetylcholinesterase (AChE), and the lack of AChE in human body would cause the nerve excitation and acute poisoning to bring a whole range of symptoms, such as sweating, shaking, unconsciousness and death. Therefore, it is necessary to establish highly selective, reliable and efficient detection methods to monitor and prevent the damage of OPs. Traditional detection methods mainly focus on the chromatography techniques including gas chromatography,[6] high-performance liquid chromatography,[7] liquid chromatography coupled with mass spectrometer/mass spectrometer, gas chromatography coupled with mass spectrometer/mass spectrometer[8] and capillary electrophoresis. However, there are many disadvantages of above detection methods, which include the complex operation, tedious pretreatment, long detection time, high cost in the chromatographic detection. Besides, other detection methods such as molecular imprinting[9] method, enzyme-linked immunosorbent assay (ELISA), are also used in the detection of OPs due to the high sensitivity, but they also have some limitations of the complex sample processing and lack of remote sensing ability.

Biosensors, as a popular detection method, have advantages of high sensitivity, low limit of detection, simple operation, small equipment, fast detection and good recovery. They are mainly composed of two steps: biorecognition and signal analysis. The biorecognition is mainly relied on the antibody, enzyme, DNA, and aptamer. On the basis of different signal transduction, biosensors are segmented to various types including optical sensors (i.e., fluorescence, colorimetric surface-enhanced Raman spectroscopy, surface plasma resonance etc.), electrochemical sensors (i.e., potentiometric, amperometric, conductivity sensor, etc.), semiconductor sensors, and calorimetric sensors (i.e., thermal resistive, magnetic conductivity, potential piezoelectric sensors).[10–14] The design of these biosensors is generally based on physical and chemical properties of the conductive medium. The signal between analytes and biorecognition element can be converted into other easily detected and quantified signal, such as optical signal, electrical signal, etc. Table 1 summarized the advantages and disadvantages of various biosensors.

The recognition element would determine the specificity of biosensor through the biological qualitative recognition. The sensitivity and response speed were affected by the affinity between the recognition element and analyte, and the precision of transducer and detection instrument. On the basis of the recognition element, the biosensors can be divided into different types, which include immunosensor, enzyme-based biosensor, aptamer-based biosensor, microbiosensor, cell-based biosensor. Enzyme-based biosensor was used to detect the target analytes due to its catalytic effect on the corresponding substrate, which further caused chemical reaction or potential change.[10] Aptamer-based biosensor was according to the specific recognition with the target analyte, being similar to antigen and antibody.[15] In order to improve the sensitivity of these detected methods, environmental-friendly materials were highly desirable for the construction of homogeneous sensing platform.

Nanomaterials have attracted tremendous interest in the biosensor due to their diversity and specific properties for versatile applications. Nanomaterials have good biological functionalization, and enzyme and aptamer can be immobilized on their surface or interior through the noncovalent bonding of electrostatic, π–π and hydrogen-bonding interactions.[16–18] The streptavidin–biotin interaction would also facilitate the fabrication of multifunctional superstructures. Besides, the covalent-bonding interaction is also the frequently-used assembly method, which has the advantages of good stability and repeatable modification. The introduction of nanomaterials would greatly amplify the response signal of enzyme- and aptamer-based biosensor to improve the sensitivity. Nanomaterials have many advantages of small size, large specific surface area to realize the more sensitive detection, which are one of the researching hotspots in the construction of biosensors.[19] The main biosensors, detection methods and classification of nanomaterials are shown in Figure 1.

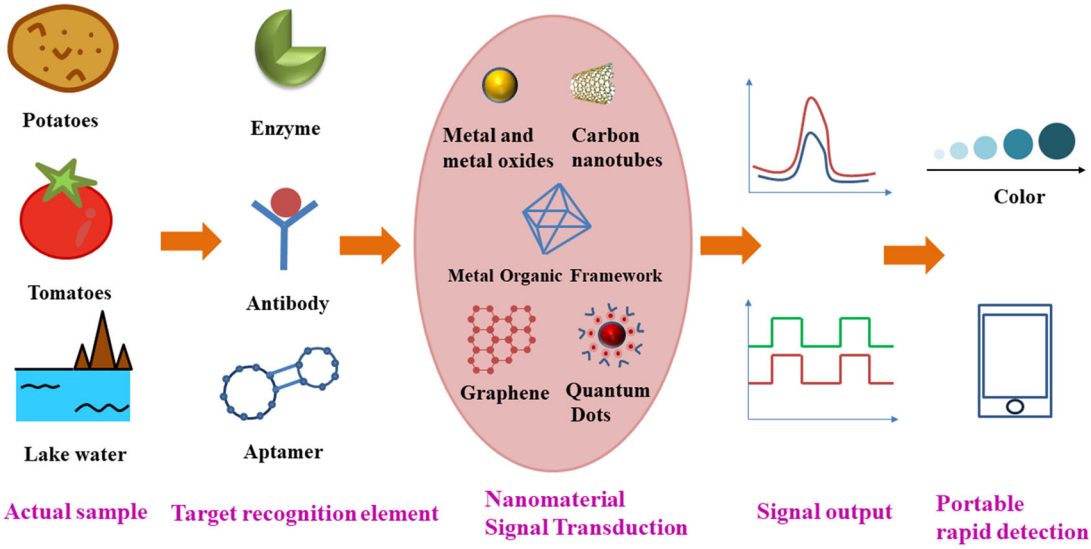


Figure 1. The principle of the detection of OPs in real samples.

In the past decades, there have been many articles on enzymes or aptamers, some of which focus on the electrochemical sensor, nanomaterials, detection methods and so on.[20–22] Yang et al. mainly introduced aptamer-based optical and electrochemical biosensors.[23] Xiong et al. summarized the detection of OPs using the enzyme/functional nanomaterial-based biosensor, and described the interaction between the nanomaterial and enzyme.[24] This review summarized the articles on enzyme- and aptamer-based biosensors with the nanomaterial as the substrate in the last five years. This review also discussed the basic principle and process of enzyme- and aptamer-based biosensors for the detection of OPs, as well as the characteristics of nanomaterials. The frequently-used detection methods and types of nanomaterials were comprehensively summarized. Unique properties of various nanomaterials endowed the biosensor with the excellent optical or electrochemical activity. The role of nanomaterials in enzyme- and aptamer-based biosensors was introduced in detail. The limitations of some nanomaterial in biosensors were also discussed. Besides, with the demand of portably onsite detection, more researchers have gradually explored the smart phone APP with more sensitivity and efficiency, which would expand the application of biosensors in real samples.

2. Biorecognition element

2.1. Enzyme-based biosensors

Enzyme-based biosensors are the earliest developed biosensor in the world. In the biochemical reaction, sugars, amino acids, adenosine triphosphate and other nutrients can be rapidly decomposed or oxidized through the special enzyme catalysis at room temperature.[] Due to the advantages of low cost, no need of large-scale instruments and good reacting performance, enzyme-based biosensor shows great potential in the detection of pesticides. Compared with the traditional detection methods, there is no need of the complex pretreatment procedure and longer time. So, enzyme-based biosensor has gained more and more attention in the detection of OPs.

There are two mechanisms (hydrolase and inhibition) for enzyme-based biosensor to detect OPs. OPs can be directly detected through the hydrolysis of enzyme including organophosphorus acid anhydrolase and organophosphorus hydrolase (OPH).[25] The catalytic activity of OPH is high and repeatable, and the reaction process can be monitored. OPH can hydrolyze methyl parathion into pnitrophenol, which can be detected by the optical instrument.[19] OPs mainly inhibit the activity of enzymes, such as acetylcholinesterase (AChE), butyrylcholinesterase, tyrosinase, etc., causing conversion signals for indirect detection. OPs basically contain the phosphate structure, surrounded by different combinations of C, N, O and S atoms, which can attack serine residue (Ser200) of cholinesterase through the nucleophilic reaction (Figure 2).[27] AChE can decompose acetylcholine (ACh) to produce choline and acetic acid, which is the most universal enzyme for the detection of OPs. On the basis of the AChE inhibition, the hydrolysis products of the reaction could be used in various ways to develop biosensors for OPs detection.

a. Biosensors could be constructed based on the pH response. Under normal conditions, AChE catalyzed the reaction to produce acetic acid, which would lead to the decrease of pH of the system. However, in the presence of OPs, the activity of AChE was inhibited to block the production of acetic acid. The change of pH was not significant. Therefore, the optical or fluorescent sensor could be constructed on the basis of the pH response.
b. Redox reaction was used to construct biosensors. The produced TCh with the -SH group, could be acted as a reducing agent to drive the redox reaction. The presence of OPs would inhibit the production of TCh and the redox reaction.
c. Biosensors were constructed on the basis of a dual enzymatic reaction. In the presence of oxidase or peroxidase, TCh can be used as a substrate to produce H_2O_2,

which in turn led to a transformed output of optical and electrochemical signals.

The current researches have focused on the indirect detection of H_2O_2, metal ions and glucose based on the inhibition of AChE toward OPs, which combine with the optical or electrochemical detection transducer. AChE-based colorimetric sensor is a rapid detection biosensor, which has the advantages of simple operation, rapid reaction, little environmental interference, low cost, easy miniaturization and onsite. The colorimetric detection is more intuitive than other detected methods, and people can observe it directly with their eyes. Many nanomaterials have catalytic properties, which can catalyze specific substrates to produce the color change. Besides, the aggregation and dispersion of nanomaterials will also cause the color change of the solution.[14] Analyte can be detected instantaneously through the construction of a reasonable detection strategy, and the color change can be displayed through the visual detection. Therefore, the colorimetric detection is the most widely used and mature method to detect residual pesticides. Generally, the inhibition of AChE toward OPs would cause the no forming or decrease of ACh, and further result in the color change or signal weakening. TCh as the hydrolysis product, can be used for the construction of dual enzyme-based biosensors. In the presence of oxidase (oxidases, peroxidases, nanoenzymes, etc.), TCh can be used as a substrate to generate H_2O_2 to construct a dual enzyme-based colorimetric biosensor. As a chromogen reagent, 3,3′,5,5′-tetramethylbenzidine (TMB) is widely used in the colorimetric detection due to its safety and stability. TMB can be oxidized to blue oxTMB in the presence of nanozyme. Ophenylenediamine (OPD), 2,2-azino-bis(3-ethylbenzthiazoline)-6-sulfonic acid (ABTS) also have similar properties, which are oxidized to yellow oxOPD and green oxABTS, respectively.[28] Besides, the AChE/choline oxidase (CHO) double enzyme system has been successfully used in the fluorescence and colorimetric detection with high sensitivity and selectivity.[29] Jin et al. reported that the electrochemical behavior of fabricated AChE biosensor was performed on an electrochemical workstation.[30] The electrochemical detection of OPs was carried out through the enzyme inhibition. Under optimum conditions, the AChE-based biosensor showed favorable affinity to acetylthiocholine chloride (ATCl). The linear range of the biosensor for malathion was 10^{-14}–10^{-8} M.

Tyrosinase mediated photochemistry and electrochemistry are often widely constructed in biosensors. The catalyzed reaction is as follows: L-tyrosine+L-dopa + O_2 L-dopa + dopaquinone + H_2O. Tyrosinase tolerates higher temperatures than AChE, making it more conducive to the fabrication of biosensor and the detection of analytes.[31] Liu et al. prepared a functional dopamine fluorescence biosensor based on the upconversion nanomaterial.[32] Dopamine quinone was produced by tyrosinase mediated oxidation of dopamine on the surface of upconversion nanomaterials, which acted as an electron receptor to inhibit the fluorescence emission of upconversion nanomaterials. OPs inhibited the activity of tyrosinase to lead to the quenching of fluorescence. Dopaquinone can quench the fluorescence of glutathione protected Au nanoclusters and Au/Ag nanoclusters. Therefore, on the basis of the different effect of dopamine and dopaquinone, the change of fluorescence was directly related to the concentration of tyrosinase.[33]

However, the enzyme inhibition-based method has its own limitations. The enzyme is not only inhibited by the target analyte, but also inhibited by other inhibitors (i.e., metal cations, inorganic substances etc.). Therefore, the enzyme lacks the specificity, and other inhibitors should be screened. Besides, the inhibition of many pesticides toward AChE is irreversible and the biosensor cannot be reused. The real samples need to be pretreated before each experiment to prolong the operation time.

2.2. Aptamer-based biosensors

Aptamers are oligonucleotide sequences (ssDNA, ssRNA or peptide molecules), which possess high specificity and affinity for targets selected from the random oligonucleotide library based on the systematic evolution of ligands by

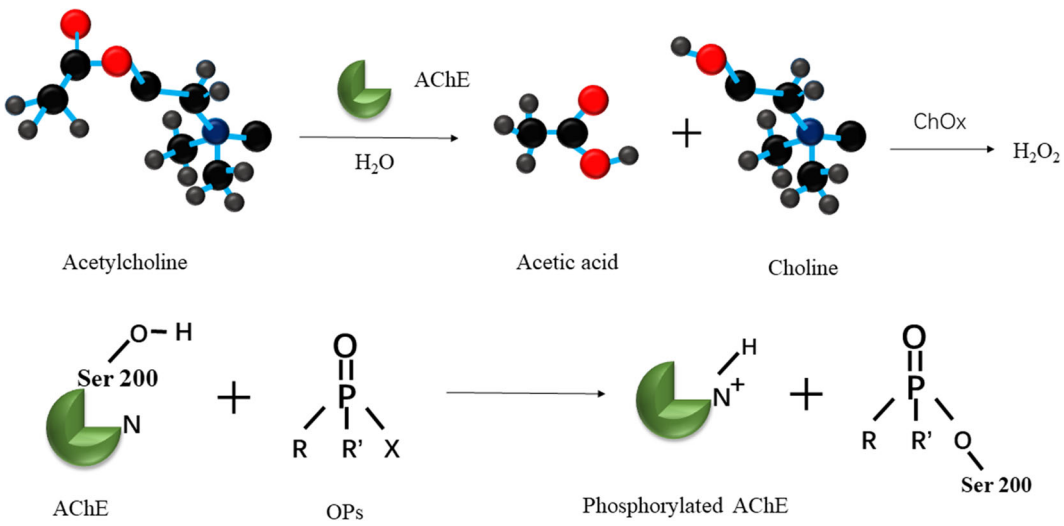


Figure 2. Inhibition principle of AChE-based biosensor.

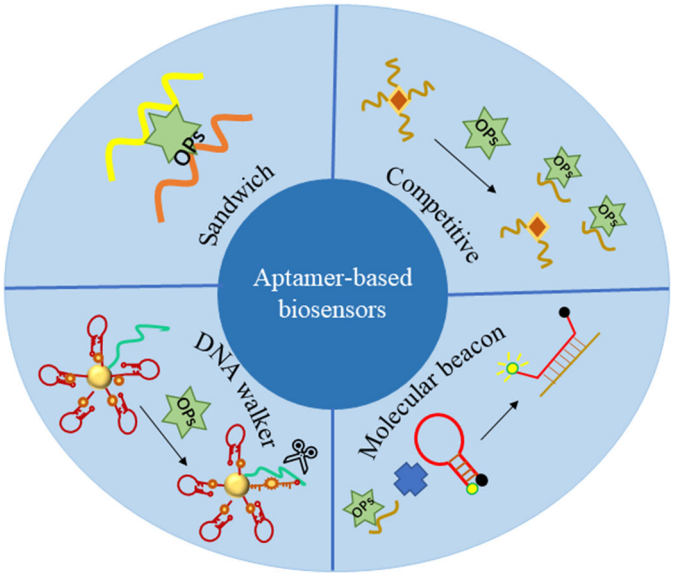


Figure 3. Assembly of aptamer-based biosensor.

exponential enrichment technology. They have a unique two- or three-dimensional structure to distinguish and interact targets.[34,35] Aptamers provide an appealing alternative to antibodies which are chemically synthesized and renewable. Besides, it can be prepared in an economical and highly reproducible method, and also is easier to be functionalized with various nanomaterials to amplify signal and achieve ultrasensitive detection. Aptamers are more widely used in biosensors to detect ions, molecules, even microbes due to the specific affinity with targets.[36,37] Through the catalysis of functionalized nanozyme coupling with the recognition of aptamer, many novel detected platforms have been built up to realize the rapid and sensitive detection toward OPs.[38]

Aptamer-based biosensors include two components of a molecular recognition element and an electrical or optical signal transducer. A molecular recognition element as the nucleic acid inducer, can specifically recognizes the target analyte. An electrical or optical signal transducer can convert the signal from a chemical/biological/physical reaction or other event into an electrical or optical signal which is easily transmitted and visible. These biosensors are designed on the principle that the binding of the aptamer to the target causes a conformational change to activate the signal of the biosensor, so the aptamer should be a target-induced structure-switching hapten.

An appropriate aptamer is the key to realize the specific detection of OPs. The aptamer screening techniques mainly include affinity chromatography, nitrocellulose membrane filtration and capillary electrophoresis, etc.[39,40] However, the analytical sensitivity of single aptamer-based sensor is limited. In recent years, the construction of the aptamer-based biosensor has focused on the signal amplification strategy to achieve high selective and accurate detection of low-abundance analytes in complex samples. Single stranded oligonucleotides, especially the secondary structure of sRNA, such as hairpin, stem ring, pseudo node, convex ring and G-tetramer, would form a unique three-dimensional structure and become a specific region for aptamer to bind with the target. The binding forces between the aptamers and targets mainly include π–π stacking, hydrogen bonding, electrostatic interaction and shape matching.

With the increasing demand of trace detection of pesticides, the sensitivity and accuracy of detection are still to be improved. Therefore, amounts of signal amplification strategies have been explored and designed (Figure 3). The sandwich assay is one of the most powerful tools in the molecular detection. Csordas et al. used "pair" aptamers with a capture probe and a signal probe to detect the target.[41] DNA nanomachine is based on the artificial molecular machine, which can carry out the precise mechanical movement under the preset condition. In particular, DNA walkers can be precisely controlled on preset tracks, which is conducive to the control and accuracy of reaction. Li et al. reported that a MnO_2 switch-bridged DNA walker was developed for the ultrasensitive sensing of ChE and OPs.[42] Firstly, the butyrylcholine was catalyzed by ChE to produce thiocholine, and then it mediated MnO_2 nanosheet reduction to Mn^{2+}, which would cause the release of fuel strands into solution to trigger the continuous operation of DNA walker. The detection of OPs was converted to DNA detection in this work. Molecular beacon (MB), as a kind of aptamer, can be used as a fluorescent indicator. Dou et al. designed an Au-based nanobeacon probe to be acted as a signal indicator based on the fluorescent quenching.[43] When OPs were interacted with the complementary ssDNA, it would reduce the hybridization between ssDNA and the Au-based nanobeacon, thus the hairpin structure was restored to regenerate the fluorescence quenching. Results showed that the limit of detection was in the range of 0.035–2.35 μM for isocarbophos, profenofos, phorate, and omethoate. Compared with other detection methods, MB was easy to operate and did not need large-scale instruments.

Aptamers are characterized with the high affinity and specificity. Thus, aptamer-based biosensors are highly sensitive and selective. Aptamer-based biosensors have longer storage life. Aptamers are used as an effective alternative to antibodies for biosensing platforms, which are characterized with high affinity, selectivity and stability compared to antigenic antibodies. However, the screening of aptamer is cumbersome and not conducive to the rapid screening and detection. Besides, the aptamer-based biosensor could only identify a few pesticides, which also limits their application.

3. Nanomaterials in enzyme/aptamer-based biosensors

Various nanomaterials, such as metals and metal oxides, carbon nanotubes (CNTs), graphene and graphene oxide (GO), quantum dots (QDs), metal organic frameworks (MOF) have been introduced into enzyme and aptamer-based biosensors for the detection of OPs.[44] Nanomaterials would catalyze the substrates to produce the optical or electrochemical signal, or load the enzymes or aptamers as carriers, or enhance the signal response. Table 2 compared the detection performance of these nanomaterials-based biosensors toward OPs, including recognition element, detection

Table 2. Applications of nanomaterials-based biosensors.

Nano-materials	Recognition element	Methods	Analytes	Samples	Linear range	LOD	Ref.
Metal and metal oxides							
Au NPs	Enzyme	Colorimetry	Triazophos,	Lake water and tap water	0–117 nM	4.69 nM	[45]
	Aptamer	Colorimetry	Omethoate	Soil samples	0.1–10 μmol L^{-1}	0.1 μmol·L^{-1}	[52]
Ag nano-enzyme	Enzyme	Electrochemistry	Malathion, Trichlorfon	Tap water apples	0.099–9.9 μg L^{-1} 0.0206–2.06 μg L^{-1}	0.032 μg L^{-1} 0.001 μg L^{-1}	[54]
Ag-rGO[a]-NH_2	Aptamer	Colorimetry	Dimethoate	River water	35–210 ppM	11.3 ppM	[48]
Fe_3O_4-TiO_2/rGO	Enzyme	Colorimetry	Atrazine	Water	2–20 μg L^{-1}	2.98 μg L^{-1}	[64]
Fe_3O_4@GO[b]	Aptamer	Fluorescent	Isocarbophos	Lake water apples	10–500 nM	3.38 nM	[66]
Carbon nanomaterial							
MWCNT[c]	Enzyme	Electrochemistry	Paraoxon	Tap water and potatoes	10–50 nM	0.1 nM	[73]
SWCNTs-CuO	Aptamer	Electrochemistry	Acetamiprid	Water samples	5×10^{-14}–1×10^{-5} M	1.7×10^{-14} M	[74]
GO	Enzyme	Colorimetry	Dimethoate, Methyl paraoxon, Chlorpyrifos	Yangtze River and Minzhu Lake	1–200 ng mL^{-1}	2 ppb	[80]
GO-Cu NPs	Aptamer	Electrochemistry	Profenofos, Isocarbopho Phorate Omethoate	Vegetables	0.01–100 nM 0.1–1000 nM 1–1000 nM 1–500 nM	0.003 nM, 0.03 nM	[86]
3D graphene /CuO	Enzyme	Electrochemistry	Malathion	Water	3×10^{-3}–46.665 nM	0.92 pM	[85]
g-C_3N_4/Au NP	Enzyme	Fluorescent	Chlorpyrifos	Fruit juice	2.0×10^{-11}–6.0×10^{-9} M	6.9×10^{-12} M	[90]
Cu^{2+}-g-C_3N_4	Enzyme	Fluorescent and Colorimetry	Malathion	Celery and tap water	70–800 nM 2.5–25 nM	6.798 nM 1.204 nM	[97]
Quantum dots							
CDs[d]	Enzyme	Fluorescence	Paraoxon Parathion Malathion	Tap water, river water, soil, rice, apple, and serum	0.000025 − 25 ng mL^{-1} 0.0000625 − 125 ng mL^{-1}, 0.000125 − 1.25 ng mL^{-1}	0.025,0.0625, 0.125 pg mL^{-1}	[108]
CDs	Aptamer	Fluorescent	Acetamiprid	Tomato, cucumber, cabbage	5–100 μg L^{-1}	1.08 μg L^{-1}	[110]
CdTe QDs[e]	Enzyme	Fluorescent	Dichlorvos	Fruit samples.	4.49–6780 nM	4.49 nM	[112]
GO/CDs	Aptamer	Fluorescence		Water, cucumber and apple	1.05–206 nM	0.13 nM	[114]
Metal–organic frameworks							
Cu-MOF	Aptamer	Colorimetry	Chlorpyrifos	Winter jujube, apple, cabbage, and cucumber	0–1250 ng mL^{-1}	4.4 ng mL^{-1}	[105]
Pt@UiO66-NH2	Enzyme	Electrochemistry	Malathion	Cabbage and apple	1×10^{-14}–1×10^{-9} M	4.9×10^{-15} M	[101]
Up-conversion nanoparticles	Enzyme	Fluorescent	Malathion	Apples and cucumbers	20–2000 ng mL^{-1}	6.7 ng mL^{-1}	[116]
	Aptamer	Fluorescent	Diazinon	Tea, apple and tap water	0.05–500 ng mL^{-1}	0.023 ng mL^{-1}	[117]

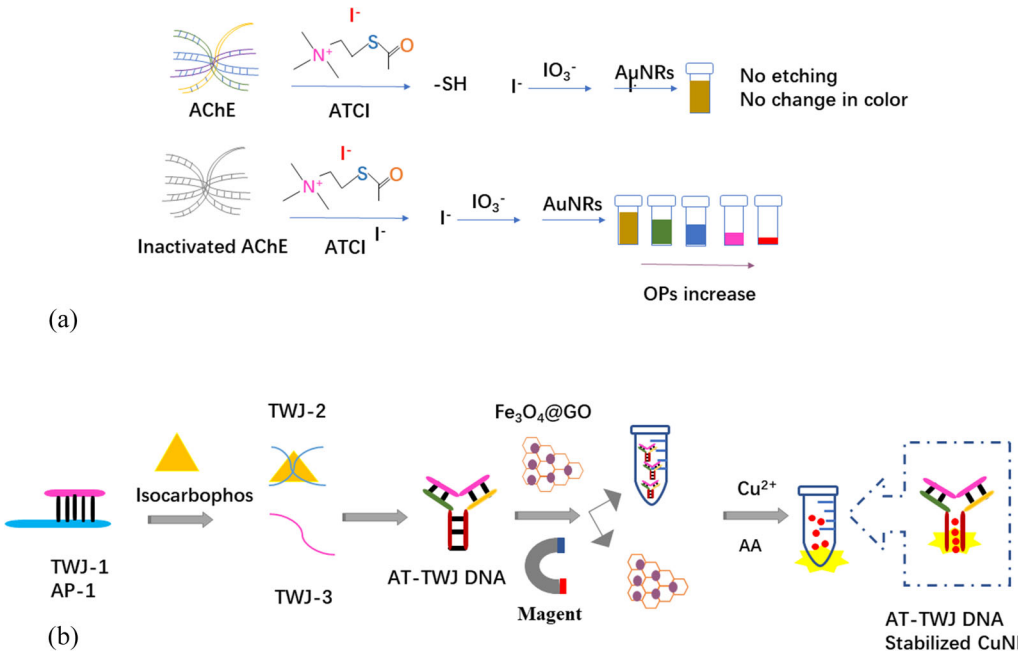


Figure 4. A: Schematic presentation of the colorimetric assay of OPs based on thiol-suppressed etching of gold nanorods (AuNRs). Repaint from Ref.[45] B: Schematic diagram of sensing platform for isocarbophos assay. Repaint from Ref.[65]

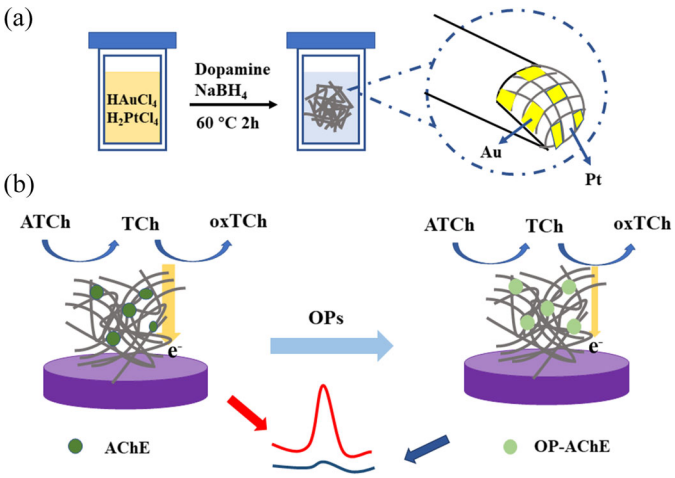


Figure 5. Schematic illustration of the regenerative electrochemical aptasensor for the selective detection of chlorpyrifos Repaint from Ref.[50]

methods, analytes, types of sample, linear range, limit of detection, etc.

3.1. Metal

The common metal-based nanomaterials include gold nanoparticles (Au NPs), silver nanoparticles (Ag NPs), palladium nanoparticles (Pd NPs) and other heavy metal materials, as well as some alloy materials. Metal-based nanomaterials possess large specific surface area to provide more immobilized sites for enzyme and aptamer. Besides, their good catalytic ability can improve the sensitivity and prolong the service life of biosensors.

3.1.1. Metal in enzyme-based biosensors

Qing et al. provided a new signaling mechanism for the colorimetric sensing based on the thiol group suppressed the I_2-induced etching of Au nanorods (Figure 4A).[45] In the presence of OPs, the activity of AChE was inhibited, in which sulfide inhibited I_2 could inhibit the longitudinal etching of Au nanorods. With the etching of Au nanorods by I_2, the solution color significantly changed from brown to blue to pink. The detection limit was 4.69 nM, and a linear detection range from 0 to 117 nM. He et al. fabricated a chemiluminescence (CL) biosensor based on Au NPs/organic metal gel.[46] Firstly, they synthesized iron-based organic metal gel nanosheet hybrid with the immobilization of Au NPs via a simple *in situ* growth strategy under environmental conditions. When Au NPs/organic metal gel hybrid dispersion was added to the luminol system in the presence of ACh, AChE and ChOx, CL emission showed 110 times enhancement than that without the hybrid. The linear range of the biosensor was 5–800 nM and the detection limit was 1 nM. The composite with a new simulated enzyme activity was highly sensitive to detect OPs.

Ag NPs have many excellent properties, such as large specific surface area, high conductivity, great biocompatibility and good catalytic activity. It can be used in the biological immobilization to retain the bioactivity of enzyme, and can also effectively catalyze the hydrogen peroxide reaction.[47] Zhang et al. reported an amperometric AChE-biosensor based on the poly (4,7-di(furan-2-yl) benzo thiadiazole) and Ag-rGO-NH_2 nanocomposite modified GCE to detect OPs.[48] The prepared nanocomposite had strong conductivity, high catalytic activity and good biocompatibility, and could also provide a large hydrophilic surface for the adhesion of AChE and maintain high loading amount of enzyme. This biosensor greatly improved the sensitivity and reduced the limit of detection. The prepared biosensors achieved the linear range of 0.0206–2.06 $\mu g \cdot L^{-1}$ for trichlorfon, 0.099–9.9 $\mu g \cdot L^{-1}$ for malathion. He et al. constructed a CL sensor array on the basis of modified

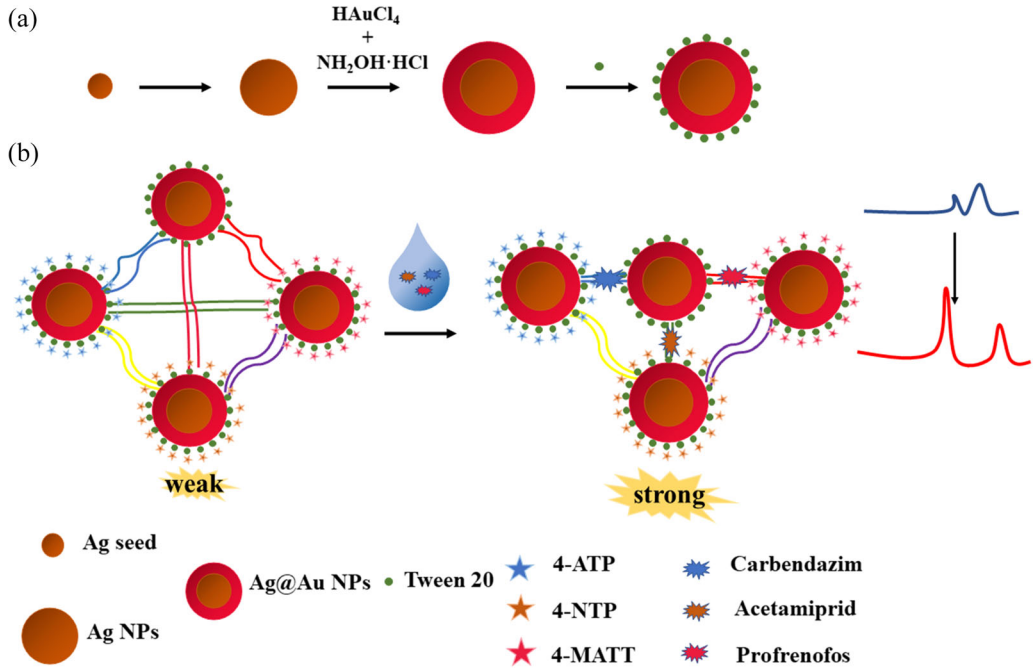


Figure 6. a. AuPt-PDA synthetic process chart of hydrogel. b. Electrochemical detection mechanism. Repaint from Ref.[55].

nanoparticles. Lminescent reagents (such as luminol), could reduce silver nitrate to form luminol functionalized Ag NPs.[49] Ag NPs could react with H_2O_2 to produce CL analysis. After the sensor array interacted with pesticides, the three-channel characteristics could be changed at the same time to produce different CL responses, that was, the "fingerprint" related to each specific pesticide. At the concentration of 24 $\mu g \cdot mL^{-1}$, the five organophosphorus pesticides could be well distinguished.

The morphological structure of metallic nanomaterials (nanomicrospheres, nanosheets, nanocages, nanoflowers, nanorods) has been studied in recent years. These diverse nanostructures have an effect on the catalytic capacity of nanoenzymes. The large specific surface area and volume could facilitate the electrical signal transmission. Wu et al. synthesized a bimetallic AuPt hydrogel on the basis of the enhanced reaction temperature and polydopamine via an one-step method (Figure 5).[50] The AuPt-PDA was prepared as irregularly interconnected nanowires with an average particle size of 5 nm. Due to the synergistic effect between components, species could realize electrochemical signal amplification through AuPt-PDA. ATCh was hydrolyzed by AChE to produce thiocholine TCh, which was an electrically active compound, so it could be detected on the electrochemical platform. The current intensity was from the oxidation of TCh. The biosensor was successfully applied to the detection of lake water, and the limit of detection was lower. The linear range for parathion-ethyl could be achieved in the range 0.5–1000 ng L^{-1} with a low limit of detection of 0.185 ng L^{-1}.

3.1.2. Metal in aptamer-based biosensors

Au NPs were widely used for the construction of sensors due to the unique properties of simple synthesis, aggregation, biocompatibility, magnetic and catalytic properties. The thiol group (–SH) was modified on the surface of Au forming metal ion-thiocholine complexes through the Au-S bond, which are widely used in the detection of pesticides. The colorimetric sensor based on Au NPs was a sensitive and convenient method for the detection of OPs. The color change in this system can be intuitive through the agglomeration of nanoparticles.[51] Wang et al. designed an aptamer on the basis of the selective colorimetric biosensor. The principle of this assay was that gold nanoparticles (Au NPs) coated with single stranded DNA (ssDNA) could resist salt induced aggregation.[52] The high selectivity of aptamers to omethoate resulted in the aggregation of Au NPs. The significant color would change in the aggregation process of nanoparticles, which was one of the important characteristics of gold nanoparticles. The linear range of the method was 0.1–10 $\mu mol \cdot L^{-1}$. The detection limit was 0.1 $\mu mol \cdot L^{-1}$. Besides, the potential of omethoate detection in real soil samples was also discussed. The aggregation discoloration of Au NPs can also be used in CL. Qi et al designed a CL biosensor for the determination of acetamiprid based on aptamer.[53] The biosensor had the molecular recognition ability of aptamers and the catalysis of aggregated Au NPs for luminol–H_2O_2 reaction. In the presence of acetamiprid, the linear range of the biosensor was 8×10^{-10}–6.3×10^{-7} M, and the limit of detection was 6.2×10^{-11}M. The biosensor was rapid and highly selective, which could complete the detection in 0.5–1 h.

Weerathunge's group established a chlorpyrifos aptamer system with the noncovalent interaction using Ag nanozyme as the biosensor probe.[54] When chlorpyrifos was introduced, the chlorpyrifos aptamer was bound to it, and the inhibited Ag nanozyme activity was restored. This system could be directly applied for the detection of analytes in real samples. It was fast and convenient, and could get the detected results within 2 min, which was conducive to the

rapid quantitative detection. Ag NPs needs to be well controlled in terms of lattice stability and size in the preparation process. It is believed that with further research, Ag NPs will play an increasingly important role in the detection of OPs. In addition, nanomaterials can also be affected by the conformation of the assembled aptamer during the signal transition. Liu et al. constructed a surface-enhanced Raman scattering (SERS) biosensor based on Ag@Au nanoparticles with an aptamer tetrahedral structure (Figure 6).[55] Aptamers for three different insecticides (propanophos, acetamiprid and carbendazim) were embedded on three sides of the DNA tetrahedral backbone and incubated on Ag@Au NPs with different SERS signal molecules. When the insecticides were successfully identified with the aptamers, the tetrahedra structure was deformed. As the Ag@Au NPs gradually got closer, the Raman signal intensity increased. The limit of detection could reach 0.0021 ng·mL^{-1}. The core–shell structure of self-contained bimetallic is also one of the common composites. The common core–shell structures mainly included Ag@Au, Au@Ag, etc. These materials can be used in SERS, CL, ECL and other detection. Huang et al. designed a model based on Cu@Au ECL biosensor.[56] In Ru (bpy)$_3^{2+}$/tri-n-propylamine (TPrA) ECL system, Au NPs mainly enhanced ECL intensity by catalyzing the oxidation process of TPrA. Cu NPs with large specific surface area and electrochemical catalytic characteristics, could produce stronger catalytic electrochemical signal. This broad-spectrum aptamer-based biosensor could detect four OPs at the same time. It had the advantages of good stability and strong sensitivity.

However, the application of Au NPs, Ag NPs are still limited resulting from the influence of the charge, surface derivatives, shape and size on their properties. Moreover, in the preparation process, the Au NPs are easy to aggregate. Therefore, the design of Au NPs is still to be attention, because the size control and modification of Au NPs is important for the extensive application.[57,58]

3.2. Metal oxides

Traditional metal oxide materials are widely used in catalysts, fuel cells, refractory and wear-resistant materials. With the development of nano-size controlled technology and the study of particle dispersion and stability, metal oxides are gradually used in the construction of biosensors, such as Fe_3O_4 NPs, CuO NPs, ZnO NPs, ZrO_2 NPs, and so on.[59] Magnetic Fe_3O_4 NPs have the special magnetic structure, excellent adsorption properties, large specific surface area and good stability. Functional magnetic Fe_3O_4 NPs can reduce the background signal of detection. Fe_3O_4 has strong adsorption capacity toward metal ions and can combine with inorganic material to prepare adsorbents. In the past, the functionalization of Fe_3O_4 usually needed to be linked with antibody and oligonucleotide chain, which was complicated and would interfere the detection.[60,61] The catalytic activity of Fe_3O_4 can be improved by modifying other materials, for example, carbon nanotubes (CNTs), graphene and graphene oxide (GO), etc., which would expand the application in the enzyme immobilization, biological separation and immunoassay.

3.2.1. Metal oxides in enzyme-based biosensors

It is necessary to consider the biocompatibility of nanomaterials to construct AChE-based biosensors. Metals and their oxides can increase the surface area to immobilize AChE and improve the electrical signal transmission. In this way, the sensitivity of biosensor is greatly improved. Besides, these nanomaterials can also shorten the response time and improve the analytical performance of biosensors.[] Singh et al. constructed a biosensor based on zinc oxide nanoflowers (ZnO NFs) with a particle size of 100 nm and large surface area.[62] ZnO NFs were deposited on the Au electrode to increase the specific surface area and enhance the electrical signal. ATCI was hydrolyzed into thiocholine under the catalysis of AChE and further dimerized into disulfide. OPs would inhibit AChE to weaken the electrical signal. Detection sensitivity could be achieved at the nM level with a range of 0.01–100 nM and a limit of detection of 0.01 nM.

Nanoenzyme is a kind of nanomaterial simulating natural enzyme activity. In recent studies, many metals (Au, Pt, Ag, Pd NPs), metal oxides (Fe_3O_4, CeO_2 NPs) and carbon materials have been successfully synthesized, which exhibit the excellent catalytic ability after the surface modification, particle size control and multi-material assembly.[] They have the activities of horseradish peroxidase and oxidase. Liang et al. developed a colorimetric biosensor based on CeO_2 nanoenzyme/AChE for the detection of paraoxon.[63] CeO_2 was prepared by hydrothermal synthesis in strips of 100 nm in width and 1000 nm in length to form a white nanoenzyme which did not affect the subsequent colourimetric reaction. TCh was produced when acetylcholine was catalyzed by AChE, which significantly inhibited the nanoenzyme catalytic activity of CeO_2. The TMB/H_2O_2 system would not become the blue color. However, when OPs were added, the production of TCh was inhibited, and CeO_2 with its original catalytic capacity to produce the blue color in the TMB/H_2O_2 system. The colorimetric sensor had a linear range of 0.1–50 pM and a detection limit of 14 fM.

3.2.2. Metal oxides in aptamer-based biosensors

Fan et al. used Fe_3O_4-loaded GO (Fe_3O_4@GO) as an adsorbent for ssDNA to reduce the detection background.[64] As shown in (Figure 4B), when isocarbopho specifically combined with its aptamer, the released ssDNA and other two ssDNA would assemble into AT-rich three-way junctions DNA (AT-TWJ DNA), which could not be adsorb by the added Fe3O4@GO.[65] In this work, AT-TWJ DNA stabilized Cu NPs as a fluorescence probe, which was highly sensitive and selective to isocarbophos. The linearity between the isocarbophos concentration and the fluorescence intensity was good and the limit of detection was 3.38 nM. Boruah et al. has constructed a Fe_3O_4–TiO_2/reduced graphene oxide (rGO) nanomaterial-based biosensor with intrinsic peroxidase mimic activity and photocatalytic

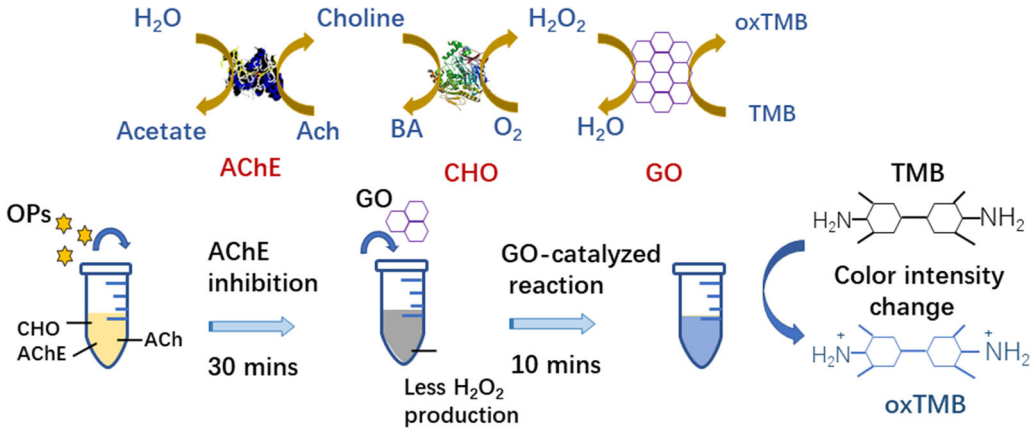


Figure 7. Process diagram of H_2O_2 and TMB catalyzed by GO. Repaint from Ref.[80]

degradation.[66] The nanocomposite was prepared by one-step hydration method, which exhibited high sensitivity in the colorimetric detection for atrazine pesticide. In the presence of H_2O_2, the Fe_3O_4–TiO_2/rGO nanocomposite as an artificial nanozyme could oxidize TMB to the blue-colored oxTMB. The linear range of the biosensor for atrazine was 2–20 $\mu g \cdot L^{-1}$, and the limit of detection was 2.98 $\mu g \cdot L^{-1}$.

Most metal oxides such as Fe_3O_4 NPs have high surface energy, are easy to agglomerate to form a single particle. It is difficult to control the size, persistence and dispersion stability, which will inhibit the surface area effect, quantum size effect and hinder their application in biosensors. There has been a lot of effort on these issues to expand its application scope, including the modification of metal oxide nanomaterials, the preparation of its nanostructured composites, the increase of dispersion and stability, and the reduction of particle agglomeration.[67,68] The adsorption specificity and structural stability of metal oxides still need to be improved in the next few years.

3.3. Carbon nanomaterials

3.3.1. Carbon nanotubes

Since the discovery of CNTs by Lijima in 1991, it has been regarded as a potential nanomaterial, which mainly composed of hexagonal carbon atoms forming several to dozens of layers of coaxial tubes.[69,70] CNTs can be divided into two categories based on the diameters: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). They have excellent electrical and thermal properties, high chemical stability, strong adsorption capacity and high mechanical strength. Thus, they are commonly used in different fields, such as effect transistors, nanoprobes, bioelectronics, and sensors, etc.[71,72]

3.3.1.1. Carbon nanotubes in enzyme-based biosensors. In order to extend the application, various groups (i.e., –OH, –COOH, $–NH_2$) functionalized CNTs have been developed and used for the signal amplification. There are many reports of CNTs modified enzyme-based biosensors for the detection of OPs. Thakkar's group directly doped AChE onto the surface of MWCNTs–COOH through the amide bond ($–NH_2–CO–$).[73] The formation of amide bond between AChE and MWCNTs avoided the use of cross-linking agent, intermediate membrane or binding material, which reduced the hindrance of electron transfer and greatly improved the sensitivity. The detected linear range was 10–50 nM, and the lower limit and upper limit of detection were 0.1 and 50 nM, respectively.

3.3.1.2. Carbon nanotubes in aptamer-based biosensors. Amount of aptamers immobilized on the surface of substrate determined the sensitivity and accuracy of biosensors. CNTs can be used as the electrode materials to construct an adsorption platform because of its large surface area and abundant binding sites. Xu et al. constructed an electrochemical sensor based on CuO nanoflowers-SWCNTs.[74] On the one hand, SWCNTs had excellent electrochemical, biocompatible and mechanical properties, which could improve the electron transfer rate and amplify the sensing signal. On the other hand, it could be used to enhance the immobilization ability of amination probe and the hybridization ability of aptamer with amination probe. Amino-modified capture probe was fixed on the CNTs via the covalent bond between the carboxyl group and amino group on CNTs. It can specifically identify the aptamers of chlorpyrifos and hybridize to the surface of CNTs. The main reactions between methyl bromide and nucleic acid chain were the specific recognition between methyl bromide and unconjugated guanine base, the insertion of double stranded DNA base pairs and electrostatic adsorption. After adding chlorpyrifos, a more compact aptamer chlorpyrifos complex structure was formed, which caused the forced dissociation of the aptamer from half duplex, and further led to the escape of methyl bromide from the sensing interface. Therefore, the change of differential pulse voltammetry signal could be used to quantify chlorpyrifos. Under the optimum conditions, the linear range of the sensor for chlorpyrifos was 0.1–150 $ng \cdot mL^{-1}$, and the detection limit was 70 $pg \cdot mL^{-1}$.

CNTs also have some limitations, for example, being difficult to guarantee the preparation of uniform CNTs to affect the properties and applications. Besides, CNTs are thermally unstable in the oxygen-rich environment and also exhibit the poor dispersion in unmodified structure, which

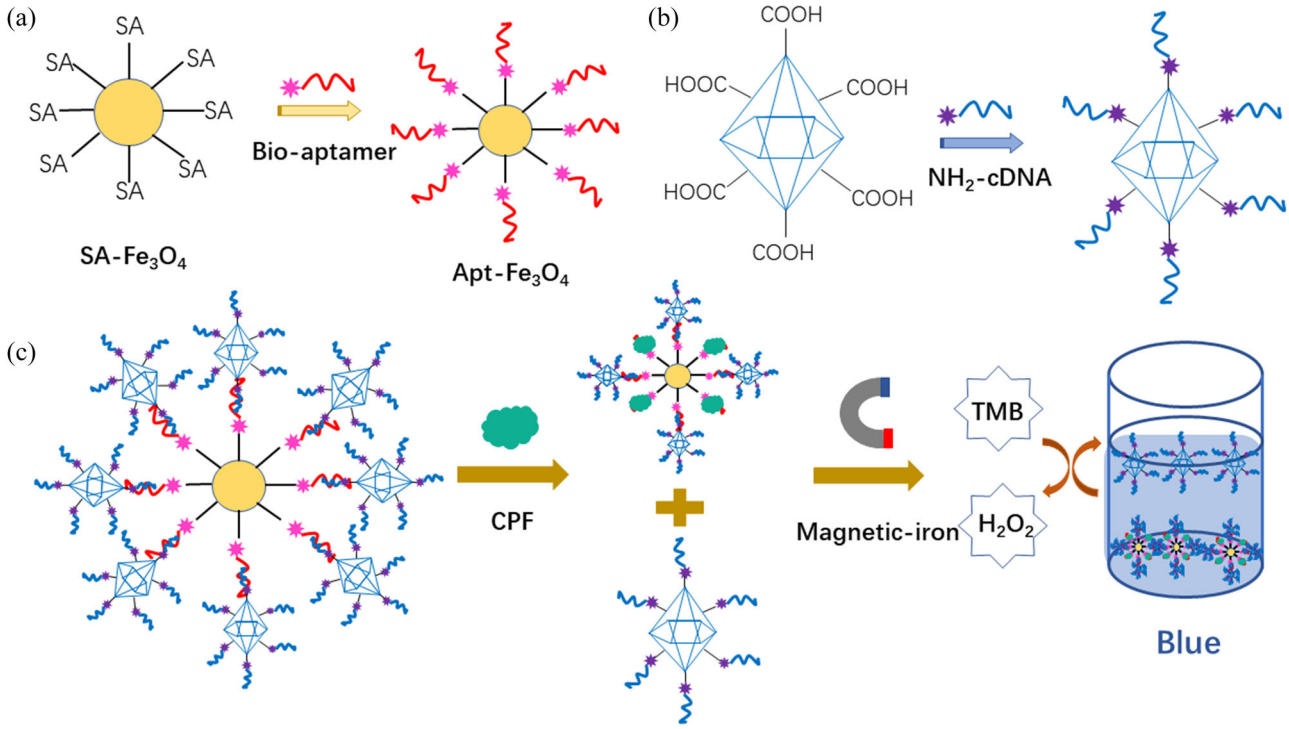


Figure 8. Schematic illustration of Cu-MOF-based colorimetric detection of CPF. Repaint from Ref.[105]

put forward higher requirements for the preparation and functionalization of CNTs. Therefore, the way to stabilize molecules can be through noncovalent bonds, such as electrostatic interaction, van der Waals force and π–π stacking. It is expected that the dispersion or solubility of CNTs can be improved by the physical adsorption or retention without destroying the sp^2 structure.[75] Surfactants, i.e., phospholipids and peptide amphiphiles, can be used to construct noncovalent functionalized CNTs-based biosensors. For example, the stable black suspension can be obtained by ultrasonic treatment in 1% aqueous solution with anionic surfactant sodium dodecyl sulfate (SDS) added to carbon nanotubes. SDS molecules are adsorbed on the surface of CNTs by van der Waals force, resulting in negative charge distribution and preventing the aggregation of CNTs.[76] Besides, the peptide amphiphile is easy to interact with CNTs in water due to the short hydrophobic alkyl tail and more hydrophilic peptide sequence.[77]

3.3.2. Graphene

Graphene is a two-dimensional (2D) material with carbon atoms arranged in a honeycomb grid by sp^2 hybridization.[78] Graphene-based composite materials are widely used for the detection of OPs due to the advantages of high surface area, strong adsorption capacity, good catalytic performance and strong conductivity.

3.3.2.1. Graphene in enzyme-based biosensors. GO is an important derivative of graphene, which could increase the affinity with targets resulted from the oxygen-containing groups on its surface. Small-sized GO would exhibit high peroxidase-like activity, which could be used for colorimetric detection of OPs through multistage enzyme-linked reaction.[79] Chu et al. fabricated a small-size GO nanozyme-based biosensor for the detection of dimethoate, methyl paraoxon, and chlorpyrifos (Figure 7).[80] AChE/ChO could catalyze the formation of H_2O_2 from ACh and choline, and convert TMB into the blue oxTMB. With the addition of OPs, the activity of AChE gradually decreased and the production of H_2O_2 decreased significantly, which would cause a significant change in color intensity. In this work, the detection limit was less than 2 ppb, and the linear range was 1–200 $ng \cdot mL^{-1}$, and the whole operation time was 40 min. The established colorimetric sensor exhibited low limit of detection, which could be used for the quantitative analysis in a short time, so it had great potential in the detection of OPs in real samples.

Three-dimensional graphene (3DG) has porous network structure, higher porosity and hydrophobicity.[81,82] The larger surface area made 3DG to provide multiple active sites and improve the loading amount of enzyme.[83,84] Bao et al. established a 3DG/CuO nano-flowers based AChE biosensor.[85] This composite could not only improve the specific surface area of binding, but also enhance the binding rate of AChE, which greatly improved the sensitivity of biosensor. Results showed that the limit of detection of this method for malathion was 0.92 pM, and the detection range was 3–46.665 nM.

3.3.2.2. Graphene in aptamer-based biosensors. In the electrochemical sensor, GO could be reduced to the reduced graphite oxide with excellent conductivity. Fu et al. established an aptamer/GO-Cu NPs-based electrochemical sensor, which were successfully applied for the analysis of phorate in vegetables.[86] The $-NH_3$ functionalized aptamer was bonded onto the surface of GO, and this biosensor

presented the enhanced conductivity and strong selectivity. This sensor exhibited low limits of detection, which were 0.003, 0.03, 0.3, 0.3 nM for profenofos, isocarbophos, phorate and omethoate, respectively.

There is a synergistic effect between metal ions, metal oxides and graphene or GO, and the composites-based sensor would present higher sensitivity and lower limit of detection. However, the preparation process of composites is complex and difficult to control. At present, the hydrothermal method has been mainly used to prepared the graphene or GO-based composites, which are carried out in a Teflon-autoclave at 160–180 °C.[87] Besides, the microwave synthesis of GO composites is also gradually concerned. It can quickly and selectively heat the reactants to high temperature, and generate high pressure in the sealed reactor which is beneficial to the preparation of GO.[88]

3.3.3. g-C_3N_4

As a new type of carbon-based materials, graphitic carbon nitride (g-C_3N_4) has attracted more attention in the fluorescence detection. Compared with graphene, g-C_3N_4 possesses fewer aromatic properties due to the sp^2 hybridization between C and N atoms in g-C_3N_4 and the decreased π-delocalization of six-membered ring with the substituted C–N bond. It has the advantages of high specific surface area, low density, nontoxicity, low cost and simple preparation. g-C_3N_4 can be prepared by the direct pyrolysis of carbon and nitrogenous organic precursors such as melamine, urea and ammonium thiocyanate in a semi-closed environment.[89] It is widely used in the detection of aflatoxin,[90] heavy metal ions[91] and nucleic acids[92] through different methods because of its strong photoluminescence, good biocompatibility and excellent stability.[93,94]

3.3.3.1 g-C_3N_4 in enzymes-based biosensors. Compared with FRET, IFE does not need the interaction between the fluorescence cluster and the receptor, which provides a simple alternative for the design of fluorescence sensors.[95] Xie et al. designed a fluorescence biosensor for the IFE of Au NPs and g-C_3N_4. The fluorescence of g-C_3N_4 was quenched by Au NPs under the influence of IFE.[96] AChE could catalyze ACh to produce thiocholine (TCh) resulting in the aggregation of Au NPs and the recovery of g-C_3N_4 fluorescence. In the presence of chlorpyrifos, the catalyzed process of AChE toward ACh was inhibited, which would prevent the aggregation and accumulation of Au NPs. Under the optimum conditions, the detection limit of chlorpyrifos was 6.9×10^{-12} M, and the linear range was 2.0×10^{-11}–6.0×10^{-9} M. Similarly, Chen et al. developed a biosensor based on the competitive complexation of Cu^2+ with TCh and g-C_3N_4 nanosheets.[97] Cu^{2+} firstly could quench the fluorescence of g-C_3N_4, and then TCh as the reacted production of ATCh and AChE, would extract Cu^{2+} from g-C_3N_4 resulting in the recovery of g-C_3N_4 fluorescence. However, OPs could reduce the production of TCh by inhibiting the activity of AChE, thus preventing the extraction of Cu^{2+}, and keeping Cu^{2+}–g-C_3N_4 nanosheets in the fluorescence "off" state. Besides, the Cu^{2+}–g-C_3N_4 nanosheets with the peroxidase activity could catalyze the reaction system of TMB and H_2O_2, so the colorimetric analysis was also carried out. The detection range of malathion by the colorimetric method was 2.5–25 nM, and the detection limit was 1.204 nM. The linear range of fluorescence detection was 70–800 nM, and the detection limit was 6.798 nM. Results indicated that he dual-response probe was sensitive and reliable in real samples. It could be used to construct a photochemical biosensor for the detection of OPs, and had great development potential in the field of aptamer binding analysis of OPs.

There are three common methods to control the pore structure of g-C_3N_4, which are hard template method, soft template method and no template method. The hard template method can prepare uniform or adjustable pores. However, the raw materials are often toxic and harmful to the environment. Besides, under the actual uncontrolled condition, the use of photocatalysts will be greatly reduced. Therefore, in practical application, the deactivation speed of catalytic effect will be faster, and the experimental condition need to be more specific.

3.4. Metal–organic frameworks

MOFs, as a type of crystalline nanomaterials, were composed of metal ions and organic ligands. Due to the nanoscale framework structure, large specific surface area, adjustable pore size, abundant functional groups, and good chemical stability, MOFs have been widely applied in many fields.[98–100] Importantly, MOFs were good candidates for the fabrication of biosensors based on the following advantages. On the one hand, the porous structure and large surface area of them provide more interfaces and active sites for the combination and interaction between targets and materials. On the other hand, the organic ligands of them provide the functionalized sites with various groups and materials including other nanomaterials, enzymes, nucleic acids, and so on.

3.4.1. Metal–organic frameworks in enzymes-based biosensors

Ma et al. designed a Pt NPs-anchored zirconium MOF (Pt@UiO66-NH_2) nanocomposite-based electrochemical biosensor.[101] PT@UiO66-NH_2 had high adsorption sites, good electron conduction channels and large surface area, which was conducive to the immobilization of AChE. The biosensor exhibited good sensitivity and stability. The linear range was 1×10^{-14} -1×10^{-9} M, and the limit of detection was 4.9×10^{-15} M. MOF-derived materials could be a more favorable and attractive alternative in the construction of biosensors due to the mechanical stability and electrical conductivity. MOF-derived carbon materials were prepared via a single-step carbonization process of MOF at high-temperature, which was simple and convenient. Dong et al. prepared a MOF-derived carbon nanocomposite through the annealing of the precursor MOF at high temperature, and further constructed an AChE-based biosensor for the detection of

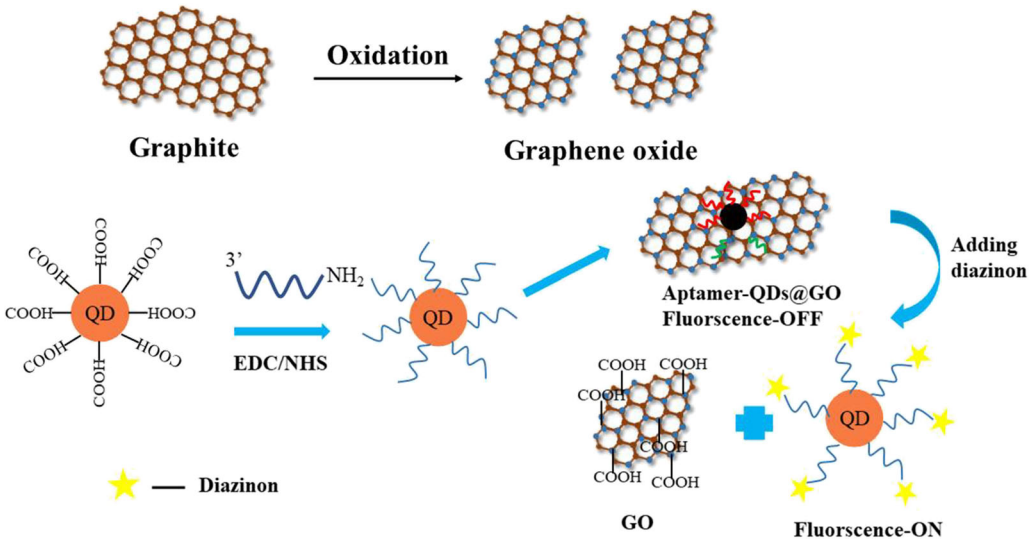


Figure 9. Detection schematic diagram and assembly drawing. Repaint from Ref.[114]

OPs.[102] Firstly, metal ions including Fe^{3+}, Zr^{4+} and La^{3+} were connected with 2-aminoterephthalate to form three kinds of MOFs, and then annealed at 550 °C in N_2 atmosphere. These MOF-derived carbon materials were successfully used as effective immobilization substrates for AChE to construct biosensors for the detection of methyl parathion. Results showed that the MOF-derived carbon materials increased the contact area with AChE, promoted the conduction of electrical signal, and greatly improved the sensitivity of biosensor. Zeolite imidazole framework (ZIFs) is a microporous crystalline MOF. This material has good chemical and thermal stability, and is suitable for heterogeneous catalysis. Bagheri et al. prepared Fe_3O_4 NPs@ZIF-8 composite, which showed the characteristics of general peroxidase substrate.[103] It could react with the oxidation of H_2O_2 to produce detectable changes. In the case of diazinon, the linear range was 5–500 nM and the detection limit was 0.2 nM.

3.4.2. Metal–organic frameworks in aptamer-based biosensors

Lv et al. summarized nucleic acids-functionalized MOFs for biosensing, and MOFs could serve as either signal probes or carriers for loading signal probes.[104] The efficient immobilization of aptamers on MOFs was an essential step, which could be achieved by covalent and noncovalent binding methods. Liu et al. fabricated complementary DNA-Cu-MOFs through the formation of an amide bond between the carboxyl group on organic ligands of Cu-MOFs and the amino group on the end of aptamers (Figure 8).[105] In this study, a magnetically controlled colorimetric sensor was fabricated for the visual and rapid detection of chlorpyrifos. The sensor was based on the competition between complementary DNA-Cu-MOF or chlorpyrifos and aptamer. MOF was regarded as a promising nanozyme due to its uniform cavity and high density of bioactive centers, which possessed peroxidase-like catalytic activity to be used as reactor catalytic TMB–H_2O_2 system for the color change. The established sensor exhibited high selectivity for chlorpyrifos toward other interfering pesticides. The linear range was 0–1250 ng·mL^{-1} and the limit of detection was 4.4 ng·mL^{-1}. It was successfully applied for the detection of chlorpyrifos in real samples. This method promoted the development of efficient and facile phase separation and also expand the application of MOF from H_2O_2 or glucose to pesticides.

The functionalization of MOFs and other types of MOF is still challenging and relatively unexplored. The complex construction steps, such as signal amplification and probe labeling, also limit the applications in the detection of food pollutants. Therefore, new sensing strategies should be developed by using the characteristics of easy modification and functionalization of MOFs. Especially, in order to detect several target analytes accurately, more MOFs-based biosensors deserve to be developed.

3.5. Quantum dots

QDs possessed unique optical and electrical properties due to the quantum confinement effect.[106] QD nanoparticles can be prepared by the II–VI or III–V elements in the periodic table of elements, and their synthesized process is different.[107] The sensing of quantum dots is based on the sensitivity of self-luminescence to the surface state of nanoparticles. Generally, the self-luminescence of quantum dots includes “turn-on” or “turn-off” types according to the target analysis. Many of its characteristics can be used in the construction of biosensors. Especially after surface modification, it is widely used in interdisciplinary fields, such as electrochemistry, biomarkers, solar cells and so on.[107]

3.5.1. Carbon dots

As a carbon-based fluorescent material, carbon dots (CDs) have been widely used in various fields. CDs generally includes graphene quantum dots (GQDs), polymer dots and carbon nanodots. CDs are a kind of fluorescent nanomaterials with particle size less than 10 nm and various oxygen-containing functional groups or organic polymers. Compared with other semiconductor nanomaterials, CDs

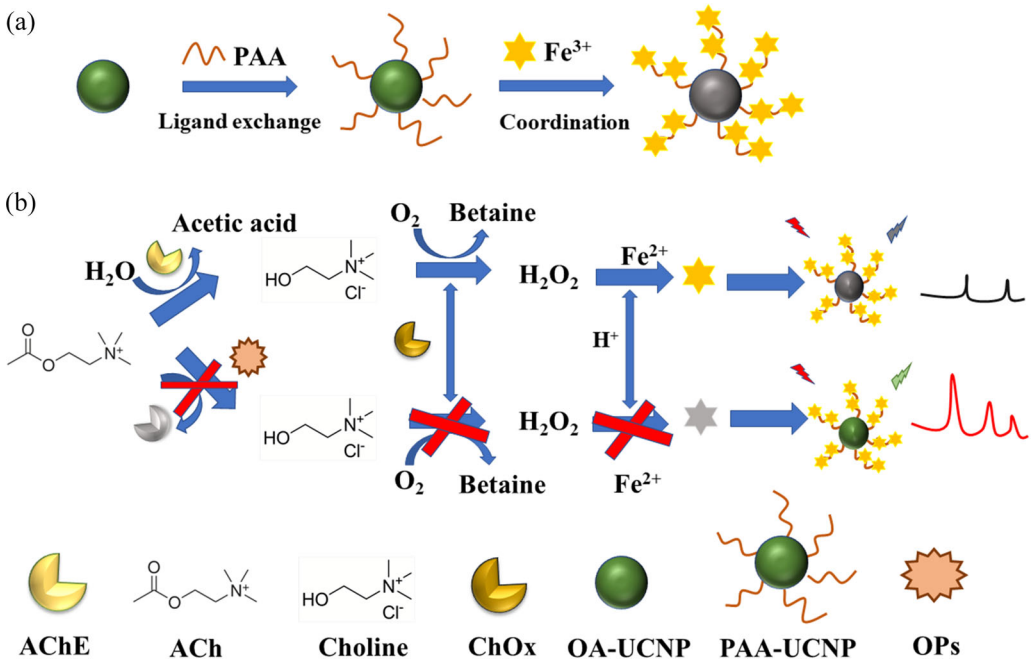


Figure 10. Schematic diagram of OPs detection using the double enzyme modulated fluorescence method. Repaint from Ref.[116]

has the advantages of low toxicity and outstanding biocompatibility. CDs can be synthesized by adjusting the precursor and changing the reacting condition to achieve the different fluorescence emission wavelength ranging from deep ultraviolet to near infrared region.

3.5.1.1. Carbon dots in enzymes-based biosensors. Su et al. designed a new strategy based on solvothermal treatment of citric acid and thiourea using dimethylformamide as the solvent to achieve the optimal emission of red emitting CDs at 610 nm.[108] After the modification of CDs surface, they could be easily constructed for the detection platform of OPs. The platform could reach the detection level of $pg{\cdot}L^{-1}$, greatly improve the detected rate, and realize the hypersensitive detection.

Besides, CDs are simple to prepare with inexpensive raw materials and easy to functionalize. Hou et al. synthesized L-tyrosine methyl ester functionalized CDs via a simple hydrothermal method using citric acid and L-tyrosine methyl ester, which were successfully used to fabricate a biosensor for the detection of methyl parathion.[109] The prepared CDs possessed a diameter of 3.7 nm, small particle size and uniform dispersion. Under the excitation wavelength of 344 nm, the synthesized methyl tyrosine-CDs was concentrated at 433 nm emission. Methyl tyrosine produced quinones in the presence of tyrosinase and O_2, which were able to inhibit the fluorescence of CDs. The fluorescence of CDs was gradually restored after the inhibition of tyrosinase activity by methyl parathion. The linear range of the constructed biosensor was 1.0×10^{-10}–1.0×10^{-4} M, with the limit of detection of 4.8×10^{-11} M.

3.5.1.2. Carbon dots in aptamer-based biosensors. Wang et al. constructed a fluorescent aptamer-based sensor for the detection of acetamiprid.[110] The S-18 aptamer sequence was encapsulated on the surface of AuNPs to make them disperse. The fluorescence of subsequent CDs could be effectively quenched by IFE. With the addition of OPs, the aptamer was bound to the target, and then the Au NPs were gradually aggregated away from CDs. Then the absorption spectrum no longer overlapped with the fluorescence emission spectrum of CDs, and finally the fluorescence recovered. The linear range of the biosensor was 5–100 $\mu g{\cdot}L^{-1}$, and the minimum detection limit was 1.08 $\mu g{\cdot}L^{-1}$. The biosensor had strong interference toward other pesticides.

3.5.2. Other quantum dots

QDs are usually synthesized from organometallic precursors and protected by organic ligands, such as trioctylphosphine (TOP) or trioctylphosphine oxide (TOPO). Therefore, these surface ligands often become the recognition sites of target analytes after the functionalization.

3.5.2.1. Quantum dots in enzymes-based biosensors. QDs can be easily modified and used to design sensible recognition units to achieve 'off', 'on' and 'ratios' of fluorescent signals. Korram et al. developed a fluorescent biosensor based on glutathione-modified CdTe QDs/AChE/choline oxidase.[111] The excitation and emission wavelengths of CdTe QDs were 360 nm and 520 nm, respectively, and its quantum yield was 41%. ACh/AChE/choline oxidase systems would produce H_2O_2 in the presence of O_2. The fluorescence intensity of CdTe QDs decreased with the increase of H_2O_2 and parathion. The biosensor could realize the detection of multiple pesticides. The linear ranges for malathion, parathion and triazophos were 0.23×10^{-9} M, 1.62×10^{-15} M and 10.6×10^{-12} M, respectively.

Through the inhibition mechanism of enzyme, Meng et al constructed a platform for the detection of OPs based on CdTe QDs/AChE.[112] The quenching of CdTe QDs in

the presence of H_2O_2 could be divided into two stages. Firstly, the quenching was resulted from the separation of thiolation from the surface of QDs. Then, the quenching of QDs was caused by the interaction of Te oxidation and the separation of thiolation from QDs. The linear range of dichlorvos was 4.49 nM to 6780 nM, and the limit of detection was 4.49 nM. The construction of the experimental method was also successfully applied to the detection of fruit samples, realizing the sensitive detection. Dual function moderator can make ECL produce dual signals. The bifunctional moderator can make ECL generate dual signals, because it could mediate two ECL signals at the same time, so it is convenient to realized their opposite change trend. He et al. constructed a novel dual signal combined nano probe, using carboxyl functionalized poly [(9,9-dioctylfluorenyl-2,7-diyl)-co-(1,4-benzo-{2,1′,3}-thiada-zole)] nanoparticles (c-PFBT NPs) as the anode electrochemical probe and L-cysteine modified CdS QDs as the cathode electrochemical probe.[113] The dual signal output was realized without adding any auxiliary reactants. The biosensor had good detection sensitivity and the detection linear range was 5.0×10^{-13}–5.0×10^{-7} M, the detection limit was 1.25×10^{-13} M. Besides, Yang et al. constructed a highly sensitive ECL biosensor based on indium nanorods (Ir NRs) as the anode emitter and CdS as the cathode emitter. They prepared water-soluble Ir NRs with high luminous efficiency. CdS QDs were combined with Ir NRs to further construct double signal nano probe (Ir NRs@CdS QDs), which loaded AChE and ChO to developed ECL ratio biosensor. The linear range of the biosensor was 5.0×10^{-12}–5.0×10^{-8} M, the detection limit was 1.67×10^{-12} M.

3.5.2.2. Quantum dots in aptamer-based biosensors. Arvand et al. designed a fluorescence sensor based on the conjugation of GO/QDs-aptamers (Figure 9).[114] In this work, GO was used as an energy acceptor, and L-cysteine capped CdTe was used as an energy donor. The fluorescence quenching was achieved by FRET When the pesticide was added to the bioconjugate containing GO, the affinity between GO and aptamer was weaker than that between aptamer and target, resulting in the separation of GO and aptamer. Therefore, the fluorescence signal of CdTe QDs can be recovered and the optical signal can be detected. The linear range of the biosensor was 1.05–206 nM, and the detection limit was 0.13 nM. This strategy could also be developed for the detection of other aptamer-specific pesticides in real samples.

Although there are many methods to synthesize amounts of CDs from a wide range of raw materials, it is still difficult to synthesize CDs with excellent properties. Many basic problems have not been solved, such as the influence of synthesized conditions on the structure, property, morphology and size and so on. The photochemical signal intensity of QDs will affect the sensitivity of biosensors. Therefore, it is particularly important to prepare QDs with an appropriate size. In electrochemical biosensors, the electrical signal generated by QDs is independent of surface chemistry and size, and can produce stable and repeatable signals. It also provides direction for the signal amplification strategy and the construction of high-sensitivity biosensors.

3.6. Up-conversion nanoparticles

UCNPs luminescence generally occurs in rare earth ions-doped compounds, including fluoride, oxide, sulfur compounds, fluoride oxides, halides and so on. UCNPs are greatly better than fluorescent dyes and QDs. Up-conversion fluorescence is an anti-stokes emission process, in which two or more low-energy photons absorb the excitation energy, then jump to different energy levels of the excited state, and further emit high-energy photons in the excited state. They can emit visible light to near infrared (NIR) light under the excitation of near NIR light (usually at 980 nm).[115] Because of several brilliant features of UCNPs such as high chemical stability, low toxicity and reducing excitation light scattering, they have attracted much attention for the applications in sensing. $NaYF_4$ is currently the matrix material with the highest up-conversion luminescence efficiency. For example, in $NaYF_4$:Er:Yb material, Yb and Er are double doped. Er acts as the activator and Yb acts as the sensitizer.

3.6.1. Up-conversion nanoparticles in enzymes-based biosensors

Lin et al. established a double-enzyme regulated fluorescence assay platform for the detection of OPs (Figure 10).[116] The fluorescence properties of up-conversion materials were quenched by Fe^{3+}. The inhibition of OPs toward AchE would decrease the production of TCh, and further reduced the lack of H_2O_2, so Fe^{2+} could not be oxidized to Fe^{3+}, resulting in the "trun-on" fluorescence of UCNPs. The linear range of this biosensor for malathion was 20–2000 ng·mL^{-1}, and the limit of detection was 6.7 ng·mL^{-1}. The platform also had a good effect for the detection of malathion in real samples. The integration of UCNPs into the double-enzymes-mediated Fe^{3+}/Fe^{2+} conversion endowed the method with high sensitivity and selectivity, outstanding rapidity (detection time <1 h), strong anti-interference capability.

3.6.2. Up-conversion nanoparticles in aptamer-based biosensors

A rapid and sensitive FRET method was developed for the determination of diazinon.[117] Aptamer modified up-conversion nanoparticles (Apt-UNCPs) were synthesized and coupled with GO via the π–π interaction. Due to the interaction between UNCPs and GO, the fluorescence intensity decreased. When diazinon was added, aptamers preferentially bound to GO, resulting in the separation of GO and the enhancement of fluorescence signal. Under the optimum condition, a wide linear detection range of 0.05–500 ng·mL^{-1}and limit of detection of 0.023 ng·mL^{-1} were achieved. The method was successfully applied to the determination of diazinon in real samples. The result showed that the proposed method was feasible, and the Apt-

UNCPs-based biosensor provided an efficient, specific and simple method for the detection of diazinon in food, which had broad application prospects and high potential in the food safety and quality control.

These luminescent UCNPs could improve the sensitivity of biosensors and have photoinitiated biological and chemical reactions. However, the efficiency of UCNPs is still limited, and the fluorescence sustainability still needs to be improved. The small-size nanoparticle is conducive to realize the single molecule imaging and *in vivo* imaging. Due to the surface quenching effect, the synthesis of small-size UCNPs is still a challenge.

4. Smart and portable devices in enzymes/aptamer-based biosensors

4.1. Smart phone-based biosensors in enzyme/aptamer-based biosensors

Due to the need of real-time detection, more and more researchers began to establish the combination technology of smart portable phones and biosensors. Smart phones image recognition and detection become the trend of current researches, because of the simple operation, no need for professional and technical personnel, fast and convenient in the detection of samples. At present, the detection devices with popular design have included portable spectrometer,[118] smart phone imaging APP recognition [119] etc. Montali et al. designed a folding paper-based detector combining 3 D printing with smart phones.[120] This biosensor was based on a series of enzyme reactions catalyzed by AChE and horseradish peroxidase. Origami allowed the addition of reagents and triggering of sequential reactions in separate steps. It had the advantages of easy to carry, easy to detect and high reliability. Jin et al. constructed a fluorescence sensor based on enzyme inhibition.[121] In the presence of OPs, AChE was inhibited, and the formation of thiocholine (TCh) was blocked, which prevented the formation of metal–polymer and further induced the oxidation of OPD to form yellow 2,3-diaminophenazine (DAP). DAP was quenched by internal filtering effect. Smartphone APP could be used to detect the fluorescence intensity in the photo linearly. Portable detection of mobile phone provided the possibility for rapid detection on site, and the detection was more convenient and reliable. Therefore, researchers have paid more attention on the portable update of instruments. Besides, the newly designed wearable biosensor was used for in situ pesticide analysis, which could improve the accuracy and high screening, and played an important role in the promotion of precision agriculture.[122]

4.2. Paper-based biosensors in enzymes/aptamer-based biosensors

Paper analysis biosensor had become a low-cost analysis tool for onsite detection of pesticide residues. In addition, they were portable, disposable and low-cost. Nouanthavong et al. prepared a paper-based biosensor based on CeO_2.[123] In the presence of ACh, AChE/ChOx catalyzed the production of H_2O_2, which was detected by colorimetry with nano ceria coating equipment to produce yellow. Wang et al. fabricated a QDs-nanoporphyrin fluorescent paper for the visual detection of OPs.[124] Combining double QDs with highly active nano porphyrins, the double nano signal amplification was realized resulted from different color change responses of three organic porphyrins. The biosensor had high sensitivity and selectivity.

4.3. Screen-printed electrode-based biosensors in enzymes/aptamer-based biosensors

In electrochemical analysis and measurement, screen printed electrode (SPE) has become a wide substitute for the traditional electrode, but the accuracy still needs to be improved. Hua et al. fabricated an enzyme-based disposable electrochemical biosensor.[125] The working electrode consisted of AChE immobilized on the surface of multi SPE modified by MWCNT, chitosan and AuNPs. Ibáñez et al. constructed a SPE based on the characteristics of electrochemical activated pesticide-SERS.[126] The activation of metal SPE via the electrochemical method can produce nanostructures with excellent SERS performance to detect various OPs.

4.4. Other biosensors

Many portable devices (pesticide meters, microcantilever beam array) have been successfully used in the detection of pesticides. There was also a new integration of personal glucose meters with the onsite quantitative detection of organophosphorus. Tang et al. developed a rapid quantitative monitoring biosensor based on the $[Fe(CN)_6]^{3-}$/AChE/TCh.[127] $[Fe(CN)_6]^{3-}$ was used as the medium in glucose test strips to transfer electrons to the electrode, which could be rapidly reduced to $[Fe(CN)_6]^{4-}$ in the presence of TCh. The amount of TCh produced was influenced due to the inhibition of OPs toward AChE. This method avoided the complex sample pretreatment and allowed for direct drop testing. It also avoided signal interference from some enzymes and allowed for direct deduction of background interference, which was more user-friendly and convenient. Meanwhile, the biosensor was successfully implemented for the detection of OPs in apples and cucumbers.

In addition to portable detection using electrochemistry, there have been innovations in colorimetric scanning detection. Meng et al. designed a quantitative colorimetric on the basis of the scanning readable plastic microchip biosensor.[128] The detection principle relied on AChE catalyzing the hydrolysis of ATCh to TCh, which in turn reacted with dithiodinitrobenzoic acid to produce a yellow product (deprotonated 5-thio-2nitrobenzoic acid, TNB). The production of TNB decreased with the increase of OPs concentration. On the basis of the principle of enzyme inhibition, a plastic microreactor was prepared and the images were scanned by an office scanning device to obtain assay data. There were significant deviations in color intensity when shooting from a mobile phone versus a camera. The color

intensity of the pictures taken by the scanner was more reasonable. Multiple samples could be simultaneously detected with high sensitivity.

Besides, Li et al. constructed an aptamer-based microcantilever beam array sensor for the detection of propamocarb in the stress mode.[129] The biosensor had the advantages of being label-free, high sensitivity, one-step immobilization, and being capable of quantitative and real-time detection. The microcantilever beam was functionalized with a profenofos-specific aptamer, and the specific binding of profenofos to the aptamer caused the deflection of the microcantilever beam, which was monitored by optical methods in real time. Microcantilever deflection was positively correlated with the concentration of propamocarb. This microcantilever beam array might produce a somewhat nonspecific response with the actual solution composition, refractive index. However, there was still good detected results in real samples with more complex colors and solutes.

Generally, most of these new biosensors are still in the laboratory stage, there are no more commercial applications. Therefore, how to realize large-scale commercialization is still worth thinking. In addition, the design and optimization of paper-based sensing equipment should be straightforward. And the analysis and collection of test results should be more intuitive and easy to understand. In this way, consumers can see the experiment results more intuitively, and it is also convenient for researchers to make statistics. Finally, accurate automation and quantification of portable devices are necessary to avoid cumbersome operation steps and excessive manpower.

5. Conclusion and future

In this paper, various methods for the detection of OPs were introduced mainly including AChE- and aptamer-based biosensors. The AChE-based biosensors generally adopted the indirect detection. Firstly, the enzyme activity was inhibited, and then it was converted into the increase or decrease of optical or electrical signal being easy to detect. The aptamer-based biosensor was based on the affinity between aptamer and target to realize the specific recognition. Some RNA secondary structures, such as hairpin, stem ring and G-tetramer, could make nucleic acid molecules form a variety of three-dimensional structures, which is the basis of nucleic acid molecular recognition targets. DNA walker structure can travel along a specific orbit, and it has attracted great interest in the construction of amplified signal system. A majority of colorimetric detection can get quantitative analysis by connecting to mobile phone APP.

Nanomaterials were an indispensable part in the detection system to produce the signal response, load the recognized element, or enhance the signal. Many nanomaterials such as metal and metal oxides, MOF, GO, and so on, have the characteristics of oxidases-like activity, which can catalyze the reaction of TMB with H_2O_2 to form the blue product of oxTMB. QD (i.e., CDs, CdTe QDs, etc.) and UCNPs materials with fluorescence properties have specific absorption and emission wavelengths. The successful construction of these sensors can achieve the rapid detection, high sensitivity, simple operation and facilitate operation. Some detection devices were explored to realize the portable and real-time detection.

Above all, the enzyme- and aptamer-based biosensors still need higher detection sensitivity in real samples. The enzyme-based biosensors have universality and no specificity for the detection of OPs. In addition, the types of OPs aptamers are not complete enough, which can be further screened to achieve the specific detection of OPs. In the aspect of nanomaterial synthesis, it can be more environmentally friendly and nontoxic. It is believed that the enzyme, aptamer, and nanomaterials-based biosensors will be fully explored and applied in the detection of fruits and vegetables.

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Disclosure statement

The authors declare no conflicts of interest.

ORCID

Wei Wu http://orcid.org/0000-0002-1772-3841
Qingli Yang http://orcid.org/0000-0003-4732-6465

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