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Review

Advances in Noble-Metal Nanoparticle-Based Fluorescence Detection of Organophosphorus Chemical Warfare Agents

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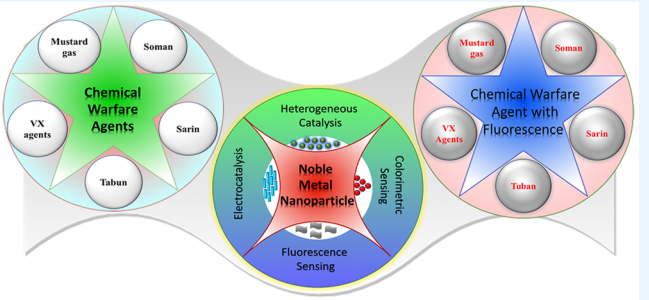
ABSTRACT: Efficient and simple detection of chemical warfare agents (CWAs) is an essential step in minimizing the potentially lethal consequences of chemical weapons. CWAs are a family of organic chemicals that are used as chemical weapons because of their enormous severity and lethal effects when faced with unforeseen challenges. To stop the spread of CWAs, it is critical to develop a platform that detects them in a sensitive, timely, selective, and minimally invasive manner. Rapid advances in the demand for on-site sensors, metal nanoparticles, and biomarker identification for CWAs have made it possible to use fluorescence as a precise real-time and point-of-care (POCT) testing technique. For POCT-based applications, the new capabilities of micro- and nanomotors offer enormous prospects. In recent decades, significant progress has been made in the design of fluorescent sensors and the further development of noble metal nanoparticles for the detection of organophosphorus CWAs, as described in this review. Through this work, recent attempts to fabricate sensors that can detect organophosphorus CWAs through changes in their fluorescence properties have been summarized. Finally, an integrated outlook on how noble metal nanoparticles could be used to develop smart sensors for organophosphorus CWAs that communicate with and control electronic devices to monitor and improve the health of individuals.



1. INTRODUCTION

Despite the global ban imposed by the Chemical Weapons Convention (CWC), the number of incidents involving chemical warfare agents (CWAs) has increased in recent years. Chemicals have always been used in warfare, starting with foul-smelling things, irritants, poisonous plants and animals, and decaying corpses.[1] Toxic chemical agents and pesticides are used in the form of gases, vapors, and liquids. With the advancement of science, it is possible to develop chemical weapons that are only incapacitating or lethal and that do not cause physical damage or damage to infrastructure, but can still incapacitate or kill the enemy.[2]

In the First World War (1914−8) CWAs were used on a large scale, which can be regarded as the most tragic fact in contemporary history.[3] CWAs are chemicals used in military activities to destroy, harm, or immobilize people through physiological effects, and their use has increased dangerously in recent years.[4] Depending on their effect on the body, they were divided into groups, such as nerve, blood, or blistering agents, respiratory or pulmonary, blood, and incapacitating agents.[5] In the twentieth century, CWAs were used regularly. Tragically, this has continued into the twenty-first century to terrorize military and civilian populations. The attacks in Syria are a recent example of murderous acts in which the nerve agent sarin has been used on many occasions in that country.[6] These toxic compounds have been used in a variety of activities and have serious consequences for human health.

Over time, as new and more lethal chemicals were discovered, CWA weapons evolved and became even more lethal. Weaponized chemicals are designed to pose an imminent threat to human existence and more, including the extraction and use of fossil fuels and the industrialized synthesis of selected chemicals. They lead to the emission of hazardous and dangerous substances into the atmosphere and affect people's quality of life.[7] CWAs are classified according to their chemical structure and their effect on the human body. Neurotoxins, asphyxiants/blood poisoning agents, vesicants, asphyxiants/respiratory agents, lacrimators, incapacitating agents, and cytotoxic proteins are just some of the classifications for CWAs.[8] Regardless of their form, however, they all have the same purpose: to frighten and subdue people by the horrible nature of their effect.

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Table 1. Reported Concentrations of the Most Significant Organophosphorus Nerve Agents[a]

nerve agent	solubility(g/L) at 20 °C	vapor pressure (mmHg) at 25 °C	volatility (mg/m^3) or at 25 °C	LCt_{50} (mg/(70 kg of human weight))	LD_{50} on skin (mg/individual)	persistency hydrolysis half-life (20 °C and pH 7)
mustard gas	0.0007	0.11	610	1000−1500		days to weeks
sarin	miscible	2.1 at 20 °C	16400−22000	1700	1700	39−80 h
soman	21	0.40	3060−3900	350	300	80−83 h
tabun	72	0.037 at 20 °C	610	1500	4000	8.5 h
VX agents	slight	0.0007	3−30	5	10	400−1000 h

[a]LCt_{50}, agent lethality; LD_{50}, liquid agent lethality.

Due to their potency and the fact that nerve agents can be easily synthesized, they are the most commonly used CWAs. Nerve agents are a group of organophosphorus chemicals (OP) that affect the transmission of nerves and organs.[9] OP nerve agents are colorless, odorless, and tasteless, making them ideal for use in biological warfare.[10] It works by blocking the enzyme acetylcholinesterase, causing neuromuscular paralysis throughout the body. This in turn inhibits muscle contraction, resulting in suffocation.[11] Highly toxic OP-based nerve agents have been developed by various countries for use as CWAs. These chemicals are used as invisible, lethal weapons and have been used in wars and humanitarian crises against civilian populations around the world.[12] The vapor pressure, volatility, fatal effects, fatal dose (LD_{50}), solubility, and persistence of the most important OP nerve agents are shown in Table 1.[13,14]

They are extremely lethal and have varying levels of persistence; some pose only a short-term threat on the battlefield, while others can persist for years or even decades. These gases are also associated with a number of significant environmental problems currently facing our civilization, including global warming, acid rain, and ozone depletion, as well as the destruction of natural ecosystems.[15−17]

It is estimated that more than 3000000 people are poisoned with OPs each year, with pesticide-related hospitalizations accounting for more than 80% of these cases. The overall mortality rate is estimated at 20%.[18,19] They affect anything in the area that can breathe, including animals. If these highly toxic substances come into contact with the skin or are inhaled, they can cause death within minutes, making it impossible to defend against them or treat those affected.[20] OP compounds enter the blood through a variety of sources, including body parts such as the skin, and through inhalation. They also enter the blood through consumption of food and drink. It also crosses the blood−brain barrier and irreversibly inhibits acetylcholinesterase. This can also cause miosis, hypersalivation, lacrimation, involuntary urination and defecation, convulsions, and fast death from respiratory failure.[21,22]

Following the release of CWAs into the environment, the first step is the rapid detection of these contaminants, which is then followed by the appropriate decontamination technique. The development of effective sensors is critical and has the ability to detect and protect against the effects of chemical contamination and exposure from OPs. Nerve agent safety technologies are being materialized to rescue military personnel and innocent civilians of any country from exposure to nerve agents. A number of detection methods exist for the detection of OP are flame photometry (FP),[23] ion mobility spectrometry (IMS),[24] mass spectrometry (MS),[25] gas chromatography (GC),[26] liquid chromatography (LC),[27] and Fourier transform infrared spectrometry (FTIR).[28] Currently available technology suffers from high costs, operational complexity, slow response times, and limited portability, which limit their practical applications.[29]

Presumptive identification can also be done with simple and inexpensive fluorescence assays that can detect the difference between different functional groups of CWAs. This technology is less precise than spectrometric methods, but it is affordable, easy to use, and portable.[30] Fluorescence-based techniques are widely used in trace detection, biological imaging, diagnostics, optoelectronics, and forensics because they represent simple and ubiquitous analytical approaches.[31,32] With its fast response time, low false alarm rate, low cost, and realistic temperature range, it provides "naked eye" detection with contrast and versatility. It is portable and allows point-of-care testing (POCT) to perform real-time monitoring of the analyte of interest.[33] Fluorescence platforms rely on on/off fluorescence signals and wavelength shifts with overlapping fluorescence pairs. Fluorescence detection may have a low detection limit due to the limited extinction coefficients and labeling ratios of organic dyes. The current development of nanotechnology has opened up new possibilities for fluorescence detection and led to the development of materials with sub-micrometer dimensions and unique optical properties.[34]

To achieve high fluorescence enhancement factors, the potential of metal nanoparticle-based fluorescence biosensors has been widely investigated in the scientific literature.[35] In the past 5 years, the application of metal nanoparticles as fluorescent biosensors has also seen a tremendous upsurge. The detection of OP chemicals is an optimal alternative and has been explored by several researchers using fluorescence techniques.[29,30,36−38]

However, in addition to the ease with which these nanostructures can be fabricated from metal nanoparticles, the focus of this analysis is on cases where metal nanoparticles have already been effectively used to develop fluorescent nanosensors for organic pollutants. In this study, critical variables such as the shape of the nanostructures, the selection of the metal nanoparticles, the sensing principles, and the fluorescence quantification technique for the target biomarkers are discussed with respect to their application in real data. This work thus provides a comprehensive overview from a sensing perspective and demonstrates the enormous potential of metal nanoparticles when used in fluorescent biosensing approaches to increase signal sensitivity and specificity.

2. OUTLOOK ON THE ROLE OF BIOMARKERS FOR DETECTION OF OP

Biomarkers are used in various areas of health surveillance to diagnose disease, monitor drug administration or metabolism, and limit chemical exposure. Exposure to organophosphates that range from low-dose acute exposure to toxic chronic exposure is hazardous to human health.[39] The most dangerous

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Table 2. Different Types of Biomarkers and their LOD by Conventional Methods[a]

biomarker	organophosphorus agent	LOD	analytical technique	ref
		Urine Biomarkers		
thiodiglycol	sulfur mustard	without titanium trichloride—3 ng/mL; after treatment with titanium trichloride—104 ng/mL	GC-MS	47
thiodiglycol sulfoxide	sulfur mustard	10 μg mL^{-1}	ICA	48
β-lyase	sulfur mustard	0.1−0.5 ng/mL	LC-MS-MS	49
IMPA	sarin	0.025 ppm	GC-FPD	50
PMPA	soman	0.2 ng/mL	GC-NPD, FPD, MS; LC-MS	51
EMPA	VX	1 μg/L	GC-MS-MS	52
		Blood Biomarkers		
BuChE adducts	VX	10 pg/mL	GC-MS	53
BuChE adducts	VX	0.5 ng/mL	IMS HPLC-MS/MS	54
adduct to albumin	VX		LC-MS-MS	55
adduct to BuChE	cyclohexylsarin	250 mM	GC-NPD, FPD, MS	56
adduct to albumin	soman	0.5−250 pg	LC-MS-MS	55
N-(2-hydroxyethylthioethyl)-*N*-terminal valine	sulfur mustard	1 pg	LC-MS	57
adduct to albumin	tabun		LC-MS-MS	55

[a]BuChE, butyrylcholinesterase; GC-FPD, gas chromatography−flame photometric detection; ICA, immunochromatographic assay; IMPA, isopropylmethylphosphonic acid; PMPA, pinacolyl methylphosphonic acids.

OPs have been developed, stored, and weaponized from time-to-time. Excess acetylcholine causes the main toxic consequences of OP nerve agents at neuronal synapses. It causes overstimulation of the nervous system in the regulation of smooth muscle, cardiac muscle, and exocrine gland activity, causing muscle spasms and probably death by suffocation.[40]

OP nerve agents are mainly effective in liquid or vapor form. They enter the body of human or animal by inhalation or by direct contact with the skin or the anterior eye region.[41] The main toxic effects of OP nerve agents are caused by an excess of acetylcholine at neuronal synapses, resulting in overstimulation of the nervous system in the control of smooth muscle, cardiac muscle, and exocrine gland activity, causing muscle spasms and possibly death by asphyxiation. There are three main reasons to detect and identify biological indicators of exposure to neurotoxins: In situations where use is suspected, verification of exposure for forensic purposes is desirable; detection/identification will support the establishment of the most effective medical countermeasures during exposure; and workers in defense laboratories and demilitarization facilities are subject to occupational health surveillance.[42,43] Blood-based, filtration-free monitoring of biomarkers is the gold standard in health care diagnostics. Toxic agent markers may be detected in whole blood taken from people who have been exposed to toxic chemicals or from animals poisoned for research reasons in vivo. Many assays are carried out in vitro using commercially accessible blood components such as plasma, proteins, and enzymes. In most cases, whole blood analysis requires a more sophisticated sample preparation technique than in vitro applications.[44] To allow identification of biomarkers in the blood and blister exudates, many alternative techniques of sample preparation for analysis were employed. However, direct insertion of sensors or devices into blood vessels is problematic because of many factors. Therefore, non-invasive biofluids such as sweat, saliva, urine, and tears are recommended for biofluid sampling. There are several approaches to biofluids collection.[45]

Chromatographic analysis is most commonly used to detect biomarkers of OP poisoning. These methods have specific strengths and weaknesses in the detection of nerve agent molecules. These detection methods are either too slow, too complicated, or too unselective for use in the field, or the equipment is too expensive. However, these approaches can only be used in comparison with other methods to attain lower and more specific detection limits for CWA compounds.[46]

An alternative detection method is optical scanning. This method uses a chemical whose absorption or emission is affected by contact with the neurotoxicant. Device mobility, real-time monitoring, and rapid and selective detection are potential advantages of optical detection systems. If the functionality of the sensing material is designed to respond precisely to a nerve agent, optically sensed signals are less susceptible to interference.[12] Early detection of OP biomarkers may help clinicians to begin treatment sooner, increase patient adherence by boosting medication effectiveness, and reduce the risk of poor health status and death. Table 2 depicts the suggested biomarkers for OPs detection.

3. REPRESENTATIVE TYPES FOR FLUORESCENCE DETECTION OF OPS

Clinical diagnostics, following the motto "prevention is better than cure", is one of the most expanding fields of modern medicine. Researchers are focusing not only on improving existing analytical tools and developing new ones, but also on developing more precise techniques for identifying chemical or biological agents that can shed light on how to minimize the harmful effects of CWAs. When performing rapid tests, sometimes referred to as "bedside" tests, the time required to perform the analysis is critical. For tests performed in the ICU, the patient must not be made to wait long for possible results, usually due to the need for urgent therapeutic decisions. One of the main focuses in the global fight against nerve agents is on solutions for their effective and reliable detection and destruction.

Fluorescence detection is one of the most powerful methods for detecting ecologically and physiologically relevant analytes in the presence of interfering matrices.[58,59] It has attracted considerable attention because it combines the advantages of

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low-cost and robust detection due to its high sensitivity, great selectivity, fast response time, low detection limit, and ease of use.[60]

Fluorescence biosensors can measure intensity, anisotropy, decay time, energy transfer efficiency, and quantum yield. Numerous compounds have natural fluorescence, meaning they are fluorescent in one state and nonfluorescent in another. Fluorescence-based devices are divided into different categories depending on the fluorescence parameters monitored. Fluorometers measure steady-state fluorescence intensity at preset excitation and emission wavelengths (wavelength-based).[61] This is achieved by changing the intensity of steady-state photoluminescence (PL) and the color of PL ("turn on" or "turn off"). Kumar et al. have shown that the dye squaraine (SQ) can be used for highly selective and sensitive detection of SM. As shown in Figure 1, the presence and

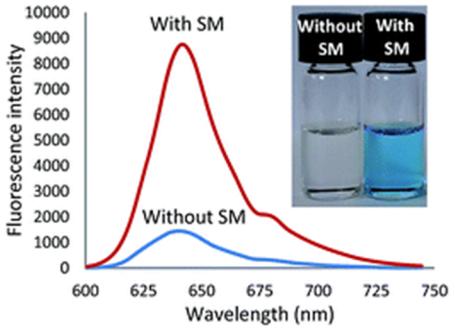

Figure 1. SM detection via fluorescence and color shift in PL. Reproduced with permission from ref 62. Copyright 2015 Royal Society of Chemistry.

absence of SM have different effects on the behavior of a SQ dye, resulting in different chromogenic and fluorogenic responses.[62] It is also possible to keep track of various PL parameters at the same time (for example, color and intensity) to enhance selectivity.

In general, fluorescent probes have attracted attention because of their sensitivity and ease of use. To achieve the desired selectivity in approaching a particular analyte, the detection site of a fluorescent probe is designed to enhance binding interactions. Usually, weak molecular interactions, such as hydrogen bonding, are used to favor the analyte over competing molecules.[60]

Recently, turn-on fluorescent probes have been developed that are activated by chemical interactions between the probe and analytes. Chemical probes consist of two parts: a binding unit/recognition site and a signaling subunit. This molecular recognition process is accompanied by electronic and optical changes in the signaling unit, which provides us with visible fluorescent or electrochemical signals, depending on the type of analyte to be detected. One of the most important characteristics of an efficient chemical probe is that it has high selectivity and sensitivity to the target analyte. It is necessary to combine the detection process with the photophysical behavior in a unique way to overcome the significant challenges. Due to their simplicity, reproducibility, and potential for point-of-care (POC) testing, colorimetric assays offer themselves as a general approach for molecular diagnostics.[63,64] A variety of chemical systems use selective color changes to detect the presence of an active ingredient or degradation product in the environment. Because of the small amounts of OPs in the atmosphere and in biological samples, they are difficult to detect.

3.1. Noble Metal Nanoparticle-Mediated Fluorescence Detection of OPs. Conventional optical detection methods may be biased due to the uneven distribution of NPs and instability of image sensors. Colored NPs and fluorescent markers can only detect reflection or fluorescence within the two-dimensional upper layers of the detection area. Magnetic NPs can display all magnetic signals in the test area. In addition, magnetic LFTS show low background magnetic signals from the analytes. They can be used as fluorescent dyes with variable fluorescence emission by changing the chemical composition, size and other factors. To detect magnetic signals, metallic materials are usually chosen as external coatings to effectively protect electromagnetic waves from external interference.[65]

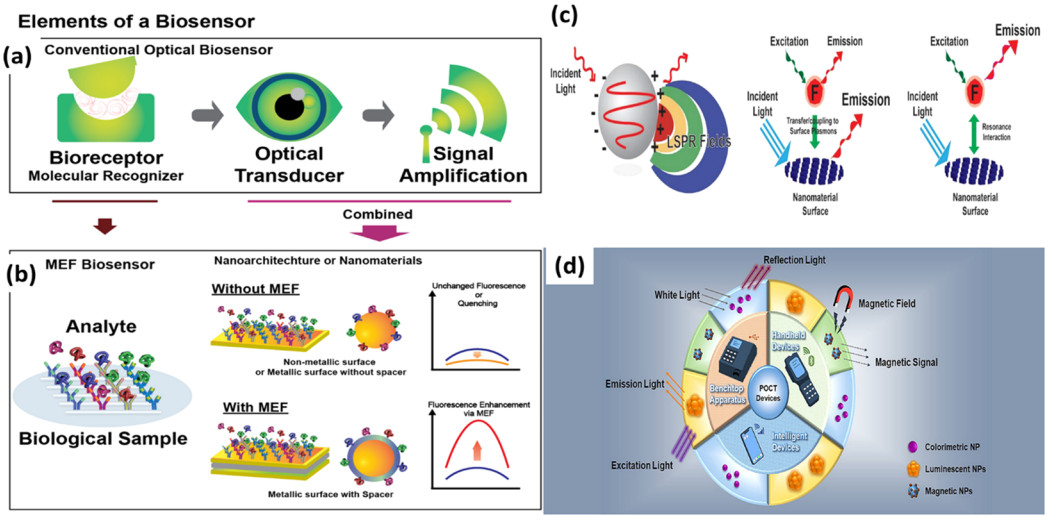

Figure 2. (a and b) Concept of conventional optical biosensor and its correlation to MEF platforms for optical biosensors. (c) Mechanism of MEF. Panels a–c reproduced with permission from ref 68. Copyright 2018 Elsevier. (d) Detection platforms for POCT. Reproduced with permission from ref 65. Copyright 2019 Elsevier.

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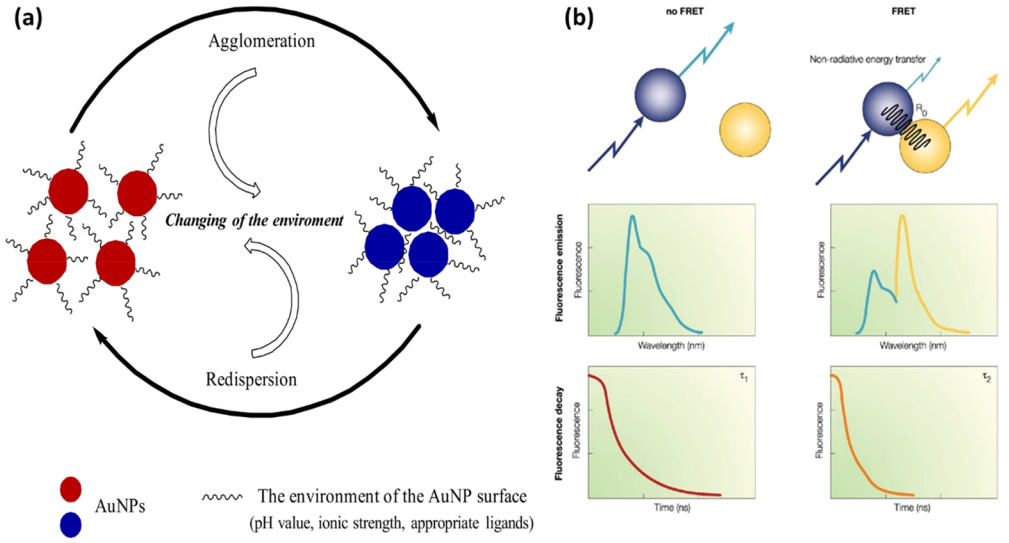

Figure 3. (a) Possible mechanism for the colorimetric AuNP sensors. (b) Mechanism of fluorescence resonance energy transfer (FRET). Panels a and b reproduced with permission from ref 36. Copyright 2016 Elsevier.

Color signal sources for magnetic signal detection are mainly based on colored immunoreactivity markers, such as silver, copper, gold, titanium, platinum, zinc, magnesium, iron, and algal nanoparticles. Others include metal oxide nanoparticles, which include titanium dioxide, silver oxide, zinc oxide, and other types of metal oxides.[66] Metal NP with local surface plasma resonance plays an important role in enhancing metal-enhanced fluorescence (MEF) and surface-enhanced Raman scattering (SERS).[67]

The fabrication process for such colored NPs is relatively mature, which greatly facilitates immediate detection. Moreover, with the development of nanotechnology, colored NPs have also been widely used for POCT due to their optical stability and high specificity. In addition, magnetic NPs, especially superparamagnetic NPs, have also been used in POCT because of their unique magnetic properties, as they are chemically inert and have different physiological properties. The considerable potential of metal NPs-based POCT is shown in Figure 2.

3.1.1. Gold Nanoparticles. Gold nanoparticles (AuNPs and GNPs) have distinct physical and chemical properties that make them a suitable scaffold for the development of new chemical and biological sensors. Due to their high interaction with visible light, AuNPs are excellent candidates for labeling applications. When free electrons in gold atoms are exposed to light, they are excited to a collective vibration known as surface plasmon resonance (SPR), which allows the gold to absorb and scatter visible light.[69] Well-dispersed AuNPs with particle sizes ranging from 3 to 10 nm form a red-colored solution due to their high SPR value at 520 nm. However, as shown in Figure 3a, the agglomeration of these AuNPs leads to surface plasmon coupling between the particles.[36]

AuNPs are effective fluorescence quenchers due to their extremely high molar extinction coefficients and broad energy range. As shown in Figure 3b, the fluorescence-based AuNP detection technique depends on the fluorescence change when the system hits the target due to surface-modified fluorescence (SMF) or fluorescence resonance energy transfer (FRET).[70]

Initial fluorescence research on AuNPs focused on fluorescent ligands such as pyrenyl, polyoctylthiophenyl, fluorenyl, and others. Later, water-soluble AuNPs were shown to exhibit photoluminescence. However, on solid surfaces, AuNPs show enhanced fluorescence at suitable fluorophore−metal distances. This effect is thought to be caused by far-field radiation reflected back to itself from the fluorophore.[71,72] The use of GNPs in the design and development of next-generation sensors is booming. They have unique properties such as the ability to detect analytes in situ, excellent selectivity for the analyte of interest, rapid response, and high sensitivity. The use of GNPs, especially in the development of fluorescence-based sensing techniques, is highly appreciated. The function of GNPs is essential for the occurrence of SMF, an effective mechanism that can be used to detect analytes of interest, especially CWA. GNPs offer a dual benefit for the design and development of fluorimetric sensors.[73] Knighton et al. showed imidazole and amine dansyl-ligated gold nanoparticle proof-of-concept capacity to detect sulfur mustard chemical warfare agent. As illustrated in Figure 4, the detection method involves the displacement of a quenched fluorophore on a nanoparticle surface, resulting in a "switching-on" fluorescence sensing response.[74]

Compared to other ratiometric sensors, ratiometric fluorescent quantum dots (RF-QDs) have a number of advantages, including improved resistance to photobleaching, narrower spectral line width, and ease of fabrication.[75] The internal filter effect (IFE) between AuNPs and quantum dots was used in Yan's group to detect organophosphorus pesticides. It was developed by hybridizing two quantum dots of different colors and has a built-in correction that minimizes environmental effects and improves the accuracy of the sensor. Under ideal conditions, the inhibitory efficiency was proportional to the logarithm of the PM concentration with a detection limit of 0.018 ng mL^{-1}, and the detection range was 0.04−400 ng mL^{-1}.[76]

In recent years, graphitic carbon nitride (g-C3N4), the most stable allotrope of carbon nitride, has emerged as a new class of carbon-based materials, particularly for its high fluorescence quantum yield.[77] It has been reported that the fluorescent probe g-C_3N_4 can be used to detect OPs. More importantly, for the field of spectrofluorometry, Xie and colleagues demonstrated that AuNPs-based IFE with fluorescent probes is a viable technique. A simple, green, and sensitive dual

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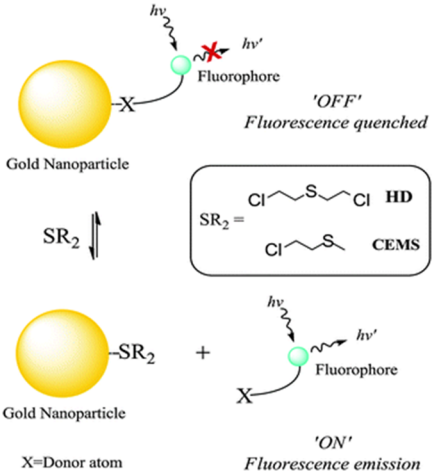

Figure 4. Mechanism of sensing of sulfur mustard by displacement sensing assay. Reproduced with permission from ref 74. Copyright 2013 Royal Society of Chemistry.

signaling (fluorometric and colorimetric) detection technique for OPs was developed for the first time using g-C_3N_4 as a fluorescent probe and AuNPs as a colorimetric probe. The inner filter effect of AuNPs may effectively quench the fluorescence of g-C3N4. AChE may catalyze the conversion of acetylcholine (ACh) to thiocholine, resulting in the aggregation of AuNPs and fluorescence recovery, as well as a color shift from claret red to blue. OPs have the ability to permanently block AChE activity, preventing AuNPs from aggregating and fluorescence recovery, when added into the system as demonstrated in Figure 5a. The suggested technique enabled the detection of OPs at concentrations as low as 6.9×10^{-12} M, and more significantly, the sensor demonstrated potential applications for OPs analysis in real samples.[78] Another possible strategy to consider is the use of gold nanoparticles in the development of chromofluorogenic probes for nerve agent detection. Yet, another possible strategy that should be considered is the use of gold nanoparticles in the development of chromofluorogenic probes for the detection of the nerve agent soman and its mock-up diethyl chlorophosphate (DCP). The *N*-(rhodamine B)-lactam-2-(4-cyanophenyl)-thiourea probe (RB-CT) with a rhodamine core coupled to a cyanophenyl thiosemicarbazide group responded rapidly and exceptionally sensitively to DCP. The probe showed significant fluorescence and color change. As shown in Figure 5b, the detection limit is as low as 2×10^{-6} M.[79]

A semiquantitative visual detection method for organophosphate pesticides was described by Wu et al. It is based on the property of AuNRs that their absorbance is proportional to their aspect ratio. This is due to the presence of gold nanorods that exhibit localized surface plasmon resonance (SPR). The Au(III) complex developed with cetyltrimethylammonium bromide (CTAB) can be used to change the aspect ratio. It is affected by AChE-mediated hydrolysis. This reaction is inhibited by OPs. The amount of remaining Au(III)-CTAB complexes is negligible in this case, and no etching of AuNRs occurs. However, in the presence of OPs, AChE activity is suppressed. Au(III) has the ability to etch AuNRs and change the aspect ratio of the etched AuNRs. This results in a color shift from brownish to gray, cyan, green, blue, violet, red, and colorless, which is clearly visible to the naked eye. The technique had a detection limit of 1.2 ppb and a linear range from 0.01 to 1.84 ppm when it was used to detect parathion.[80]

3.1.2. Silver Nanoparticles. Silver (Ag) nanostructure is considered one of the best options for the application of SERS due to its highly desirable plasmonic properties, low cost, and ease of fabrication/synthesis.[81] Rhodamine 6G (R6G)/Ag nanowires (NWs) were developed by Jeong et al. for the detection of CWA based on the sensitive fluorescence changes of R6G by adsorption of various CWA derivatives. This shows that R6G/Ag nanowires can be used for the detection of CWA.[82] Lafuente et al. conducted further research that led to the development of SERS substrates for chemical detection of certain CWA. They achieved this by depositing Ag nanoplatelets on three different substrates: (i) conventional SiO_2/Si wafers, (ii) stainless steel mesh, and (iii) graphite foil. SERS signal amplification was investigated using rhodamine 6G (R6G) as a typical liquid-phase probe molecule. They performed a detailed investigation of all substrates with wavelengths of 532, 633, and 785 nm. Graphite was found to be the most effective material for this application due to its

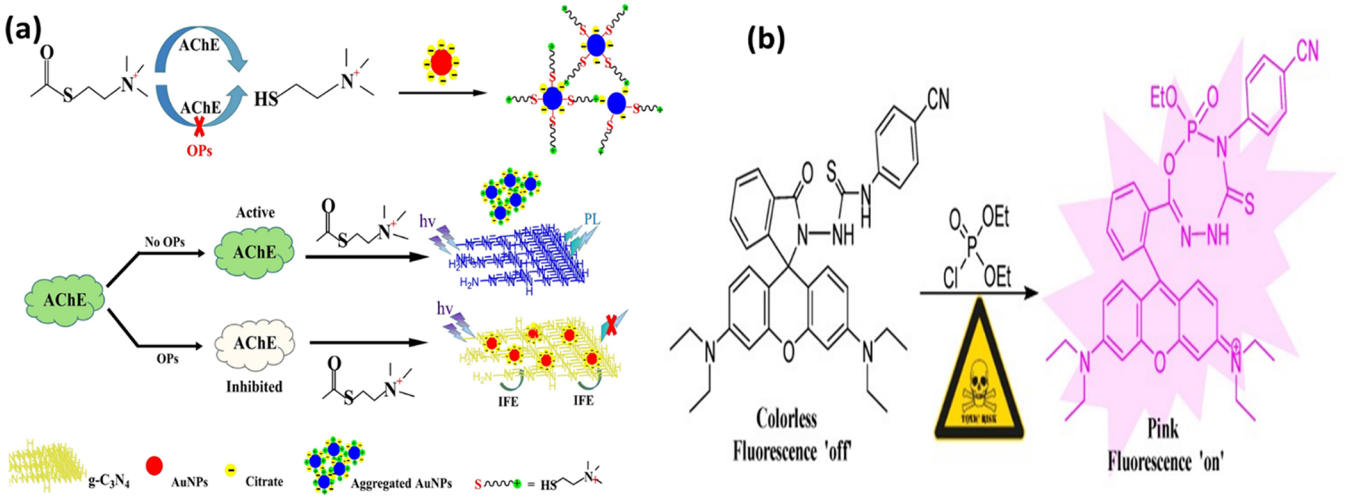

Figure 5. (a) Schematic illustration of the organophosphorus pesticide dual-signaling assay. Reproduced with permission from ref 78. Copyright 2018 Elsevier. (b) Proposed mechanism of RB-CT with DCP. Reproduced with permission from ref 79. Copyright 2019 The Authors under Creative Commons International CC BY 4.0 License, published by MDPI.

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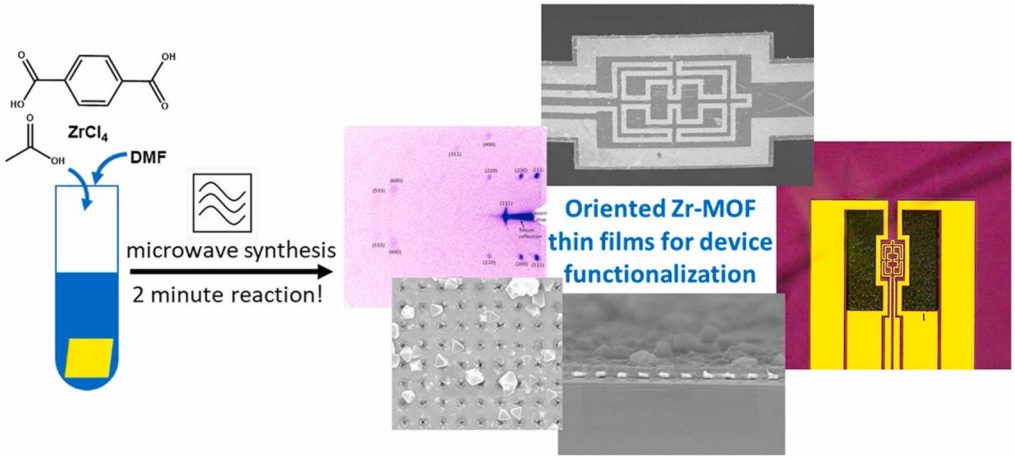

Figure 6. Functionalization of two sensor architectures, plasmonic nanohole arrays and microresonators, on UiO-66 thin films. Reproduced with permission from ref 88. Copyright 2021 Elsevier.

high efficiency in quenching the fluorescence signal. Using the optimal laser wavelength of 785 nm, which corresponded to the plasmon resonance of the silver nanoplatelets, the best substrate was determined and investigated. A clear spectrum of R6G was detected only on a graphite substrate. The interactions of the DMMP molecule with the silver surface alter the intensity and position of the vibrating Raman bands. The SERS tests performed on various prepared samples using the portable Raman instrument for 2.5 ppmV in the gas phase showed a short response time. In addition, a repeatable molecular fingerprint and a relative standard deviation of 5% in the SERS intensity signal were demonstrated, opening the door to practical applications.[83]

3.1.3. Zinc Nanoparticles. Among several metals, zinc has attracted the most interest due to its high reduction potential, low reactivity, and five stable isotope compositions. Among the various types of zinc-based nanostructures, such as sulfide, ferrite, phosphide, selenide, and telluride, zinc oxide (ZnO) is the most interesting due to its wide range of applications, environmental friendliness, and diverse physiochemical properties.[84] Yoo et al. have demonstrated the use of hydrothermally prepared Al-doped ZnO NPs to fabricate a dimethyl methyl phosphonate (DMMP) gas sensor. Over a range of operating temperatures, the response and recovery times of the Al-doped ZnO NP sensors differed dramatically, with the fastest response and recovery times occurring at room temperature at 2 and 96 s, respectively. The Al-doped ZnO NP sensor showed excellent sensitivity and selectivity for DMMP, according to the results.[85]

Since the discovery of MOFs, increasing efforts have been made to develop materials that target specific gases, as MOFs offer unparalleled tunability compared to other conventional porous materials.[86,87] The discovery of a chemically stable MOF that maintains its structural integrity even when exposed to moisture and corrosive gases has also inspired scientists to develop CWA-trapping MOFs. Using MOFs as a tool to identify potential CWAs is another option worth considering. Appelhans et al. developed thin films of zirconium MOFs on gold and silicon for CWA detection applications. They reported that thin films of UiO-66 and UiO-66-NH_2 formed on gold substrates in a very short time span of 2 min, while they could be generated on Si substrates in 30 min. The thin film synthesis with two sensor architectures is shown in Figure 6.[88]

3.1.4. Other Metal Ion Complexes. The development of electrochemical CWA sensors is favored by the use of other metallic nanomaterials, such as Cu, Ni, and Co nanomaterials, due to their excellent properties, which include high conductivity, large specific surface area, and environmental friendliness. Verma et al. synthesized copper oxide (CuO) nanoparticles, by DC magnetron sputtering, that were used for adsorptive degradation of 2-chloroethyl ethyl sulfide (CEES) to detect sulfur mustard. XRD, TEM, FE-SEM, N2- BET, FT-IR, and TGA were used to characterize the synthesized CuO nanoparticles. This experiment allows a wide range of particle sizes, and a chemical mechanism for CEES decontamination is proposed, in which CuOH breaks the S−C bond. The material was studied at different annealing temperatures: 200, 400, 600, 750, and 900 °C. The kinetics of the degradation of CEES over CuO nanoparticles was studied, and it was found that DC-sputtered CuO nanoparticles have better decontamination ability vs CEES.[89] Ni nanoparticles have been repeatedly used as an effective modifier in electrochemical sensors to detect CWAs. Alali's group has fabricated 3D hybrid Ni-MWCNTs/CNFs nanomaterials for the detection of sarin. Due to the enormous specific surface area and good electrochemical performance of the 3D Ni multiwall carbon nanotube/carbon nanofiber nanostructure, it has attracted great attention. The hybrid 3D Ni-MWCNTs/CNFs had a larger surface area of 530 m2/g than Ni/CNFs, which had a surface area of 375 m2/g. At room temperature, a 3D hybrid Ni/carbon nanomaterial exhibits 18.8 responses to 1 ppm DMMP. Moreover, the newly fabricated sensor exhibits excellent sensitivity, specificity, and stability.[90] Alali et al. synthesized a composite of Co_3O_4/CuO NTs with p−p heterojunction. Further functionalization of Co_3O_4/CuO NTs with HFIP leads to a highly detectable DMMP. The enhanced detection of DMMP is the result of photoactivation of p−p heterojunctions, Co_3O_4/CuO NTs, and functionalization of HFIP. Due to the H-bonding in the HFIP Co_3O_4/CuO NTs, strong DMMP selectivity was shown upon light activation. Photoactivation significantly improved the sensing capability of the hybrid HFIP-Co_3O_4/CuO NTs.[91]

4. CONCLUSIONS AND OUTLOOK

Public safety is an ongoing topic of discussion. With the increasing number of incidents involving the use of chemical warfare agents, scientific research efforts continue to find a

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reliable method to detect such threats and provide early warning. The introduction of CWA is unfortunately a fact of life in the modern world. The use of chemical weapons by rogue states or terrorist organizations has shown their true colors in the past and even more so in recent years. Therefore, the CWA outbreak has shown the importance of being prepared for the next global threat of chemical toxins. Nerve agents are extremely toxic and act quickly, requiring rapid detection and intervention. Therefore, it is critical for first responders to determine their exact nature at the scene of a CWA attack so they can respond with appropriate countermeasures to minimize harm, underscoring the need for rapid detection and clinical intervention.

From a medical point of view, different biomarkers are present in different concentrations from patient to patient. As a result, the amplification factor required for diagnosis is different and the values of the amplification factor are different. Consequently, calibration is required between the amount of the present biomarker and the value of a "positive result". For this, combining different techniques, such as SERS and MEF, could further increase the reliability of biomarker detection. Clearly, concentrated efforts are needed to focus on the ideal characteristics of a clinically useful assay. This can only be achieved in collaboration with doctors.

Simplicity, accessibility, and affordability are critical for successful clinical implementation of screening technology. To have the desired impact for individuals and society, early detection of OP must be accessible to all and integrated into healthcare systems—because, regardless of the form of implementation, downstream decisions, testing, and treatment will depend on experts. Crucially, there is a need to link earlier detection with optimal treatment paradigms. Fluorescence detection, in which the sensing material undergoes a chemical reaction with the active ingredient that causes a significant change in brightness, is one of the most commonly chosen methods for detecting and specifying nerve agents. The likely advantages of optical detection include device portability, real-time monitoring, and rapid and selective detection. If the functionality of the sensor material is carefully selected to be specific to a nerve agent, optical detection is less susceptible to interference.

As indicated earlier, future development toward on-site fluorescence detection that benefits from little to no background signal from biological agents is desirable. Because of their exceptional stability, increased sensitivity and selectivity, and capacity to decrease overall analysis time, metals have recently appeared as potential nanomaterials for on-site fluorescence detection of CWAs containing nerve agents. By synthesizing various metallic nanostructures in solution and on a substrate, optimizing plasmonic properties to couple with a specific fluorophore to enhance signal and sensitivity is feasible. Selecting examples where MEF has already been used for detecting different biomolecules will exhibit the potential for clinical translation as the next step forward. As a result, metal nanoparticles are progressively being used in fluorescence detection of CWA.

Proceeding investigation is required to identify reliable and encouraging solutions for unintentional and intentional CWA exposure. In conclusion, we highlight the significance of bridging the gap between materials science and chemical reactivity in detecting CWA. All current technologies discussed in this work have benefits and drawbacks, and there is room for advancement based on the following main points:

- The main problems remain improving detection reliability and minimizing false responses. Combining multiple sensing approaches and developing a "single probe" for CWAs could be a proven strategy to address this issue.
- Quantitative detection of CWAs is needed to develop viable multicolor colorimetric platforms based on noble metal nanomaterials. Color discrimination by the naked eye could only provide half-meaningful results. Therefore, multicolor sensing needs to be improved to meet the requirements of practical applications. Consequently, the combination of multicolor monitors and POC devices could enable the qualified use of plasmon-based colorimetric studies.
- However, the challenge of bridging the gap between simulation experiments and real conditions remains real. The design of appropriate experimental tests should take into account relevant environmental conditions such as those encountered on a battlefield.

The transformation of this technique from the laboratory to the large-scale application brings both opportunities and challenges. Looking ahead to the next century, the highest priority in research into reactive decontamination is to identify both liquid and solid decontaminants that have no adverse impact on the environment.[92]

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Notes

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ACS Omega 2022, 7, 27079−27089

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