Review Article

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Latest developments in the upconversion nanotechnology for the rapid detection of food safety: A review

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Abstract: Food safety has become a topic of global concern in the recent decades. The significant food safety incidents occur from time to time around the world, seriously threatening the public health and causing extensive economic losses. In particular, the occurrence of COVID-19 highlights the importance of the food safety for the public health. Therefore, there is an urgent need to establish a fast, simple, sensitive, and efficient method for the detection of food safety. In recent years, the upconversion (UC) nanotechnology has been widely used in the field of food detection. The UC fluorescence analysis technology possesses the advantages of ultra-sensitivity detection, non-invasiveness, light stability, etc., and has broad application prospects in the field of food safety. After cladding and surface modification, it can be combined with other substances through a variety of mechanisms, such as electrostatic interaction, thereby expanding its application in the food safety detection. Thus, overall, there is a vital need to evaluate and utilize the potential of UC nanoparticles in the field of rapid detection of food safety.

Keywords: food safety, upconversion nanoparticles, rapid detection, sensors, surface modification

1 Introduction

Food safety exhibits that the food is non-toxic, harmless, green, and healthy, along with meeting the required nutritional requirements. In addition, it does not cause any acute, subacute, or chronic harm to the human health. With the rapid economic development, the living standards have also been significantly improved. Thus, the food is also needed to be supplied at an accelerated pace, thereby prospering the food markets [1]. However, owing to the contradiction between the people’s growing needs for a better life and the unbalanced and insufficient development, the food safety incidents occur frequently, such as an excessive content of additives in food [2,3], use of illegal additives [4,5], presence of heavy metals [6,7], excessive veterinary drug residues [8,9], and microbial contamination [10]. These issues have aroused an unprecedented attention of the consumers and industry with respect to the food contamination issues [11,12].

In recent years, the food-borne diseases and food poisoning incidents caused by the pathogenic microorganisms and pesticide residues have been frequently observed. Among these, the food-borne diseases resulting due to the pathogenic microorganisms represent a vital food safety and public health issue [13–15]. Recently, the popularity of the functional foods has prompted a large number of food manufacturers to start their production. Though such foods provide consumers with health benefits, the excessive use of some additives is worrying [16]. Diclazuril is a broad-spectrum anti-coccidial drug which is widely used to eliminate insects in chickens, ducks, and other animals. It often causes poisoning and other harmful
effects in the human body. Therefore, a rapid and sensitive method for the determination of diclazuril in chickens is urgently needed [17]. *Clostridium perfringens* is a well-known pathogen leading to food-borne diseases, it can cause diseases such as gas gangrene and food poisoning, thus, causing a serious harm to the human body [18–20].

In the coming years, the applications of nanomaterials in the food and food chain are expected to increase, continuously. Although this brings exciting opportunities to the consumers and the food industry, the potential harmful effects on the human body needs to be carefully considered, thus reiterating the need to establish rapid and safe methods for on-site inspection and supervision [21]. Sausages or ham extracted from the deer skin, red deer, or spores are the typical meat products in the high mountainous regions of Germany, Italy, Austria, and Switzerland. However, a considerable number of products do not declare their contents, thus, it is urgent to establish a rapid method for the accurate determination of their content [22]. The pasta salad recall in 2018 and the watermelon recall in 2019 at different places indicate that the fresh produce-borne diseases caused by the pathogens represent a serious food safety issue facing the world [23]. As a global public health problem, food safety has attracted a great deal of attention [24]. Therefore, the efficient analysis of the food safety issues and establishment of the rapid and effective detection methods are needed to protect human health, to ensure the healthy and stable development of the food safety system, as well as realize the food safety strategies [25].

The traditional laboratory detection methods include atomic absorption spectrophotometry, gas phase chromatography, high-performance liquid chromatography, etc. These methods have cumbersome sample preparation, protocols, and long detection time [26–28]. Using such methods, it is difficult to meet the needs of high throughput, effective, and low-cost on-site detection and supervision. Therefore, the development of new materials and technologies for the rapid food inspection is becoming increasingly important [4].

The literature studies have reported that the supercritical nanoparticles, especially the rare earth-doped supercritical nanoparticles, possess significant optical properties (including high photobleaching resistance and clear emission band) and demonstrate the eye-catching characteristic spectra [29,30] (fairly long emission lifetime and no autofluorescence background). As a series of functional materials, the luminescent material can absorb incident energy and subsequently emit it in the form of photons. The majority of the luminescent materials follow Stokes law, which stipulates that the energy of the emitted light is lower than the energy of the absorbed light, thus, they are also called downconversion materials [31,32]. In contrast, rare earth doped upconversion fluorescent nanoparticles represent a new generation of fluorophores, which can convert low-energy long-wavelength near-infrared light into high-energy short-wavelength light (ultraviolet and visible light). Hence, the upconversion nanoparticles’ (UCNs) phenomenon follows the anti-Stokes process [33–36]. The rare-earth-doped UCNPs possess significant advantages. As a result, they are increasingly employed in many emerging applications [37–40], such as background-free imaging [41,42], biological tags [43,44], magnetic field detection [45], biological detection [46,47], UC micro-lasers [48,49], solar cells [50,51], etc.

In recent years, the upconversion luminescence (UCL) technology has received a significant research attention, and the application of the UCL materials for the detection of the food microorganisms and toxic pollutants [52–55] has gradually become a research hotspot [56]. In particular, the rare earth-doped UCNPs can excite light in the continuous-wave near-infrared lasers, which increases its penetration depth in the tissues and reduces the damage to the organisms [4,57–60]. As a powerful and sensitive luminescent nanoprobes, UCNPs have obvious advantages in detecting the toxic ions [61,62], dyes, and drug molecules. For this reason, for overcoming the sample preparation, long detection time, and low detection accuracy [63–65]. This study mainly reviews the luminescence mechanism, synthesis methods, surface modification challenges, and applications of the UC luminescent nanomaterials for food safety inspection.

### 2 Introduction of UC nanomaterials

#### 2.1 Luminous mechanism

The UCL is essentially an anti-Stokes luminescence process, representing the process of obtaining the high-energy photons from the low-energy excitation. As the energy level life of the metastable state is relatively long, photon can stay at a metastable energy level for a longer time, and there is no cross-relaxation before the second photon is absorbed. In other words, the multiphoton absorption process can be used to achieve the transition from the ground state to the high-energy excited state, which in turn produces a high-energy radiation [66]. There are many types of UCL processes associated with the earth ions. The luminescence mechanism has been summarized in detail in Figure 1.
2.1.1 Excited state absorption (ESA)

ESA is the continuous absorption of (at least) two photons in a single ion UC process. The electrons that absorb the ions are mainly organized in the ground state electron configuration G. As long as the resonance condition is met, the single-photon absorption takes place, and the ground state electron is simultaneously elevated to the first metastable excited state E1. This transition is called ground state absorption. In case a resonance state is encountered, the long-life characteristic of the metastable excited state allows the absorption of the second further excited electron excite to a higher excited state E2. This transition is termed as the ESA. The radiation relaxation returns the excited electron to the G state, thus, resulting in the emission of a photon with a higher energy (shorter wavelength) than the two absorbed photons. Assuming that the energy difference between G to E1 and E1 to E2 is equal, the excitation can be achieved by a monochromatic excitation source, as the resonance requirements for each electronic transition are the same [67].

2.1.2 Energy transfer upconversion (ETU)

The UC emissions achieved through the ETU approach are similar to the core ESA process. In order to attain the highest metastable excited state E2, two sequential absorptions of the resonant excitation photons are needed. The unique feature of the ESA and ETU approaches is that there is a non-radiative energy transfer channel between the adjacent ions. As shown in Figure 1(b), as a sensitizer, Ion1 absorbs the pumped photons that are excited from the G state to the intermediate energy level E1. Ion2 (denoted as an activator) can correspondingly be excited to the metastable state E2 due to the non-radiative energy transfer from the Ion1 (denoted as a sensitizer), followed by its return to the G state. Once the high-energy electron returns to the G state twice, the Ion2 will be excited to the upper emission state E2. This non-radiative energy transfer process can be replaced by three different ways, including continuous energy transfer, coordinated UC, and cross-relaxation [68].

2.1.3 Cooperative sensitization upconversion (CSU) and cross relaxation (CR)

As shown in Figure 1(c), the CSU process involves three lanthanide ions, among which the Ions1 and 2 are usually of the same type. Both Ions1 and 2 absorb the photons that are excited to an excited state, followed by the interaction with the Ion3 to excite it through the coordinated energy transfer. The excited Ion3 emits the upconverted photons and returns to the G state. Obviously, the efficiency of the CSU process cannot be compared with the efficiency of the ESA or ETU process. CR is a non-radiative relaxation process involving two identical or different ions. In the CR process, as shown in Figure 1(d), the Ion1 transfers a part of the energy of the E2 energy level to the Ion2, such that the Ion2 is transferred to a higher excited state, and Ion1 returns to a lower energy state. Although CR is related to the deleterious concentration quenching effect, it can be utilized to regulate the emission spectrum of UCNPs.

2.1.4 Photon avalanche (PA)

The PA process is a combination of the excited state absorption and cross relaxation (CR). Specifically, ESA is the beginning of the PA process, as shown in Figure 1(f), the Ion2 rises from E1 to the higher energy state E2. Afterwards, the CR process takes place, resulting in the E1 state of the intermediate Ions1 and 2. In the end, the Ion1 transfers the obtained energy to the G state electron 2 for populating the E1 level, thus, realizing a complete loop process and doubling the population of the Ion2 at the
2.2 Synthetic methods

In recent years, the nano-luminescent materials doped with the rare earth or transition metal ions have attracted much attention, and many synthetic methods have been explored. As a result, the rare earth nanomaterials of various shapes and sizes are constantly being developed [70,71], such as spheres, rods, lines, flakes, hexagons, etc. [72–76]. Herein the traditional methods to synthesize the rare earth luminescent nanomaterials are summarized, as shown in Table 1.

2.2.1 Hydrothermal synthesis

The hydrothermal method refers to the nanomaterial synthesis by hydrothermal reaction under high-temperature and high-pressure conditions, using water or steam as the reaction system [77]. A typical hydrothermal reaction is carried out in special reactor. Zhang et al. [78], by hydrothermal reaction, synthesized monodisperse and uniform $Y_6O_5F_8:RE_{3+}$ ($RE = Yb, Er, and Ho$) microarchitectures with various morphologies. Hollow hexagonal prisms, microbundle gatherings by rods, and solid hexagonal prisms were designed by employing different additives. Xu et al. [79], using phase change delay, presented that the orthorhombic crystal structure of the UCNPs was stored by hydrothermal method. The optimum doping concentration of Y$^{3+}$ or Gd$^{3+}$ was increased from 10% mol to 30% mol merely by using the oleic acid as a solvent instead of H$_2$O, which could efficiently increase UC performance. Because of the breakdown of the symmetry of lanthanide site, this change would happen.

2.2.2 Phase transfer hydrothermal synthesis

The phase transfer synthesis mechanism of alkyl carboxylic acid and its heavy metal brine thermal system is summarized as follows. First, through the ion exchange process, the heavy metal ions containing the rare earth salts enter the solid phase to exchange the sodium ions to metastable state $E_1$. As the cycle progresses, the avalanche effect takes place, followed by the UC of PA caused by the E2 state of the Ion2. In addition, UCL derived from PA depends on the power of the pump, and only a specific threshold can be generated to produce a significant UCL process [69].
form an alkyl chain carboxylic acid complex. Subsequently, it is reduced at the liquid–solid or solid–solid interface, and the periphery of the nanoparticles is wrapped with the alkyl chains to form a hydrophobic outer layer structure. As the nanoparticles develop to a certain extent, they settle down due to the action of gravity, followed by collection at the bottom [80]. By using phase transfer hydrothermal method, the UCNPs with control-label size and shape can be prepared with different nano-dimensional architectures.

2.2.3 Co-precipitation method

The chemical co-precipitation method involves the dissolution of the raw materials in a solvent to form a salt solution containing a variety of soluble cations. A suitable precipitant is subsequently added to form an insoluble co-precipitate, and the required powder is obtained after the post-treatment of the sediment. The synthesis conditions are mild and the equipment is easy to operate. The uniform particle size distribution and reliable particle size. Marciniak et al. [81], using co-precipitation method, prepared the upconverting nanocrystals of KLa₉ₓErₓYbxP₅O₁₄ and La₉ₓ₋₀·₇Erₓ₀·₃YbxP₅O₁₄. The nanocrystalline powders consist of well crystallized, agglomerated nanograins of average grain size 30 nm. Chen et al. [82], with the method of co-precipitation, successfully obtained the core–shell NaGdF₄:Yb,Er@NaGdF₄-Yb,Nd UCNPs. The probe of these UCNPs was applied to real sample analysis with satisfactory results.

2.2.4 Sol–gel method

In the sol–gel method, organic or inorganic compounds are prepared from oxides or other solid compounds by sol-gelation and heat treatment to produce molecular or even nanostructured materials [83]. As it is difficult for this method to control the shape and size of the nanoparticles, it cannot achieve monodisperse nanoparticles, and the product is often doped with carbon particles. Hyppänen et al. [84] prepared nanocrystalline upconverting phosphors with zirconium oxide (ZrO₂) as the host lattice with sol–gel method. By this method, mixture of both the cubic and monoclinic form and good luminous intensity material can be obtained. Liao et al. [85], by the simple sol–gel method, prepared Gd₃TiO₇:Yb⁺³⁺/Er⁺³⁺ nano- phosphors. To obtain the Yb, Er, and Gd nitrates, the Yb₂O₃, Er₂O₃, and Gd₂O₃ are dissolved in dilute nitric acid. Then, citric acid, as a chelating agent for the metal ions, was added. Subsequently, the tetrabutyl titanate dissolved in ethanol was added to obtain a transparent solution with stirring. At 80°C, the sol is converted into gel, which is dried at 120°C and annealed at 1,100°C.

2.2.5 Thermal decomposition method

The thermal decomposition method involves mixing of the organometallic compounds (trifluoroacetate containing rare earth elements) with the long-chain alkyl surfactants (oleic acid, oleylamine, 1-octadecene, etc.) followed by decomposition at a high temperature. The process involves the formation of the crystal nuclei, along with maintaining a certain temperature for re-growth [86]. Wang et al. [87] fabricated inexpensive and eco-friendly carbon dot fluid by the direct thermal decomposition method. It has great application potential in the field of printable electronics, solid state lighting, and so on. Although pyrolysis has proven to be an effective method for the synthesis of monodisperse, highly crystalline, homogeneous and pure UCNPs, it still has some shortcomings, such as long time, high temperature and the production of toxic substances during the synthesis process.

2.2.6 Microemulsion method

A microemulsion refers to an isotropic, transparent or translucent, and thermodynamically stable dispersion system formed by two mutually insoluble liquids (water and oil phases) by the action of a film composed of the surfactants and co-surfactants [88]. Bensalah et al. [89] reported the synthesis of undoped as well as Yb- or Er-doped CaF₂ nanocrystals using a reverse micelle method. The products were single phased and rather monodispersed with an average particle size around 20 nm. By heating the as-obtained nanoparticles at different temperatures, the particles’ size was increased.

2.2.7 Combustion synthesis

The combustion synthesis refers to the combustion reaction of the precursors to obtain the products. The process is as follows: after uniformly mixing the reactants and combustion agent, the precursor is transferred to a crucible and is placed in an electric furnace at a certain temperature. As the precursor attains the temperature sufficient to initiate the exothermic reaction, ignition takes place, and the reaction is subsequently maintained by the released heat. The combustion product represents the desired synthesis product [90]. For the first time, Zhang et al. [91], by using decomposition method,
prepared the triangular LaF₃ nano powders with plate-like morphology by decomposition method using La(CF₃CO₂)₃ precursor in OA/ODE at 280°C. They discovered the instant decomposition of La(CF₃COO)₃ followed by simultaneous LaF₃ nuclei formation.

2.3 Surface modification

Generally, the UCNPs are hydrophobic and can be dispersed in the non-polar solvents. However, a majority of these cannot be dispersed in water. Their non-dispersibility in water significantly limits their application in the field of food safety testing [92,93]. As an alternative, the surface modification of the UCNPs can overcome this issue. A number of methods have been developed to modify the UCNPs [94–102], as classified in Figure 2. After surface modification, the UC fluorescent nanomaterials can be combined with other substances through covalent coupling, such as the coupling of carboxyl and amino ligands, electrostatic adsorption, and van der Waals forces, thereby achieving a rapid detection of food safety.

2.3.1 Surface passivation

The surface passivation method involves the coating of a passivation layer (such as a rare earth layer) on the surface of the nanoparticles to protect the exposed doped ions. Such a process effectively prevents the excitation energy from being transferred to the surface of the nanoparticles, thus, improving their luminous efficiency. For instance, the coating of a SiO₂ layer on the surface of the UC luminescent nanomaterials, which hydrolyses the precursor of tetraethoxysilane, demonstrates the advantages of high stability, water solubility, and dual compatibility. As a result, this system is widely used for surface modification of the UC fluorescent nanoparticles. Duan et al. [68] obtained meso-porous silica structure by using the CTAB to form micelles during silica shell formation. Then, at certain pH or by refluxing particles, the micelles can be taken away through washing the colloid. The mesoporous silica shell of UCNPs was successfully prepared.

2.3.2 Surface functionalization

The chemical or physical modification of the UCNPs can generate the functional groups with unique chemical or physical properties. For instance, the ligand oxidation method involves the strong oxidants to oxidize the unsaturated bonds on the surface of the nanoparticles into active functional groups (such as carboxyl, aldehyde, etc.), so as to realize the connection and molecular labeling between the nanoparticles and biomolecules. This method has no obvious adverse effects on the morphology, composition, and UCL performance of the UCNPs. However, this method is only suitable for the ligands containing the carbon–carbon unsaturated bonds. As the surface of the nanoparticles is mostly coated with oleic acid or oleylamine ligand molecules, this method can be employed for the surface modification of a majority of the UCNPs. The polymer coating method uses the hydrophobic end of an amphiphilic polymer (such as PEG) and UCNPs so as to coat the surface of the nanoparticles through van der Waals force. The hydrophilic end is compatible with water and forms a hydrophobic/hydrophilic organic core–shell structure [103]. The method can effectively overcome the water solubility issue of the nanoparticles and weakens the fluorescence quenching effect of water on it.

The methods presented in Figure 2 can be divided into two categories: surface passivation and surface functionalization. Surface passivation includes SiO₂ coated, while surface functionalization includes ligand oxidation, ligand exchange, amphiphilic ligand coating, ligand stripping, and layer by layer self-assembly. Ligand exchange includes direct and indirect substitution; Ligand coated
includes phospholipids coated and amphiphilic polymer package.

3 Application in food safety detection

Food safety is a vital priority related to the human health. With the development of technology, the rapid food safety detection methods are also constantly improving [12]. The unique luminescence mechanism of the UC luminescent nanoparticles makes them the superior biomarker materials. At present, the research on the UC luminescent nanotechnology in the field of food safety is mainly focused on the detection of microorganisms in food [104,105], small molecule organic pollutants [106], heavy metals [107], etc.

3.1 Detection of food-borne pathogens

The food-borne diseases caused by the pathogenic bacteria represent one of the main threats to the food safety. For instance, the investigations reveal that the food-borne diseases are still a public health problem threatening the developing countries like India [108]. In the densely populated provinces of South Africa, the detection rate of the multi-drug resistant Escherichia coli isolated from the fresh vegetables sold by the regular and informal traders is higher than other countries [109]. Therefore, it is of high significance to develop a simple and effective method to identify the food pathogens.

Jin et al. [110] developed a novel detection platform based on the fluorescence resonance energy transfer (FRET) process for the rapid, ultrasensitive, and specific bacteria detection. In this process, the gold nanoparticles (AuNPs, acceptor) were conjugated with aptamers, while the UCNPs (donor) were functionalized with the complementary DNA (cDNA). The spectral overlap between the fluorescence emission of UCNPs and absorption of AuNPs enabled the FRET process to take place, leading to the UC fluorescence quenching. The aptasensor successfully detected Es. coli ATCC 8739 (as a model analyte) with the detection range of 5–10⁶ cfu mL⁻¹ and a detection limit of 3 cfu mL⁻¹. It was further used to detect E. coli in the real food and water samples (e.g., tap/pond water, milk, etc.) within 20 min. Comparing to traditional methods, it greatly shortened the detection time and improved the detection efficiency. Overall, the developed sensor demonstrates a high potential in the field of food safety detection and supervision. Due to the specificity of DNA, this method can only detect a single kind of bacteria, thereby limiting its application range.

Wang et al. [111] realized the identification of seven common food-borne pathogens by constructing an UC fluorescent sensor array based on the anti-Stokes lumiphores, as shown in Figure 3. The method employed the linear discriminant analysis with an accuracy of 100%. In addition, the developed method accurately identified the bacterial mixture. The bacteria in the real samples (tap water, milk, and beef) could also be effectively identified with an accuracy rate of 92.1%. The sensor overcame the time-consuming bacteria culture and heavy dependence on specific recognition elements. The high efficiency of the whole bacterial cell detection can brighten the application of fluorescence sensor array.

3.2 Biotoxin detection

3.2.1 Bacterial toxin detection

Almost all bacteria synthesize toxins to maintain survival by regulating the different cellular processes as well as cause disease by interacting with the host cell. Generally, the “bacterial toxin” refers to the virulence factors that harm the host [112]. In many countries, the water-borne diarrheal diseases such as the travelers’ diarrhea and cholera still threaten the public health. A rapid diagnosis of the infectious diseases is essential to prevent the disease outbreaks from escalating into epidemics [113].

Wang et al. [114] employed the UC luminescent nanoprobe technology to detect Staphylococcal enterotoxin. Specifically, an ultra-sensitive detection method for Staphylococcal enterotoxin B (SEB) was established based on the nucleic acid aptamer recognition-upconversion fluorescent nanoprobe technology. It combined the resonance energy transfer and enzyme-catalyzed signal amplification technologies. SEB revealed a linear relationship in the concentration range of 0.001–1 ng mL⁻¹, and the detection limit was determined to be up to 0.3 pg mL⁻¹. The detection method demonstrated a positive correlation with the traditional ELISA method and was proven to be a fast and ultra-sensitive method.

3.2.2 Detection of mycotoxins

Mycotoxins are the toxic metabolites of fungi that contaminate the food and feed. These toxins pose acute and
chronic health threats to both humans and animals [115]. For instance, Fusarium head blight is a common fungal disease, which not only affects the human health, but also damages the food crops worldwide. It poses a major threat to the food security and world grain trade [116,117]. Therefore, the biosensors are impressive for the detection of mycotoxins through UCNPs [114].

Wang et al. [118] constructed a sensitive aptamer sensor based on the single particle detection (SPD). The analysis of aflatoxin B1 (AFB1) in the peanut samples was carried out using the luminescence resonance energy transfer (LRET) between the aptamer-modified UC (UCNPs-aptamer) and AuNPs, with UCNPs-aptamers acting as the luminescent donors and AuNPs employed as the energy receptors. The linear dynamic detection range of AFB1 was determined to be 3.13–125.00 ng mL$^{-1}$. The limit of detection was 0.17 ng mL$^{-1}$, which was much lower than the allowable concentration in the food products. Therefore, the developed method exhibited a broad application potential for the sensitive detection of AFB1 in the food, feed products and promising an important contribution to the food safety and public health.

Kim et al. [119] developed a solid-phase, single-step aptasensor, which revealed a higher performance than the solution-phase aptasensors, along with high reusability (Figure 4d). Specifically, the aptasensor was based on UCNPs (Au/UCNPs) supported by the gold nanocaps partially embedded in a solid substrate polydimethylsiloxane (PDMS). The gold nanocaps allowed the UCNPs to emit the upconverted light only from the restricted area of UCNPs and the area not covered by the nanocaps and PDMS. The functionalization of the restricted region with an aptamer labeled (with a quencher) enabled the effective quenching of the upconverted light from Au/UCNPs via FRET after target (ochratoxin A, OTA) detection. The sensor demonstrated a linear range of 0.1–1,000 ng mL$^{-1}$, under the optimal condition with 0.022 ng mL$^{-1}$ detection limit, and a detection time of 30 min. Thus, the developed sensor

Figure 3: Based on UCNPs@COPs bacterial pattern recognition of material fluorescent sensor array; (a) the principle of fluorescence emission intensity enhancement of UCNPs materials and (b) schematic diagram of sensor array and the obtained fluorescence response pattern are used to identify and classify bacteria by linear discriminant method [111].
Figure 4: Schematic diagram of upconversion nanotechnology for detection of agricultural and veterinary drug residues, mycotoxins, and antibiotics: (a) UCNPs@MIP, the preparation and imprinting process of the product are illustrated [123]; (b) schematic diagram of detection principle of upconversion test paper for thiram [124]; (c) schematic diagram of norfloxacin detection principle [129]; (d) based on FRET-induced quenching, the schematic diagram of OTA detection using aptamer (labeled with quenchant) functionalized bare UCNPs on glass substrate [119].
exhibited a high potential for the development of portable and reusable biosensor platforms, which can be applied to field supervision and detection.

Wu et al. [120] proposed a fumonisins B1 (FB1) sensor based on FRET, process between the NaYF4:Yb, Ho upconversion fluorescent nanoparticles and AuNPs. AuNPs were connected to the 5’ flanking region of the molecular beacon (MB), whereas UCNPs were connected to the 3’ end of MB. Due to the binding of FB1 and FB1 specific aptamers, the separation of the complementary DNA from the magnetic nanoparticles (MNPs) took place. In the presence of the cDNA, MB spontaneously underwent a conformational change, leading to the separation of UCNPs and AuNPs as well as the restoration of the UC fluorescence. Hence, the fluorescence of UCNPs was recovered in a FB1 concentration dependent manner, which formed the basis of the FB1 quantification. The linear range was 0.01–100 ng mL⁻¹, whereas the detection limit in water buffer was determined to be 0.01 ng mL⁻¹. To demonstrate the practical application, the sensor was used to monitor the FB1 level in the natural contaminated corn samples.

Yang et al. [121] developed a smart phone portable device based on the barcode technology of the multicolor UCNPs and fluorescence image processing. The authors used the multicolor upconversion nanoparticle-encoded microspheres (UCNMs) as the coding signals to simultaneously detect the different types of mycotoxins. After using UCNMs for an indirect competitive immune analysis, the images could be captured by the cameras and smartphones. Subsequently, a self-written Android application representing an image recognition program based on HSV (hue, saturation, and value) was installed on the smartphone, which could reliably and accurately analyze the image in less than 1 min. The detection limit was determined to be 1 ng, which was lower than the standard detection system. The developed sensor has the advantages of high sensitivity, low detection limit, wide application, and short detection time.

### 3.3 Detection of pesticide and veterinary drug residues

The edible agricultural products are the foundation for human’s survival. Thus, activities such as planting, forestry, and aquaculture are closely related to the daily diet. In this respect, the agricultural product safety issues have a significant impact on the human health. With the economic development and gradual improvement in the living standards, stringent requirements with respect to the safety of the agricultural products have also been put forward. The pesticide and veterinary drug residues in the food products pose a serious threat to the human health. Thus, there is an urgent need for a fast, ultra-sensitive, accurate, and cost-effective detection technology [122].

Yu et al. [123] described the fabrication of an imprinted fluorescent nanoprobe, which is based on the SiO₂-coated NaYF₄:Yb,Er UCNPs encapsulating with a molecularly imprinted polymer (MIP) for the determination of acetamiprid (Figure 4a). The preparation of the fluorescent MIP nanoprobe was achieved by using UCNPs as the material for the fluorescent signal readout, acetamiprid as the template molecule, methacrylic acid as the functional monomer, and ethyleneglycol dimethacrylate as the cross-linking agent. Under optimal conditions, this method exhibited a linear relationship between the reduction in the fluorescence intensity (excitation/emission peak at 980/542 nm) and change in acetamiprid concentration in 20–800 ng mL⁻¹ range. The detection limit was determined to be 8.3 ng mL⁻¹. The sensor has the advantages of wide linear range and low detection line. It should be noted, however, that the number of detectable samples is comparatively small.

Hua et al. [106] prepared the water-soluble green β-NaYF₄:Yb,Er UCNPs via a facile wet-chemical technique, followed by conjugation with rabbit anti-2,4-dichlorophenoxyacetic acid immunoglobulin G (2,4-D-IgG) and rabbit anti-fenitrothion IgG (fenitrothion-IgG), respectively. The content of 2,4-D-IgG and fenitrothion-IgG in the labeled samples were quantitatively analyzed by the Coomassie Brilliant Blue method. The 2,4-D-IgG (or fenitrothion-IgG) labeled with β-NaYF₄:Yb,Er UCNPs conjugates could be used as the fluorescent bio-labels to detect 2,4-D and fenitrothion under 980 nm infrared excitation. Subsequently, the immunochromatographic strip was successfully constructed based on the antibody UCNPs complex. The detection limits for 2,4-D and fenitrothion were determined to be 5 and 11 ng mL⁻¹, respectively. Taken together, the results suggest that the sensor could detect 2,4-D and fenitrothion with both high sensitivity and selectivity.

Mei et al. [124], developed an auxiliary reusable device by using the 3D printing technology. The device assembled a 980 nm micro-laser, a filter, and a micro-cavity in sequence. It was used to digitally image the changes in the luminescence on the test paper to quantitatively analyze thiram (pesticide) through a smart phone (Figure 4b). Specifically, the copper ion modified NaYF₄:Yb/Tm UCNPs were immobilized on the filter paper to form a test sheet. After thiram was added through the mechanism of the...
luminescence resonance energy transfer, the blue luminescence was quenched. The smartphone camera could monitor the changes and calculate by the self-edited Android program installed on the smartphone so as to quantify the amount of thiram, thereby providing reliable and accurate detection limit of 0.1 μM. The study provides a preliminary demonstration for combining the UC nano-sensors with the smart-phone digital imaging for the real-time analysis on a paper-based platform. Compared to the first two sensors, this sensor was portable and more suitable for the onsite rapid detection.

3.4 Antibiotic detection

Antibiotics as the basic therapeutic drugs are widely used in medicine, animal husbandry, aquaculture, etc. However, the residual antibiotics owing to their excessive use also pose a serious threat to the ecological environment, food safety, and human health. The matrix environment of the antibiotic residues is complex. Therefore, the development of cost-effective, rapid, sensitive, efficient, and stable antibiotic detection methods is vitally needed. In addition to regulating the use of antibiotics, it is of great significance to ensure the safety of food and human health. The temptation of economic benefits leads to the improper use or abuse of the hormonal drugs. Therefore, there is an urgent need for an accurate, effective, and rapid detection technology to overhaul the current protocols.

Ren et al. [129] used the 808 nm near-infrared laser and thermal imaging applications on the smartphone to develop a fast and ultra-sensitive colorimetric/photothermal dual readout detection method (Figure 4c). Norfloxacain was used as a model pollutant to verify the universal rapid detection method. The sample was added to the test strip, and flowed through the strip by the capillary action until it reached the control line, where the immune complexes were formed due to the presence of the secondary antibodies. The added black phosphorus could be captured by the antigens directly exposed to the test line, and the brown band was observable by the naked eye. After 1 min of exposure to the near-infrared light, the thermal imaging analysis was performed by using the phone camera to obtain the real-time temperature for the quantitative analysis. The developed method could detect norfloxacain in the water samples within 20 min, and the detection limit of the colorimetric and photothermal readout reached up to 45 pg mL\(^{-1}\). Compared with the traditional strips, the developed method enhanced the sensitivity by about two orders of magnitude.

Hu et al. [130] developed the NaYF\(_4\):Yb/Tm UCNPs bound to the antibodies as the fluorescent signal probes. The authors used the antigen-modified monodisperse magnetic polystyrene microspheres as the immunosensing probes to capture and separate the signal probes (Figure 5a). Overall, a novel fluorescent immunoassay method was established for the detection of sulfamethoxazole (SMX) in the animal food-derived foods. Based on the competitive immunoassay, the detection limit of the method was 0.1 μg L\(^{-1}\) in buffer and 0.5 μg kg\(^{-1}\) in the food samples. The recovery rate of the added sample was determined to be 69.80–133.00%, with the coefficient of variation in the range of 0.24–25.06%. The developed method demonstrated the advantages of sensitive fluorescence response, simple and rapid extraction process, and environmental friendliness, etc., and could be applied for the determination of sulfamonomethoxine in the animal-derived food.

Wang et al. [131] developed a high-throughput and a high-sensitivity avidin–biotin complex immunoadsorbent assay based on the controlled assembly of the UCNPs (ABC-ULISA). For the detection of antibiotics, the developed system could carry out an accurate quantitative detection within a short period of time (Figure 5b). Streptavidin and biotin labeled UCNPs formed an avidin–biotin–upconversion complex, which was subsequently combined with the biotinylated antibody to achieve a double amplification of the signal and an improved detection sensitivity. ABC-ULISA could detect three antibiotics at the same time. The detection limit of sulfamethazine was 0.15 ng mL\(^{-1}\), whereas the detection limits of sarafloxacin and tetracycline were 0.03 ng mL\(^{-1}\) and 0.05 ng mL\(^{-1}\), respectively. The detection limit of the developed method was much lower than that of the traditional ELISA and ordinary ELISA methods. Further, ABC-ULISA could detect the corresponding target by changing different antibodies, thereby exhibiting its versatility. The obtained findings are observed to be stable and reliable, with the possibility of equipment miniaturization, thus, exhibiting significant commercial application potential. In conclusion, the sensors of antibiotic detection can move towards high sensitivity, short detection time, portable instrument, and high-throughput detection techniques.

3.5 Hormone testing

Illegal addition of low-dose multi-component hormone compounds has become a cunning strategy to evade health supervision; however, it poses hidden dangers to the health and food safety. The temptation of economic benefits leads to the improper use or abuse of the hormonal drugs. Therefore, there is an urgent need for an accurate, effective, and rapid detection technology to overhaul the current protocols.
Figure 5: Schematic diagram of upconversion nanotechnology applied in the detection of antibiotics and hormones; (a) schematic diagram of detection principle of Sulfadoxine (SQ) [130]; (b) schematic diagram of avidin biotin complex immunosorbent assay for detection of three antibiotics based on controllable assembly of UCNPs [131]; (c) schematic diagram of MIP-coated UCNPs preparation procedure [135].
Li et al. [133] developed an ultra-sensitive sensor by employing the FRET between the modified UCNPs and tetramethylrhodamine to detect the trace amounts of bisphenol A (BPA). In order to overcome the challenges of the low efficiency of FRET and low sensitivity of the sensor, the authors quantitatively modified the fluorescence efficiency of the UCNPs. Under optimal detection conditions, the peak intensity at 547 nm had a linear relationship with the logarithm of the BPA concentration, and the detection limit was determined to be 0.05 ng mL\(^{-1}\). Without any pretreatment, the recovery rate of tap, river, and disposable paper cup water are generally between 91.0 and 115.0%. Therefore, the developed sensor is suitable for the effective detection of the trace amounts of BPA in the water samples. Wang et al. [134] successfully developed a fluorescence sensor based on the hybrid chain reaction (HCR) and triple-stranded structure (TS). In the sensor, the nucleic acid aptamer was competitively bound to BPA and cDNA. The unbound cDNA was subsequently obtained by magnetic separation. HCR could be triggered by cDNA to form the long double-stranded DNA products. The UCNPs-modified single-stranded DNA (ssDNA) could form TS with the HCR products. As a result, the distance was shortened, thus, extinguishing the fluorescence and altering the signal. HCR and low background UCNPs could collectively improve the sensitivity of detection. The detection limit of the sensor was as low as 0.057 ng mL\(^{-1}\) and also successfully applied for the actual sample detection. This sensor, relative to the first, improved the sensitivity, specificity, and expanded the range of application.

Wang et al. [135] also developed a novel fluorescent sensor based on the MIP-coated UCNPs to detect diethylstilbestrol (DES). The authors used a simple one-step method to modify the surface of the UCNPs (Figure 5c). Afterwards, the MIP was synthesized on the carbon nanotubes by using the surface grafting molecularly imprinted method. It combined the advantages of UCNPs, including strong fluorescence, stability, reusability, superior adsorption capacity, and high specificity. After removing the template molecules, the nanoparticles could selectively recognize DES, and the fluorescence intensity decreased as the DES concentration was increased. A linear relationship was obtained in the concentration range 50–1,000 ng mL\(^{-1}\), with the correlation coefficient of 0.9989. Further, the detection limit was 12.8 ng mL\(^{-1}\) (S/N = 3). Overall, the developed fluorescence sensor provides a convenient, simple, and highly specific on-site detection of DES, thus, exhibiting a broad application prospect.

### 3.6 Detection of prohibited additives

The common connection between the food color and quality makes the color one of the most important physical properties of the food. Thus, the color is highly valued by the food industry. Adding colorants to enhance, homogenize, or even change the food color to make it more attractive to the consumers has become a common practice. However, occasionally the prohibited additives are added to the food products in the pursuit of profit. The prohibited additives are harmful to the body as compared to the genuine food additives [136].

Wu et al. [137] developed a melamine nanosensor based on the FRET of UCNPs and AuNPs. UCNPs with a positive charge were used as donors, while AuNPs with a negative charge were used as acceptors. Both UCNPs and AuNPs were bound together through electrostatic interaction, thus, leading to the fluorescence quenching of UCNPs. After adding melamine, owing to the nitrogen–gold interaction between melamine and AuNPs, lead to their aggregation. It resulted in the gradual recovery of the fluorescence of the UCNPs. Under optimal conditions, the concentration of melamine at which the fluorescence enhancement efficiency exhibited a linear response ranged from 32.0 to 500 nM, whereas the detection limit was 18.0 nM. Compared with other fluorescent methods, the developed fluorescence nanosensor demonstrated a sensitivity of up to 0.968, along with simple operation. To demonstrate the actual application, the sensor was used for the determination of melamine in the raw milk. In future, this sensor can be moved toward the high-throughput and commercialization.

### 3.7 Detection of heavy metal

In recent decades, the heavy metal ions pollution has adversely affected the environment, food safety, and human health. The heavy metals are leached from the industrial wastewater to the water sources and can subsequently enter the food chain of animals. With ever-growing industrialization and urbanization, the presence of heavy metals poses a serious threat to the human health. Owing to this, their detection has attracted a widespread attention [138].

Zhang et al. [139] developed a label free detection scheme based on fluorescence, which employed the use
of the photon UC particles to report the presence of Hg$^{2+}$. A ssDNA served as the Hg$^{2+}$ capture element and was covalently connected to the photon upconverting NaYF$_4$:Yb$^{3+}$,Tm$^{3+}$ nanoparticles. Under 980 nm laser irradiation, the energy transfer occurred between the NaYF$_4$:Yb$^{3+}$,Tm$^{3+}$ nanoparticles as the donor and SYBR Green I as the acceptor. By monitoring the ratio of the acceptor emission to the donor emission, the presence of the mercury ions could be quantitatively detected. The UCNP biosensor is highly selective for the Hg$^{2+}$, even in a mixed state with several other metal ions. Correspondingly, the directly observed detection limit was 0.06 nM. The extremely high signal-to-noise ratio of the photon UC particles revealed remarkably high sensitivity and specificity without the need of the fluorescent labeling.

Sun et al. [140] used UCNP as the energy donor, and single-walled carbon nanotubes or graphene oxide (GO) as the energy acceptor, along with utilizing DNA to connect UCNP and receptors. In the developed system, the emission could be restored through the G-tetramer-Pb$^{2+}$ structure, which could be used to determine the Pb$^{2+}$ content (Figure 6a).

To further refine the UCNP probes-based sensor, Yan et al. [141] synthesized a dual colorimetric and fluorometric nanoprobe for the detection of Cu$^{2+}$ ions. Ligand-free UCNP and porphyrin hydrate (tetrphenylporphyrin tetrasulfonic acid hydrate, TPPS), based on strong synergism, cause a reduced fluorescence from the UCNP and green color fluorescence from the TPPS due to the FRET. When the concentration of Cu$^{2+}$ became higher, the color of UCNP/TPPS-Cu$^{2+}$ complex displayed pink color attributed to the inhibition of FRET process. By using a color scanning mobile APP, real-time qualitative and quantitative Cu$^{2+}$ detection can be achieved. The lowest detection line of the colorimetric and fluorescence methods was 0.13 and 0.32 μM, respectively. The method demonstrated the bright future of onsite rapid detection and supervision.

3.8 Detection of other pollutants

Food is the main substance that all mankind depends on for survival, and its safety is self-evident. Food safety is related to everyone’s health. People are becoming more and more aware of the close connection between food safety and health. Food safety is not only related to the source of human energy but also a feasible way to prevent future human diseases. The ultimate goal of food analysis is to ensure food safety, for this reason, researchers around the world are committed to developing modern and advanced detection and analysis technologies to solve this problem [142,143]. In addition to the earlier-mentioned contaminants, the other miscellaneous contaminants in food include chemicals such as H$_2$S, hypochlorous acid (HClO), and polychlorinated biphenyls (PCBs). The following is a brief introduction of the application of the UC nanotechnolgy for the detection of these substances.

Zhang et al. [144] prepared a nanoprobe based on the UCNP for the specific sensing and imaging of HClO (Figure 6b). The Ru@UCNP nanoprobe consisted of two functional components, namely NaYF$_4$:Yb,Tm UCNP, which could convert the near-infrared light into visible light as an energy donor and HClO-responsive ruthenium(II) complex [Ru(bpy)$_2$(DNCH-bpy)](PF$_6$)$_2$ (Ru-DNPH) as an energy acceptor and an UCL quencher. In this system, the on-off emission of UCL was specifically triggered by HClO. One of the advantages of this sensor was high specificity and sensitivity. Thus, the trigger reaction could be used to detect HClO in the aqueous solutions.

Wang et al. [145] developed an UC fluorescent sensor based on hybridization chain reaction and etching endonuclease for the detection of PCBs. It combined the dual advantages of UCNP and HCR (Figure 6c). First, two harpins (H1 and H2) were designed based on the partial complementary sequence (cDNA) of PCB 72/106. As the aptamer specifically recognized the targets, cDNA was separated from the magnetic microspheres. Second, the gene could trigger a hybrid chain reaction (HCR), then, opening the stems of H1 and H2. After adding endonuclease, UCNP were pushed away from the quenching enzyme. The fluorescence intensity of the UCNP could be restored by FRET process, the UC emission intensity rose with the increase in of the PCBs’ concentration. Under optimal detection conditions, PCB 72/106 could be analyzed in the range of 0.004 to 800 ng mL$^{-1}$, and the detection limit was 0.0035 ng mL$^{-1}$ (S/N = 3). The developed sensor was also used for the detection of the water and soil samples, with average recovery rates of 93.4–109.7% and 83.2–118.5%, respectively. The findings from this study also provide an opportunity to use the dual amplification strategy to develop the fluorescent aptamer sensor for other targets.

4 Conclusion and future prospects

This study reviews the luminescence mechanism, synthesis methods, and surface modification of the rare earth-doped UCNP, along with exploring their applications in the field of food safety (Table 2). From the dietary perspectives, the application of the UC nanotechnology has been summarized for the rapid detection of food safety
Figure 6: Schematic diagram of upconversion nanotechnology applied in detection of heavy metals and other pollutants; (a) schematic diagram of Pb$^{2+}$ detection [140]; (b) schematic diagram of LRET system and HClO detection [144]; (c) dual amplification strategy of upconversion fluorescence aptamer based on HCR and endonuclease for detection of PCB 72/106 [145].
It can be seen that the UC nanotechnology can effectively provide the safety detection of our daily diet, owing to its wide application spectrum. In the recent years, a significant progress has been made in synthesizing UCNPs with controllable shape, size, morphology, and phase by employing various methods. Specifically, the UC luminescent nanoprobe technology has achieved a remarkable success in the fields of medicine, biology, and life sciences, along with food safety detection. For instance, the detection of pesticide residues, antibiotics, biological toxins, and food additives represents a unique application prospect. The potential of UCNPs in the field of rapid detection of food safety is full of infinite possibilities. First, it is expected to achieve rapid detection for field and laboratory detection, thereby increasing efficiency and effectiveness of the routine food safety supervision and inspection. Meanwhile, there is a certain usefulness for improving corporate social responsibility, firm reputation, and firm performance. Second, the technologies promise to the accomplishment of rapid qualitative screening inspection, semi-quantitative, and quantitative assessment. Third, it can avoid the complex process of the sample pretreatment, and achieve advanced and rapid methods of the sample pretreatment. Fourth, hopefully, the lack of rapid detection technology for the disposal of food safety accidents can be made up. After understanding the reaction mechanism, further combinations can be made to expand the application range of the UC technology. However, some restrictions are yet to be resolved. First, the immunochromatographic test strips, which is based on antibodies, represent the main research direction. However, the related findings are mostly limited to the laboratory stage, with only a few mature commercial products. It is necessary to develop portable on-site

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screening technologies and equipment that can be applied for rapid food safety testing, to promote a healthy and rapid development of the Food Industry. Second, whether the complex structure of UCNPs can be degraded in the environment is still an environmental safety issue. Therefore, it is necessary to study the long-term degradability of the urban sewage. Third, the biggest challenge in the surface modification of the UC fluorescent nanomaterials is the aggregation and fluorescence quenching of the modified nanomaterials. Therefore, in the future, efforts are required to decrease the fluorescence quenching degree through appropriate chemical modification, thereby expanding the application of the UC materials in food safety detection. Fourth, the UCNPs are related to the bio-safety. One way to overcome this challenge is to use ultra-small UCNPs (<10 nm) as they can be easily excreted or degraded by the body. However, a smaller size will also lead to the enhanced surface quenching effects, thus, designing new methods and new synthetic approaches for the fine dispersity, small and strong fluorescence of UCNPs also need to be studied. Overall, combining the UC technology, enzyme-linked immunoassay, and colloidal gold technology to achieve rapid and sensitive detection is of great significance in food safety and hygiene, medical detection, and other aspects.

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