Review on the application of upconversion nanomaterials in heavy metal detection

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Abstract

As a widespread element, heavy metals have a significant impact on human health and threaten human health. It is of great significance to develop analytical technologies that can detect heavy metal ions quickly and accurately. In comparison to conventional fluorescent materials such as organic dyes, quantum dot (QD) labels, and carbon quantum dots (CD), fluorescence detection technology utilizing lanthanide (Ln) ion-doped upconversion nanoparticles (UCNPs) stands out due to its distinctive attributes. These include a notably reduced autofluorescence background, enhanced tissue penetration capabilities, biocompatibility with cellular tissues, and minimal photodamage inflicted on biological samples. The utilization of this technology has garnered considerable attention across multiple fields. In the domain of heavy metal detection, traditional laboratory methods necessitate costly instrumentation and a fully equipped laboratory, involving intricate sample processing procedures and protracted detection periods, as well as a demand for skilled personnel. In contrast, the implementation of this material offers rapid and cost-effective detection, significantly mitigating the technical barriers for operators. Consequently, this represents an exceptional avenue to curtail expenses and broaden the scope of detection within the analytical process. This paper reviews the research progress of UCNPs in the detection of heavy metal ions, encompassing a brief elucidation of the luminescence principle of upconversion nanomaterials and commonly used detection principles. Additionally, it provides a detailed overview of the research status of several common non-metal ions and essential heavy metals. Furthermore, it summarizes the current focal points in UCNP detection and discusses the challenges and prospects associated with it.

Keywords: Heavy metals; Upconversion nanoparticles; Gold nanoparticles; Nanosensor; Fluorescence detection technology

Figure 1
**Introduction**

Heavy metals are characterized as metals with a density exceeding 4.5g/cm³. These metals have the potential to impact various cellular organelles and components, including cell membranes, mitochondria, lysosomes, endoplasmic reticulum, cell nuclei, and certain enzymes associated with metabolism, detoxification, and damage repair processes [1].

Heavy metals are typically classified into two categories, distinguished primarily by their toxicity levels. (1) Essential heavy metals are considered harmless or relatively harmless at low concentrations. (2) Non-essential heavy metals, on the other hand, exhibit high toxicity even at low concentrations [2]. In general, non-essential heavy metals encompass mercury (Hg), lead (Pb), arsenic (As), cadmium (Cd), and chromium (Cr) [5, 4]. In recent years, there has been a global increase in heavy metal pollution, attributed to heightened productivity and industrial machinery activities. Polluting sources encompass various sectors, including industry, agriculture, and households [5–10].

Heavy metals typically engage in the formation of coordination complexes with biological and chemical substances containing elements such as sulfur, nitrogen, and oxygen. This interaction can potentially disrupt cellular processes, inducing alterations in protein molecular structure, enzyme activity inhibition, and hydrogen bond rupture. Consequently, heavy metal complexes may be implicated in carcinogenic processes [11].

Currently, various methods exist for detecting heavy metals, including atomic emission spectrometry (AES) [12], atomic absorption spectrometry (AAS) [13, 14], inductively coupled plasma mass spectrometry (ICP-MS) [15], and inductively coupled plasma atomic emission spectrometry (ICP-AES) [16, 17], etc. However, these traditional techniques are associated with high costs, lengthy procedures, and reliance on skilled operators, thereby limiting their applicability in everyday settings.

In the last decade, methods utilizing optical materials for sample detection have garnered significant attention from researchers. Fluorescence detection technology has been extensively employed in sample analysis across various domains, owing to its benefits such as low detection limits (limit of detection [LOD]), heightened sensitivity, superior analytical precision, ease of operation, and rapid detection [18, 19].

Fluorescent probes facilitate qualitative or quantitative analysis of target chemical substances by altering fluorescence emission intensity, fluorescence lifetime, or color [20]. Traditional methods for fluorescence labeling include the use of organic dyes, quantum dots (QDs), and carbon quantum dots (CDs). Despite their widespread application, these methods have inherent limitations. Organic dyes suffer from short fluorescence lifetimes and high autofluorescence background. Quantum dots pose issues related to cytotoxicity, high cost, and chemical instability, while carbon quantum dots face challenges in surface modification due to their chemical instability [21–24].

Up-conversion nanomaterials have emerged as prominent luminescent materials in recent years. These materials are doped with rare earth ions from lanthanide elements. They manifest numerous electronic transitions within the 4f electron shell, facilitating the conversion of long-wavelength, low-energy infrared light into short-wavelength, high-energy light emission, a phenomenon known as the anti-Stokes shift [25]. This characteristic bestows upon upCNPs a low autofluorescence background, strong tissue penetration, non-toxicity to cellular tissues, and minimal photodamage to biological samples [22, 26], highlighting their superiority over traditional optical materials.

Henceforth, this article provides a succinct exposition of the luminescence principles governing up-conversion nanomaterials and the detection methodologies associated with upCNPs. Subsequently, it delineates the fluorescence detection technologies applicable to up-conversion nanomaterials, focusing on several prevalent non-essential metals.

**Up-conversion luminescence principle**

Upconversion nanomaterials exhibit a distinctive luminescent phenomenon known as the anti-Stokes shift. This phenomenon enables the conversion of near-infrared light into visible light or light with shorter wavelengths, facilitating emission. Unlike other substances lacking this capability, upconversion materials circumvent self-fluorescence background interference during detection [27]. This stands in contrast to conventional optical bioprospects such as ultraviolet (UV) or blue-green visible spectrum probes. In samples under examination, chromophores may also fluoresce autonomously, resulting in fluorescence imaging characterized by a low signal-to-background ratio. Consequently, results obtained using UCNPs surpass those achieved with traditional materials. The luminescence mechanism of UCNPs encompasses multiple processes, including excited state absorption (ESA), energy transfer upconversion (ETU), and photon avalanche (PA), facilitated by the continuous absorption of two-photon or multi-photon particles [22, 28].

**ESA**

When a single electron sequentially absorbs multiple photons, transitioning from the ground state to an excited state, it undergoes ESA (Figure 2A). The electron absorbs the energy of one photon, reaching an intermediate metastable state. Subsequently, under the excitation of a second photon, it transitions to a higher energy level. If additional photons, such as a third or fourth, are present, the electron can be excited to even higher energy levels [29], resulting in upconversion luminescence. ESA has been demonstrated to be the least efficient among several UC mechanisms because it reduces the concentration of dopant ions. These emitting species exhibit small absorption cross-sections, with ions possessing energy level structures such as Er³⁺, Ho³⁺, Tm³⁺, and Nd³⁺ ions [30].

**ETU**

ETU is a process where activators are indirectly excited to higher energy levels, resulting in upconversion luminescence (Figure 2B). The primary mechanism involves the capture of energy by acceptor electrons in the ground and excited states E1. After donor electrons absorb photons and progress from the ground state to the metastable state E1 via non-radiative transitions, this captured energy stimulates acceptor electrons to transition to higher energy levels, ultimately resulting in upconversion luminescence [31, 32].

**PA**

The photon upconversion mechanism of PA is the most complex among upconversion processes and relies on ESA and ETU to generate excited electron populations capable of producing UC emission (Figure 2C). The PA process initiates with the absorption of electrons from the non-resonant ground state at the E1 level, followed by a resonant ESA process to reach a higher energy level, E2. Subsequently, resonance cross-relaxation occurs between the highly excited ions and nearby ground-state ions, leading to both ions occupying the intermediate level, E1. This process exponentially populates intermediate states above the excitation threshold, ultimately triggering a cascade effect that results in intense UC emission [22].

**UCNPs detection principle**

In detection applications, the predominant detection mechanisms entail fluorescence quenching based on fluorescence resonance energy transfer (FRET), a process involving non-radiative energy transfer through dipole-dipole interactions. This results in the excitation of the fluorophore donor UCNPs and subsequent transfer of energy to another fluorophore acceptor, thereby quenching the fluorescence of the donor UCNPs [33]. This mechanism necessitates a considerable distance between UCNPs, typically around 10 nm between two fluorophores [34]. Moreover, alternative detection mechanisms include the internal filter effect (IFE), electron transfer, and transition
metal quenching. Gold nanoparticles (AuNPs) are commonly employed as fluorescence quenchers. In reagent detection, UCNPs are frequently combined with magnetic nanomaterials or gold colloidal nanomaterials to construct "turn-off" and "turn-on" sensors, employing the signal quenching mechanism and emission recovery mechanism, respectively.

The subsequent section provides a synthesis of existing literature on heavy metal detection using upconversion nanomaterials, encompassing diverse domains such as food safety, environmental monitoring, in vivo and in vitro experiments, and more. For comprehensive details, please refer to Table 1.

Table 1 Detection of heavy metals using upconverting nanomaterials

<table>
<thead>
<tr>
<th>Test sample</th>
<th>Target analyte</th>
<th>UCNPs</th>
<th>Functionalized materials</th>
<th>Detection principle</th>
<th>LOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>Cu(II)</td>
<td>UCNPs@mSiO₂–RBH</td>
<td>rhodamine Blydrazide</td>
<td>LRET</td>
<td>4.6 ppb</td>
</tr>
<tr>
<td>-</td>
<td>Cu(II)</td>
<td>UCNPs-RB-hydr azide</td>
<td>RB-hydrazide</td>
<td>FRET</td>
<td>106 M</td>
</tr>
<tr>
<td>In vivo and in vitro experiments</td>
<td>Cu²⁺</td>
<td>UCNPs – CYDAC 16</td>
<td>Organic fluorescent probe CYDAC16</td>
<td>LRET</td>
<td>37 nmol/L</td>
</tr>
<tr>
<td>-</td>
<td>Cu²⁺</td>
<td>UCNPs-PEI</td>
<td>Branched polyethyleneimine (PEI)</td>
<td>energy transfer</td>
<td>57.8 nM</td>
</tr>
<tr>
<td>-</td>
<td>Cu²⁺</td>
<td>UCNPs-DNAzyme</td>
<td>Cu²⁺-dependent DNAzymes labeled with BHQ1 dye</td>
<td>The chemical stimuli can cleave of a targeted BHQ1-labeled DNA enzyme strand</td>
<td>220 pM (0.22 nM)</td>
</tr>
<tr>
<td>tap water</td>
<td>Cu²⁺</td>
<td>UCNPs-Au NPs</td>
<td>4-mercaptopbenzoic acid (4-MBA)</td>
<td>FRET</td>
<td>18.2 nM</td>
</tr>
</tbody>
</table>

Figure 1 A Systematic Review of Up-conversion Nanomaterials for Safe Detection of Heavy Metal Ions. (Created with BioRender.com)

Figure 2 Main upconversion processes for lanthanide-doped upconversion nanoparticles (UCNPs) (a) excited state absorption (ESA), (b) energy transfer upconversion (ETU), (c) photon avalanche (PA). Source: Reprinted with permission from John Wiley and Sons.
### Table 1 Detection of heavy metals using upconverting nanomaterials (Continued)

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</tr>
</thead>
<tbody>
<tr>
<td>milk, water ground glutinous rice flour, peanut oil, pork, and mineral water</td>
<td>Hg^{2+}</td>
<td>PDANPs-Apt-EB SUCNPs sensor</td>
<td>Aptamer-modulated thymine-Hg2+ - thymine</td>
<td>FRET</td>
<td>0.28 µg/L [41]</td>
</tr>
<tr>
<td>-</td>
<td>Hg^{2+}</td>
<td>N719- UCNPs</td>
<td>Hg^{2+}-responsive ruthenium complex(N719)</td>
<td>FRET</td>
<td>1.95 ppb [42]</td>
</tr>
<tr>
<td>aqueous solution</td>
<td>Hg^{2+}</td>
<td>UCNPs@RBT</td>
<td>Rhodamine B thiolactone (RBT)</td>
<td>LRET</td>
<td>3.7 nM [43]</td>
</tr>
<tr>
<td>-</td>
<td>Hg^{2+}</td>
<td>β-NaYF₄@SiO₂-RB</td>
<td>Rhodamine B hydraide (rb - hydraide)</td>
<td>Rhodamine B (RB) and Hg^{2+} generate a delocalized xanthene moiety of the RB group</td>
<td>- [44]</td>
</tr>
<tr>
<td>aqueous solution</td>
<td>Hg^{2+}</td>
<td>Ru/UCNPs@HmSiO₂ /PEI</td>
<td>Hg^{2+} responsive ruthenium (Ru) complex</td>
<td>UCL/LRET system</td>
<td>0.16 µM [45]</td>
</tr>
<tr>
<td>tap water/ milk</td>
<td>Hg^{2+}</td>
<td>UCNPs -aptamers-GNPs</td>
<td>the stable binding interactions between Hg^{2+} and thymine</td>
<td>FRET</td>
<td>60 nM [46]</td>
</tr>
<tr>
<td>Green Tea</td>
<td>Hg^{2+}</td>
<td>UCNPs – AuNPs</td>
<td>Cysteine (Cys): Hg^{2+} possessed a very high affinity for Cys to form [Hg(Cys)n]₂⁻ complexes through the Hg – S bond</td>
<td>LRET</td>
<td>13.5 nM [47]</td>
</tr>
<tr>
<td>-</td>
<td>Hg^{2+}</td>
<td>UCNP-LFA</td>
<td>DNA probe/the antibody probe</td>
<td>sandwich format</td>
<td>About 5 to 10 times lower than the clinical critical value. [48]</td>
</tr>
<tr>
<td>tap water and lake water</td>
<td>Hg^{2+}</td>
<td>UCNP-DNA1</td>
<td>A single-stranded DNA containing thymine bases</td>
<td>LRET</td>
<td>0.14 nM [48]</td>
</tr>
<tr>
<td>Living Cell</td>
<td>Hg^{2+}</td>
<td>2-UCNP</td>
<td>Hg^{2+}-responsive thiazole derivative dye (compound 2)</td>
<td>LRET</td>
<td>0.063 µM [50]</td>
</tr>
<tr>
<td>aqueous solution</td>
<td>Fe^{3+}</td>
<td>mPEG-UCNPs-NRD</td>
<td>Nile red derivative (NRD) fluorescent probe</td>
<td>LRET</td>
<td>89.6 nM [51]</td>
</tr>
<tr>
<td>unsealed ferrous lactate oral solution</td>
<td>Fe^{2+} and Fe^{3+}</td>
<td>UCNPs@CD</td>
<td>1,10-phenanthroline: The chelate (Fe^{2+}-phen) formed</td>
<td>Fe^{2+}: IFE Fe^{3+}: electron transfer mechanism</td>
<td>3.17 µmol L⁻¹ [51]</td>
</tr>
</tbody>
</table>
### Table 1 Detection of heavy metals using upconverting nanomaterials (Continued)

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</tr>
</thead>
<tbody>
<tr>
<td>human serum sample</td>
<td>Fe^{2+}</td>
<td>UCNP@PEP</td>
<td>Polypepinephrine (PEP)</td>
<td>non-radiative electron transfer process</td>
<td>0.2 μM</td>
</tr>
<tr>
<td>industrial circulating cooling water</td>
<td>Fe(III)</td>
<td>UCNPs@SHMP</td>
<td>Inorganic phosphate sodium hexametaphosphate (SHMP)</td>
<td>Fe(III) combines with phosphate groups to form complexes</td>
<td>0.2 μM</td>
</tr>
<tr>
<td>environmental water samples.</td>
<td>Ag^{+}</td>
<td>Cit-UCNPs-ssDNA</td>
<td>Random coil ssDNA: Forms a hairpin structure with 'C–Ag^{+}–C base pairs</td>
<td>LRET</td>
<td>60 pM</td>
</tr>
<tr>
<td>water and black tea</td>
<td>Pb (II)</td>
<td>GO-NHM UCNPs-AuNPs-MNPs</td>
<td>Graphene oxide (GO) Aptamer</td>
<td>Raman scattering</td>
<td>1.15 × 10^{-6} g/mL 5.7 nM</td>
</tr>
<tr>
<td>Live cells and zebrafish</td>
<td>Pb (II)</td>
<td>UCNP-DNAzyme</td>
<td>Pb^{2+}-specific 8–17 DNAzyme</td>
<td>LRET</td>
<td>0.097 nM</td>
</tr>
<tr>
<td>urine sample</td>
<td>Cr(III)</td>
<td>UCNPs-AuNPs</td>
<td>Dimercapto succinic acid</td>
<td>FRET</td>
<td>0.8 nM</td>
</tr>
<tr>
<td>Naturally contaminated samples and human serum samples</td>
<td>Pb^{2+} and Hg^{2+}</td>
<td>UCNPs-Apt-AuNPs</td>
<td>Apt1 binds Pb^{2+} to form G-quadruplexesApt2 binds Hg^{2+} to form T–Hg^{2+}–T complex</td>
<td>FRET</td>
<td>Pb^{2+}:50 pM Hg^{2+}:150 pM</td>
</tr>
<tr>
<td>human plasma</td>
<td>AChE and Cd^{2+}</td>
<td>UCNPs-AuNPs</td>
<td>GSH</td>
<td>FRET</td>
<td>AChE:0.015 μ/mL Cd^{2+}:0.2 μM GSH:0.016 μM Cd^{2+}: 0.059 μM</td>
</tr>
</tbody>
</table>

**Application of upconversion luminescent materials in the detection of heavy metal ions**

In the initial stage, we compiled a summary of several prevalent essential heavy metals, which encompass Zn^{2+}, Cu^{2+}, and Fe^{3+}.

**Zinc ion**

Juanjuan Peng [64] et al. reported on a sensing platform designed for the sensitive detection of Zn^{2+} content in aqueous solutions (Figure 3). This sensing platform also demonstrates utility in the detection of Zn^{2+} in AD brain and zebrafish amylloid plaques, both in vitro and in vivo. Its potential application extends beyond the medical field to environmental contexts as well. The experiment was based on the principle of fluorescence resonance energy transfer (FRET) (Figure 1A). The platform employs a material known as compound 1 (Figure 1C), which functions as an energy acceptor because its broad absorption band overlaps with the emission spectrum of UCNPs. In an environment devoid of Zn^{2+}, UCNPs are excited by a 980 nm laser, causing the electrons of thulium (Tm^{3+}) ions to transition from a low-energy level ('G_e') to a high-energy level ('H_e'), releasing a specific amount of energy. This energy difference precisely corresponds to the generation of blue light, which is then quenched by compound 1. Conversely, in an environment containing Zn^{2+}, compound 1 undergoes intramolecular charge transfer upon coordination with Zn^{2+}, resulting in a blue shift in its absorption spectrum and reduced overlap with the emission spectrum of UCNPs. Consequently, this inhibits the energy transfer (ET) process. Upon restoration of the UCNPs signal, the reappearance of blue light allows for quantitative monitoring of Zn^{2+}. This response mechanism constructs an "open" sensor (Figure 1).

In subsequent experiments, researchers discovered that the detection sensitivity of 1-PAA-UCNPs was as low as 0.78 μM and exhibited rapid response characteristics within 5 seconds, facilitating swift detection in everyday applications. The sensor demonstrated exceptional selectivity and remained unaffected by other metal ions (such as Ca^{2+}, Fe^{3+}, Mn^{2+}, Ba^{2+}, Na^{+}, K^{+}) and amino acids. Furthermore, monitoring Zn^{2+} levels in vitro and in vivo proved feasible. Overall, this sensor shows promising application prospects and robust detection capabilities.
We discovered that four years later, Zhenglin Yang [65] et al. also utilized UCNPs for Zn²⁺ detection (Figure 4). In comparison with the approach by Juannuan Peng [64] et al., Zhenglin Yang employed catalytically active DNA molecules, known as deoxyribozymes or DNAzymes, as Zn²⁺-specific nanoprobes, exhibiting high selectivity. The DNAzyme binds with the UCNP to form a complex. The substrate chain of this Zn²⁺-specific DNAzyme is designated as 8-17DNAzyme. Two quenchers (Q1, Q2) are positioned at both ends of the enzyme chain and are conjugated with carboxyfluorescein (FAM) fluorophore. In the absence of infrared light and Zn²⁺ ions, the two chains hybridize, resulting in fluorescence quenching. The substrate chain is modified with a 2'-nitrophenyl group to protect the cleavable ribonucleotide adenosine (A) in the middle of the substrate chain from cleavage. Upon illumination with near-infrared light at 980 nm, the UCNP converts it to 365 nm light. This luminescent wavelength can photodissociate the 2'-nitrophenyl group in the DNAzyme, rendering the substrate chain highly Zn²⁺-specific and cleaving it into two shorter product chains, thereby allowing fluorescence recovery and constructing an ‘open’ sensor.

To avoid direct exposure of the body to ultraviolet light, near-infrared light irradiation is utilized, rendering this material more suitable for detecting Zn²⁺ ions within the body. Numerous in vivo experiments were conducted during the experiment, yielding outstanding detection results. Thus, it serves as an outstanding in vivo metal detection platform.

**Copper(II) ions**

Chunxia Li [35] et al. presented a novel approach for the detection of Cu²⁺ ions utilizing rhodamine B hydrazide as a Cu²⁺-sensitive fluorescent probe (Figure 5). Rhodamine B hydrazide, a derivative of rhodamine B, was integrated into a silica-modified framework of Upconversion Nanoparticles (UCNPs) and covalently bonded to the surface of the mesoporous silica shell, thereby establishing a Cu²⁺ detection framework termed UCNPs@mSiO₂-RBH. The mesoporous silica shell provides a robust protective barrier, shielding the fluorescent probes from adverse conditions, thereby preventing photobleaching and photodegradation.

In the absence of Cu²⁺ ions, UCNPs@mSiO₂-RBH nanoparticles exhibit distinct green and red emission peaks, while the solution remains colorless. Upon the introduction of Cu²⁺ ions, the Cu²⁺-sensitive rhodamine B hydrazide forms a complex with Cu²⁺, characterized by an absorption peak that coincides with the green emission peak of UCNPs. Consequently, the green emission intensity of UCNPs experiences a notable decline, whereas the red emission intensity exhibits marginal alteration, signifying the energy transfer from UCNPs to the RBH-Cu²⁺ complex, resulting in a gradual transition of the solution to a pink hue. The investigation posits that this phenomenon arises due to the structural modifications undergone by the rhodamine B moiety within UCNPs@mSiO₂-RBH, involving ring-opening, redox, and hydrolysis reactions. As the concentration of Cu²⁺ ions escalates, the ratio of green-to-red emission progressively diminishes. The detection threshold of this platform is estimated to be 4.6 ppb.

**Figure 3** Schematic diagram of detection of Zn²⁺ using 1-PAA-UCNPs. Source: Reprinted with permission from [64]. Copyright (2015) American Chemical Society.

**Figure 4** Schematic illustration showing the synthesis of photo controllable UCNP and DNAzyme-based nanosensor and its response to Zn²⁺. Source: Reprinted with permission from [65]. Copyright (2018) American Chemical Society.
In 2021, Xindong Wang [35] et al. introduced a detection platform utilizing Cu^{2+}-dependent DNAzymes as intermediaries linking Upconversion Nanoparticles (UCNPs) and quenchers (Figure 6). The DNAzyme comprises distinct enzyme strands (depicted as orange wavy lines) and substrate strands (illustrated as green wavy lines), enveloping the catalytic core of the enzyme chain and the corresponding single nucleotide (cleavage site) of the substrate strand. The BHQ1 dye (black hole quencher 1) is affixed to the DNAzymes as an energy acceptor, while UCNPs, serving as an energy donor, are tethered to the DNAzymes via the surface shell, thus forming a UCNPs-DNAzymes detection platform. In the absence of Cu^{2+}, BHQ1 dye quenches UCNPs. Conversely, in the presence of Cu^{2+}, the catalytic core of Cu^{2+}-dependent DNAzymes complexes with Cu^{2+} ions, cleaving the enzyme strand. Consequently, the quencher dissociates from the UCNPs, leading to light emission, thereby constituting a 'turn-on' sensor.

Subsequent experiments revealed that employing DNAzymes as fluorescent probes for specific Cu^{2+} detection offers outstanding selectivity, stability, and repeatability. A paramount characteristic of this fluorescent probe is its remarkably high sensitivity, with a Limit of Detection (LOD) of 220 pM (approximately 7 times lower than that of the integrated system (1.5 nM)), coupled with a broad detection range spanning 3 orders of magnitude (from sub-nM to μM). This advantageous feature renders this detection platform an innovative approach to high-sensitivity biochemical detection.

Figure 5 The synthetic procedure for the UCNPs@mSiO₂–RBH nanoparticles and their interaction with Cu^{2+} ions.[35]

Figure 6 Schematic illustration of the sensing mechanism, which involves utilization of Cu^{2+} ions (blue ellipse) to cleave BHQ 1 (black ellipse) in DNAzymes (paired wavy lines) from the surface of NaYF₄/Yb³⁺/Er³⁺ nanoparticles (yellow sphere), recovering upconversion luminescence. Source: Reprinted with permission from [39]. Copyright (2021) American Chemical Society.
After a meticulous examination of prior literature concerning the detection of Cu\(^{2+}\) ions, Hong Shao [40] et al. proposed refinements to this methodology (Figure 7). They posit that compounds such as benzoyl-15-crown-5-modified chemosensors and rhodamine-based materials, involving the conjugation of rhodamine B with a quinoline derivative, exhibit pronounced toxicity and entail intricate synthesis protocols due to their reliance on organic constituents, thereby constraining their practical utility. Instead, they employed Upconversion Nanoparticles (UCNPs) as energy donors and Gold Nanoparticles (AuNPs) as energy acceptors, subsequently modifying them with Poly(acrylamide) (PAAM) and 4-mercaptobenzoic acid (4-MBA), respectively. The resultant UCNPs-PAAM-4-MBA-AuNPs hybrid assembly is achieved through electrostatic interactions between positively charged PAAM and negatively charged 4-MBA. In the absence of Cu\(^{2+}\) ions, Förster Resonance Energy Transfer (FRET) transpires between UCNPs and AuNPs, leading to the quenching of fluorescence emission from UCNPs. Conversely, the presence of Cu\(^{2+}\) ions prompts the reaction between Cu\(^{2+}\) and 4-MBA on the surface of AuNPs, causing the dissociation of AuNPs from UCNPs and thereby interrupting FRET, leading to the reinstatement of upconversion fluorescence. This diagnostic platform thus constitutes a "turn-on" sensor. Subsequent experimental validation of the detection platform demonstrated commendable sensitivity (Limit of Detection (LOD) of 18.2 nM), a wide linear range (0.02-1 μM), and exceptional selectivity in Cu\(^{2+}\) detection. In contrast to its predecessors, this platform abstains from the utilization of toxic and complex synthetic fluorescent probe materials. Furthermore, it reduces the detection limit (compared to 106 M [35]), consequently enhancing sensitivity and broadening the scope of eco-friendly and versatile applications.

Iron(III) ion

Ruoyan Wei [51] et al. synthesized a novel fluorescent probe derived from Nile red (NRD) with selectivity towards Fe\(^{3+}\) ions and incorporated it into Upconversion Nanoparticles (UCNPs) modified with a water-soluble polymer (mPEG), thereby establishing a Fe\(^{3+}\)-sensitive detection platform (Figure 8). Initially, the researchers modified the synthesized PEGylated amphiphilic polymer (C18PMH-mPEG) onto the surface of UCNPs to generate mPEG-UCNPs. Subsequently, they conjugated NRD to mPEG-UCNPs to form mPEG-UCNPs-NRD. In the absence of Fe\(^{3+}\) ions, mPEG-UCNPs-NRD emits fluorescence, appearing purple under sunlight and exhibiting green Upconversion Luminescence (UCL) upon excitation at 980 nm. Upon the addition of Fe\(^{3+}\), a complex reaction ensues between NRD and Fe\(^{3+}\) within mPEG-UCNPs-NRD, featuring phenol units. During this process, UCNPs act as the energy donors, while the Fe\(^{3+}\)-responsive NRD functions as the energy acceptors. This results in Luminescence Resonance Energy Transfer (LRET), leading to fluorescence quenching, a color change to light blue, and the disappearance of fluorescence under 980 nm irradiation. This platform constitutes a "turn-off" sensor.

This platform exhibits commendable sensitivity, selectivity, and photostability, boasting a detection limit of 89.6 nM. Thanks to the favorable biocompatibility conferred by the water-soluble polymer (mPEG) modification, mPEG-UCNPs-NRD nanostructure has been effectively employed in UCNPs-based Upconversion Luminescence (UCL) detection of Fe\(^{3+}\) ions within living cells, thereby demonstrating its potential utility as an MRI contrast agent.
Yi-Lin Sun et al. reported a method for simultaneous detection of Fe$^{2+}$ and Fe$^{3+}$. Carbon dots (CDs) are materialized by low toxicity, excellent biocompatibility, and optical stability (Figure 9). The researchers integrated UCNPs with CDs to form composite UCNPs@CDs materials, which possess optical properties of both UCNPs and CDs, serving as fluorescent nanoprobes for detecting Fe$^{2+}$ and Fe$^{3+}$. This method involves qualitative and quantitative analysis by comparing $\lambda_{ex}$/$\lambda_{em}$. Upon addition of phen (1,10-phenanthroline) in water, when Fe$^{2+}$ is present, phen forms a complex with Fe$^{3+}$. The formed complex Fe$^{3+}$-phen exhibits a broad absorption peak centered at 510 nm, overlapping with the emission peak of UCNPs@CDs at 545 nm (excited at 980 nm), leading to a decrease in the fluorescence peak of UCNPs@CDs due to inner filter effect (IFE), and the fluorescence peak gradually decreases with the increase of Fe$^{3+}$ content, thus enabling quantitative and qualitative analysis of Fe$^{3+}$. It was observed that Fe$^{3+}$-phen does not cause a decrease in peak intensity at 545 nm. For Fe$^{2+}$ detection, the strong interaction between the hydroxyl and carboxylic acid groups of CDs and Fe$^{3+}$ ions leads to facile electron transfer from UCNPs@CDs to the half-filled $d$ orbitals of Fe$^{3+}$, resulting in fluorescence quenching of UCNPs@CDs [66]. As the concentration of Fe$^{3+}$ increases, the FL intensity at 434 nm gradually decreases, enabling qualitative and quantitative detection of Fe$^{3+}$. This probe exhibits excellent selectivity and good fluorescence stability in high ionic strength media, with a LOD of 3.17 µmol L$^{-1}$, demonstrating satisfactory detection sensitivity. Although this method possesses high selectivity and the ability to differentiate between Fe$^{3+}$ and Fe$^{2+}$ simultaneously, the lack of color change in the solution necessitates well-equipped laboratory facilities for qualitative analysis, indicating room for improvement in terms of the convenience of rapid detection.

In this section, we summarize the detection of several non-essential heavy metals, including mercury (Hg), lead (Pb), cadmium (Cd), and chromium (Cr).

**Lead(II) ion**

Annavaram et al. endeavored to enhance the detection efficiency of upconversion nanomaterials by incorporating graphene oxide (GO) with UCNPs materials (Figure 10). Graphene oxide, formed through the oxidation of graphene, possesses abundant functional groups and a distinctive two-dimensional structure. This synergy was exploited through the Surface-Enhanced Raman Scattering (SERS) method for Pb$^{2+}$ detection. When a laser interacts with the sample, it excites vibrational modes within the sample, generating scattered light known as Raman scattering. Molecules or substances in contact with a metal surface featuring nano-structures, such as gold, silver, or copper, interact with the laser. Nanostructures on the metal surface induce a localized surface plasmon resonance (LSPR) effect, resulting in a locally enhanced electric field at the contact site. This localized enhancement leads to a substantial amplification of the Raman scattering signal in the sample, termed the surface enhancement effect (Yang et al., 2013).

The researchers introduced Yb, Ho, and Au substances to synthesize upconversion nanomaterials and prepared GO@NaYF$_3$: Yb, Ho, Au upconversion nanoparticles via a hydrothermal method, termed GO@NHMs. This approach enhances the SERS signal intensity of UCNPs through the surface enhancement effect of GO and discerns the presence of Pb$^{2+}$ in the sample by comparing the peaks corresponding to the Raman spectrum of the standard solution spiked with Pb$^{2+}$ and the sample. Due to facilitated charge transfer between metal ions and molecules, the study demonstrates that the Raman intensity of GO@NHMs is amplified by 5-fold compared to conventional NHMs, which exhibit lower stability and photothermal efficiency.

The detection limits of NHMs for Pb(II) are relatively low, at $1.16 \times 10^{-8}$ g/mL, while the detection limit for GO-NHMs is $1.15 \times 10^{-8}$ g/mL. This suggests that compared to NHMs, GO-NHMs demonstrate higher sensitivity, as well as repeatability and reproducibility. Ultimately, these nano-hybrid materials exhibit considerable potential for sensing applications in the realms of food and environmental science.

Figure 9 Schematic of the UCNPs@CDs fluorescence sensing platform for simultaneous detection and speciation of Fe$^{2+}$ and Fe$^{3+}$. Reprinted from [52], Copyright (2021), with permission from Elsevier.

Figure 10 Schematic diagram of detection of Pb$^{2+}$ using GO@NHMs. Reprinted from [56], Copyright (2019), with permission from Elsevier.
Chen et al. functionalized aptamers on UCNPs, AuNPs, and MNPs using different aptamers to facilitate their conjugation. Aptamer 1 (Apt1) was employed to link AuNPs and MNPs, thereby yielding AuNPs-MNPs conjugates (Figure 11). Subsequently, Aptamer 2 (Apt2) was utilized to form UCNPs-AuNPs-MNPs complexes from UCNPs and AuNPs-MNPs, which functioned as a fluorescent probe. In the absence of Pb\(^{2+}\), fluorescence resonance energy transfer (FRET) transpires within this system, with the fluorescence resonance energy continuously transferred to MNPs-AuNPs, leading to the quenching of UCNPs luminescence. Upon introduction of Pb\(^{2+}\), DNAAzyme captures Pb\(^{2+}\) and catalyzes the hydrolysis of the corresponding oligonucleotide. This results in the disruption of base pairs, leading to the dissociation of UCNPs and MNPs-AuNPs, thus halting FRET and re-igniting the luminescence of UCNPs, thereby constructing a "turn-on" sensor. Finally, AuNPs and UCNPs can be segregated via magnetic separation.

The observed effect facilitates a broad operational range of 25 – 1400 nM and achieves a low detection limit of 5.7 nM for Pb\(^{2+}\), signifying a notable advancement compared to previously discussed detection methods [56]. Utilizing this nanosensor, researchers conducted lead analysis in tea leaves and wastewater, yielding satisfactory outcomes. Selective material testing, it demonstrated pronounced specificity towards Pb\(^{2+}\), rendering it suitable for deployment in intricate testing environments. However, the sensitivity of the UCNPs-MNPs-GNPs nanosensor is significantly influenced by factors such as the ratio of UCNPs to MNPs-GNPs, hybridization duration, and reaction time, indicating potential avenues for enhancement in future iterations.

Huang et al. investigated a UCNPs-DNAzyme nanosensor for the selective detection of Pb\(^{2+}\) (Figure 12). They employed a Pb\(^{2+}\)-specific 8–17 DNAzyme to conjugate with UCNPs. This DNAzyme comprises a substrate chain with riboadenosine (riA) as the cleavage site and a highly conserved bulge structure as the catalytic core. The substrate chain is then labeled at both ends with BHQ1 quencher. The amino group at the 5' end of the enzyme chain is linked to the functionalized carboxyl group of UCNPs. In the absence of Pb\(^{2+}\), UCNPs act as energy donors and BHQ1 quencher acts as energy acceptor, leading to the quenching of UCNPs fluorescence through the LRET process. The LRET process resembles the FRET principle, albeit with the capability for longer distances. Upon introduction of Pb\(^{2+}\), the DNAzyme recognizes Pb\(^{2+}\) as the target and becomes activated upon binding, cleaving the substrate chain at the RNA site, thereby separating UCNPs from the BHQ1 quencher and restoring the fluorescence of UCNPs. This experiment establishes a 'turn-on' sensor. Moreover, the sensor can be utilized for in vivo imaging of Pb\(^{2+}\).

The limit of detection (LOD) of this method is as low as 0.097 nM, which significantly surpasses the methods mentioned earlier. Additionally, by leveraging the advantages of UCNPs, such as low background interference, excellent biocompatibility, and optical stability, researchers have successfully applied this sensing strategy to image Pb\(^{2+}\) in live cells and early-stage zebrafish. The successful imaging in biological organisms can contribute to understanding Pb\(^{2+}\) metabolism pathways and lead poisoning mechanisms in various biological systems, representing a significant improvement over the previously mentioned methods.

Chromium(III) ion

Liu et al. conducted surface modifications on AuNPs and UCNPs, respectively (Figure 13). UCNPs were modified with lysine to render them water-soluble and positively charged, while AuNPs were modified with negatively charged dimercaptosuccinic acid. The modified UCNPs and AuNPs were then combined through electrostatic interactions, resulting in the Förster Resonance Energy Transfer (FRET) phenomenon, leading to the quenching of UCNPs' fluorescence by AuNPs.

Upon the addition of Cr\(^{3+}\) ions, a specific and robust interaction occurred with the dimercaptosuccinic acid on the surface of AuNPs, leading to the separation of AuNPs and UCNPs and subsequent fluorescence recovery of UCNPs, thereby establishing an "open" sensor. Additionally, the researchers investigated factors such as pH that could influence the surface charge of the material. They observed that the fluorescence increase reached its maximum value when Cr\(^{3+}\) was introduced into the system at a pH value of 8.0. This observation may be attributed to the strong coordination of Cr\(^{3+}\) with the carboxyl group of the DMSA molecule under the pH condition of 8.0. Furthermore, the researchers conducted selectivity tests on various heavy metals and determined that the system exhibited high selectivity and sensitivity.

In Cr\(^{3+}\) detection, the low water solubility of dye reagents necessitates complex organic synthesis and a detection medium comprising a mixture of water and organic solvents. Given the paramagnetic properties of Cr\(^{3+}\) ions, which typically lead to fluorescence quenching, most Cr\(^{3+}\) fluorescence probes are designed to operate on a fluorescence quenching principle. However, the researchers in this study have developed an innovative fluorescence-unveiling detection platform. With a detection limit of 0.8 nM, this platform demonstrates high sensitivity and strong selectivity, while being less susceptible to autofluorescence interference, thus facilitating the detection of biological samples.

Figure 11 a Schematic presentation of fluorescent nanoprobes based on fluorescence resonance energy transfer (FRET) between MNPs-GNPs and UCNPs. b The structure formula of combined UCNPs and MNPs-GNPs. Reprinted from [57], Copyright (2020), with permission from Elsevier.
Mercury(II) ion

Hong-Qi Chen [67] et al. investigated the detection of mercuric(II) ions (Figure 14). Instead of conventional spherical gold nanoparticles, they utilized gold nanorods (GNRs) as the fluorescence quencher of UCNPs. The rod-shaped structure of GNRs offers a higher absorption cross-section and stronger light-scattering properties compared to spherical gold nanoparticles (AuNPs). Notably, the absorption peak of gold nanorods typically resides in the near-infrared region, aligning well with the near-infrared light emission of UCNPs. This spectral overlap enhances experimental outcomes. Moreover, the light absorption, surface area, and surface energy of gold nanorods surpass those of AuNPs, thereby improving the quenching efficiency.

Gold nanorods were synthesized via a seed-mediated growth method. The researchers employed a thymine-rich anti-Hg²⁺ aptamer, known for its high selectivity for Hg²⁺ and its ability to form a T-Hg²⁺-T structure. Aptamers were individually modified on UCNPs and AuNPs to create probes. In the absence of Hg²⁺, the electrostatic repulsion of the negatively charged ssDNA on the nanoparticle surfaces led to the dispersion of both probes in the aqueous solution, allowing the detection of UCNPs emission. However, upon the addition of Hg²⁺, the formation of the T-Hg²⁺-T structure caused the DNA on both probes to hybridize and come into close proximity, resulting in the Förster Resonance Energy Transfer (FRET) effect between the two materials. Consequently, the fluorescence of UCNPs was quenched, facilitating the development of a “turn-off” sensor.

This platform offers a method for detecting ultra-low concentrations of Hg²⁺ in water, reaching as low as 2 nM, a level below the standards set by WHO and EPA for Hg²⁺ in drinking water. Leveraging UCNPs enhances the signal-to-noise ratio and detection sensitivity owing to their low background fluorescence. Additionally, the platform employs a unique T-Hg²⁺-T complex, resulting in outstanding selectivity for Hg²⁺ ions, thereby enabling highly sensitive and selective detection of other biomolecules as well.

Zou Dong-sheng [68] et al. investigated a detection platform utilizing Rhodamine and its derivative as an ‘off-on’ probe for Hg(II) ions. In the absence of Hg²⁺ ions, the rhodamine molecule adopts a non-emissive spirorolactam structure due to its superior thermodynamic stability. Fluorescence emitted at this stage originates from UCNPs at wavelengths of 521 nm and 539 nm, with peaks at 654 nm. Upon the addition of Hg²⁺ ions, the molecules undergo a transformation into the xanthene structure, exhibiting enhanced emissivity. Consequently, the emission band peak at 577 nm experiences a notable increase, while the emission band of UCNPs mentioned previously undergoes a significant decrease, indicating an energy transfer process from UCNPs to Rhodamine. By comparing the spectral changes before and after, the presence of Hg²⁺ ions can be determined.
Researchers observed that at low Hg(II) concentrations, the I/I0 value decreased, while at high Hg(II) concentrations, it increased. This phenomenon might be attributed to the partial adsorption of Hg(II) ions by the silica shell when the Hg(II) concentration is below 4 μM, thereby hindering the structural transformation of the probe and resulting in weaker emission. Conversely, when the Hg(II) concentration exceeds 12 μM, it is possible that the structural transformation of all probe molecules surrounding each Hg(II) ion is activated, leading to a significant enhancement in probe emission. Furthermore, as the color of the solution remained unchanged before and after the addition of Hg(II), this method necessitates testing in a fully equipped laboratory and does not offer the convenience of rapid on-site detection in practical scenarios. Hence, there remains significant scope for optimization in this detection approach.

**Dual-function detection platform**

Note: The term "Dual-function detection platform" refers to a detection system or platform with the capability to perform two distinct functions concurrently. It is tailored to simultaneously detect two targets, ensuring high sensitivity and specificity in detection. Engineered to enhance efficiency and convenience, it effectively conserves time and resources.

Shijia Wu et al. [60] devised a dual-function detection platform for simultaneous detection of Pb²⁺ and Hg²⁺ (Figure 15). The platform employs two distinct colors of upconverting nanoparticles (UCNPs) as donors and controlled gold nanoparticles (AuNPs) as acceptors. In the experiment, specific aptamers were utilized for each ion: Apt1 for Pb²⁺ and Apt2 for Hg²⁺. These aptamers were conjugated to UCNPs of different colors and functionalized with carboxyl groups through amino modification. Thiol-modified complementary DNA of the aptamers was then linked to the controlled AuNPs via robust Au-S bonds, thereby establishing the UCNPs-Apt-AuNPs detection platform. This platform quenches the fluorescence of UCNPs through the FRET process.

Upon addition of Pb²⁺ or Hg²⁺, these ions bind to their respective aptamers. As they naturally seek the most suitable binding sites based on their structures, the two donor-acceptor platforms operate independently, unaffected by other substances. Specifically, binding of Apt1 to Pb²⁺ generates G-quadruplexes, leading to dehybridization of cDNA1-functionalized gold nanospheres, resulting in the separation of UCNPs from AuNPs and restoration of green fluorescence. Similarly, Hg²⁺ forms a T-Hg²⁺-T complex with Apt2, characterized by strong affinity and high selectivity, thereby inducing the separation of UCNPs and AuNPs and restoration of red fluorescence.

Inspectors can deduce the substance contained within by simply observing the color of the emitted fluorescence. This method offers the convenience of inferring the substance through fluorescence observation, making it a rapid and user-friendly approach.

In previous studies, researchers have developed aptamer sensors for the simultaneous detection of Pb²⁺ and Hg²⁺; however, they utilized two fluorophores with different excitation wavelengths [63]. Therefore, the authors of this study optimized the previous research. The detection platform for both Pb²⁺ and Hg²⁺ employs a 980 nm excitation wavelength, generating two different colors of visible fluorescence, thus significantly enhancing detection convenience. The detection limits for Pb²⁺ and Hg²⁺ are 50 pM and 150 pM, respectively, demonstrating excellent sensitivity as well as high stability and selectivity.

![Figure 14 Schematic illustration of LRET assays based on DNA hybridization for the detection of Hg²⁺ ions. Reprinted from [67], Copyright (2013), with permission from Royal Society of Chemistry.](Image 196x317 to 399x468)

![Figure 15 Schematic illustration of dual FRET between the upconversion nanoparticles and controlled gold nanoparticles for the simultaneous detection of Pb²⁺ and Hg²⁺. Reprinted from [60], Copyright (2014), with permission from Elsevier.](Image 197x124 to 397x292)
Ajin Fang [61] devised a dual-functional upconversion sensing platform for acetylcholinesterase (AChE) activity and cadmium ion (Cd\textsuperscript{2+}) detection (Figure 16). The sensor is modulated using small molecules of glutathione (GSH). This platform leverages the Förster resonance energy transfer (FRET) process between gold nanoparticles (AuNPs) and upconverting nanoparticles (UCNPs) to detect samples. Citrate and cetyltrimethylammonium bromide (CTAB) were used to modify AuNPs and UCNPs, respectively, facilitating a shortened distance between the two materials through electrostatic interaction, thus initiating the FRET process and quenching the fluorescence of UCNPs.

The detection process of this platform is divided into two parts. Firstly, the detection of AChE activity is conducted in the absence of GSH. AChE catalyzes the hydrolysis of acetylthiocholine (ATC) into thiocholine, which then reacts with AuNPs via S-Au bonds. This interaction leads to the release of AuNPs from the surface of UCNPs, causing them to aggregate around thiocholine and resulting in the recovery of UCNPs fluorescence, thereby establishing an “open” sensor.

For the detection of Cd\textsuperscript{2+}, glutathione is added to regulate the sensor. Glutathione’s role is to prevent the aggregation of AuNPs. Through experiments, it was observed that upon adding GSH to the original reagent (UCNPs/AuNPs/ATC/AChE), the fluorescence recovery transitions back to fluorescence quenching, mirroring the behavior of the original sensor (UCNPs/AuNPs). Subsequent addition of Cd\textsuperscript{2+} leads to fluorescence recovery once again. This phenomenon arises from the interaction between Cd\textsuperscript{2+} and glutathione, forming a spherical (GSH)\textsubscript{2}Cd complex. This complex reduces the free GSH on the surface of AuNPs, weakening their stability and causing them to be released from the surface of UCNPs, thus gradually restoring the fluorescence of UCNPs. The detection of Cd\textsuperscript{2+} also establishes a “turn on” sensor.

The detection limit for AChE activity based on UCNPs-AuNPs in the absence of GSH is 0.015 mU/mL, while the estimated detection limit for Cd\textsuperscript{2+} detection based on UCNPs-AuNPs in the presence of GSH is 0.2 mU, which is lower compared to most reported methods. This detection platform exhibits high selectivity for both AChE and Cd\textsuperscript{2+}, with advantages such as avoiding autofluorescence and light scattering, as well as high stability. Through GSH regulation, it can easily achieve different purposes for AChE activity detection and Cd\textsuperscript{2+} detection, and the two detections do not interfere with each other, enabling expansion in sensitive and multiplex detection applications.

Leilei Sun [62] devised a dual-functional upconversion sensing platform for detecting glutathione (GSH) and cadmium ions (Cd\textsuperscript{2+}) (Figure 17). The researchers analyzed various previously reported bimolecular platforms, including the work by Ajin Fang et al., mentioned earlier (Fang et al., 2017). They observed that these platforms utilized small molecules for regulation but did not target the regulated small molecules for detection. Recognizing the simplicity, effectiveness, and selectivity of small molecule regulation, the researchers opted to enhance this approach.

This dual-functional sensing platform also operates via fluorescence resonance energy transfer (FRET). The researchers noted that unmodified gold nanoparticles (AuNPs) tend to aggregate in high-salt solutions, thereby quenching the red emission of upconverting nanoparticles (UCNPs). This aggregation is attributed to the shielding of electrostatic repulsion between negatively charged AuNPs by salt ions. Leveraging this phenomenon, the researchers introduced an amino-functionalized UCNPs and citrate-stabilized AuNPs mixture into a high-salt solution. The close proximity of the two materials through electrostatic interaction resulted in the quenching of the green emission of Er\textsuperscript{3+} by the AuNPs, denoted as result 1. This quenching efficiency increased significantly in high-salt environments, evidenced by the pronounced quenching of the UCNPs’ red emission band and suppression of the green emission, compared to AuNPs in standard conditions, termed as result 2.

Upon adding GSH, AuNPs no longer aggregated in the high-salt solution, yet the fluorescence of UCNPs remained unaltered. However, the fluorescence spectrum at this stage resembled that of the reagent (AuNPs/UCNPs), transitioning from result 2 back to result 1, allowing for comparison. By analyzing the fluorescence spectra of three mixtures—AuNPs/UCNPs, AuNPs/UCNPs/NaCl, and AuNPs/UCNPs/GSH/NaCl—, the presence of GSH can be determined. For the detection of Cd\textsuperscript{2+}, consistent with the aforementioned principle, a tetrahedral (GSH)\textsubscript{2}Cd complex forms, reducing the stability of AuNPs and leading to re-aggregation. Consequently, the red emission of the UCNPs/AuNPs/NaCl/GSH/Cd\textsuperscript{2+} mixture is quenched, transitioning from result 1 back to result 2. By comparing the fluorescence spectra, the presence of Cd\textsuperscript{2+} in the mixture can be inferred.

The authors of this paper conducted a literature review on the AChE and Cd\textsuperscript{2+} detection platform mentioned above [61]. They observed that although glutathione (GSH) was used for regulation, it was not targeted as a small molecule. Consequently, the researchers refined the platform by adjusting the distance between UCNPs and AuNPs using glutathione (GSH), enabling the detection of various targets including GSH. The detection limit for GSH on this platform is 0.016 mU, while for Cd\textsuperscript{2+} it is 0.059 mU, indicating both high sensitivity and a broad detection range. Moreover, the platform exhibits exceptional specificity for targets and performs effectively with complex real samples, rendering it an outstanding detection method.

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**Figure 16** Schematic illustration of the UCNPs/AuNPs fluorescence assay with glutathione regulation for the detection of Cd\textsuperscript{2+} (A) and acetylcholinesterase activity (B). Reprinted from [61]. Copyright (2017), with permission from Elsevier.
Arsenic
While there currently lacks a detection platform utilizing upconversion nanoparticles (UCNPs) for arsenic detection, we anticipate the future advancement of this methodology. With the continual progression of nanotechnology and optical detection techniques, we anticipate the emergence of further research and innovation, facilitating novel avenues for the highly sensitive and selective detection of arsenic. UCNPs, characterized by their distinctive fluorescence properties, have garnered widespread recognition for their potential applications in biomedicine, environmental monitoring, and related fields. Hence, we anticipate the development of arsenic detection platforms leveraging UCNPs in the future, aiming to address arsenic contamination concerns and contribute significantly to human health and environmental preservation.

Conclusions and future prospects
This article provides a comprehensive overview of detection methods employing upconversion nanoparticles (UCNPs) for various common non-essential heavy metal ions. UCNPs have garnered significant attention across diverse assays due to their remarkable selectivity, sensitivity, and the simplicity and swiftness of their detection methods. Through an extensive literature review, this study identifies a dearth in research literature pertaining to heavy metal ion detection utilizing UCNPs, particularly within the domain of food testing, thereby indicating substantial avenues for further investigation. Presently, the predominant principle utilized in this domain is the Förster resonance energy transfer (FRET) process. Several pertinent issues necessitate attention in research on heavy metal ion detection. Firstly, the interactions between UCNPs-AuNPs and heavy metal ions to achieve ‘off’ and ‘on’ mechanisms require elucidation. As discussed in this article, some experiments are conducted by altering surface charge to induce aggregation or dispersion, or by interacting with specific aptamers triggering DNASyme to cleave the substrate, or by observing changes in the fluorescence spectrum of UCNPs themselves post the addition of heavy metal ions. Secondly, the inconsistent luminescence characteristics stemming from low quantum efficiency (QE), surface defects, and alterations in size of UCNPs underscore the need for enhancing the composition of UCNPs. Thirdly, surface modification of UCNPs and AuNPs is imperative to modulate their properties and enable directional control of materials. Classical methods such as silica surface modification aim to enhance stability, alter surface properties of nanomaterials, and enhance optical properties. Alternatively, amino-functionallizing UCNPs and modifying AuNPs with citrate facilitate an amidation reaction between the two materials through amino and carboxyl groups, thus coupling them. Lastly, certain experimental methodologies remain relatively intricate, and the instrumentation employed is often expensive, thereby somewhat diminishing the advantages of UCNPs in terms of convenience and swiftness, and reducing the accessibility of these techniques. Consequently, further research is warranted to delve deeper into the research content of UCNPs and streamline experimental procedures, which could potentially serve as a future research direction.

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