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# Metal-based quantum dots: synthesis, surface modification, transport and fate in aquatic environments and toxicity to microorganisms

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Semiconductor quantum dots (QDs) have attracted considerable attention for their superior optical properties and wide utilization in biological and biomedical studies. Recently, intense concerns have been focused on the cytotoxicity assessment of QDs because most QDs are made of heavy metal ions (*e.g.*, $Cd^{2+}$), which pose a threat to human beings and simultaneously hamper the practical applications of QDs. This review provides an overview of the synthetic methods, surface modification, dissolution mechanism and cytotoxicity of core–shell QDs. Accordingly, the effects of polymer coating materials and environmental conditions on the dissolution kinetics of polymer-coated core–shell QDs are discussed in detail. To offer a systematic analysis of the cytotoxicity of QDs to microorganisms, correlative factors such as particle size, surface coating materials, photolysis and oxidation, charge, concentration, exposure time and mechanical stability are taken into consideration with respect to the mechanism of their toxicity. Future research will concentrate on toxicological and pharmacological studies of QDs to find new strategies with lower risk and higher benefits for public health, providing a unique technique for nanopharmaceutical applications.

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## 1. Introduction

A variety of engineered nanoparticles (ENs), such as carbon nanotubes, quantum dots (QDs) (*e.g.*, CdS, CdSe, and CdSe/ZnS), metal-containing nanoparticles (*e.g.*, ZnO, Ag, and $TiO_2$), dendrimers, and fullerenes, have been extensively used in numerous consumer goods, including detergents, printing, paints, cosmetics, bactericides, coatings, computer electronics, sunscreen, tires and drug delivery systems.[1–5] QDs, also known as semiconductor crystals, are a class of inorganic fluorophores with outstanding photophysical properties that are being increasingly used in medical imaging and industry.[6,7] Recent studies have shown that QDs have great potential for promoting

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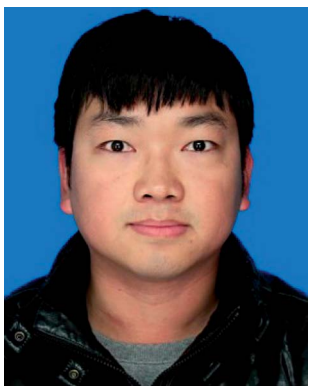

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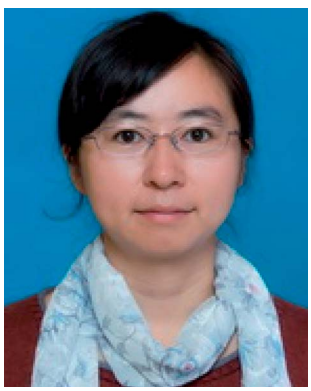
the applications of image sensors.[8–10] The main unique properties of QDs are: (i) narrow emission spectra, which can be controlled by varying the core size; (ii) broad absorption spectra, which allow for excitation by a wide range of wavelengths; (iii) high quantum yield and photostability.[11] In spite of their growing popularity and widespread use, the impacts of these materials on human health and the environment are poorly understood.[12–14]

QDs have highly stable "size-tunable" fluorescence because their photoluminescence emission bands are easily adjustable from the UV to the IR region.[15] These properties of QDs prepared from binary alloys are acquired by using distinct synthesis routes with strict control of the constituent materials, shape, size, and surface chemistry.[16,17] For example, the colloidal chemistry method is a common route to synthesize QDs because the surface of the nanocrystals can be functionalized during the production process. This process enables nanocrystals to interact with selected species, providing narrow size distribution as well as high luminescence efficiency.[3,18] Moreover, QDs should also be stabilized by materials to prevent agglomeration when they are dispersed in solvent. QDs are very hydrophobic because many nonpolar surfactant molecules are located on their surfaces. Therefore, it is of significant importance to find appropriate ligand materials for the surface modification of QDs. This could not only affect the properties of the nanocrystals in solution but also limit their potential use. Meanwhile, the selection of ligand materials on the surface of QDs plays a key role in the shaping of nanocrystals.[9] For example, the ligand materials can control the particle size and size distribution during synthesis of the QDs as well as the structure and stability of the nanocrystals.[16,19–22]

With their rapid development in commercial and biomedical applications, QDs may eventually enter the environment.[23–25] Residual QDs may release toxic metal ions into the environment during the weathering process, exhibiting toxicity to *Chlamydomonas reinhardtii*,[26] bacteria,[27,28] macroinvertebrates,[29] and even human beings. Therefore, it is of great importance to understand the environmental transport and fate of QDs.[30,31] Meanwhile, a systematic cytotoxicity assessment of QDs is also necessary for their practical biological and biomedical applications. To date, a large number of studies on the cytotoxicity of QDs have been carried out.[32–36] For example, Derfus *et al.*[32] demonstrated that the surface oxidation of QDs released free $Cd^{2+}$, which is directly correlated with cell death. Parak *et al.*[36] reported that in addition to the release of $Cd^{2+}$, the precipitation of QDs on cell surfaces could also damage cells. They suggested that QDs presented lower cytotoxicity when they only existed in the medium surrounding cells rather than being ingested by cells. Further, several published reports indicated that QDs can generate reactive oxygen species (ROS), which are cytotoxic and genotoxic.[31,33,34,37,38] For instance, in Green and Howman's study,[33] they speculated that DNA damage occurred because a ZnS shell was oxidized to generate $SO_2^{\bullet-}$, which then generated superoxide and hydroxyl radicals. Ipe *et al.*[37] also reported similar results: irradiated CdS QDs generated superoxide and hydroxyl radicals, and irradiated CdSe QDs generated hydroxyl radicals. Thus, the release of $Cd^{2+}$ and the oxidative stress induced by ROS could function as mechanisms of the cytotoxicity of QDs.[39–43] However, the dissolution kinetics and mechanisms of QDs have not yet been systematically investigated. Moreover, the environmental conditions and the inherent physicochemical characteristics of QDs, which are significant factors in assessing their toxicity, also have not been well documented.

The aims of this article were to overview and highlight recent studies on the transport and fate of QDs in aquatic environments and evaluate their toxicity to microorganisms. The effects of environmental factors (*e.g.*, light, pH, dissolved oxygen, ionic strength, natural organic matter, and extracellular polymeric substances) and the polymer coatings on the dissolution kinetics of polymer-coated core–shell QDs were summarized. Finally, we also discussed the cytotoxicity of QDs to microorganisms by analyzing the particle size, surface coating materials, photolysis and oxidation, charge, concentration, exposure time, and mechanical stability of QDs. To the best of our knowledge, this is the first discussion of the effects of polymer coatings and environmental factors on the dissolution kinetics of core–shell QDs in aquatic environments, as well as their cytotoxicity to microorganisms. The current knowledge of cadmium nanoparticle pharmacology and toxicology indicates the directions for future



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research. Focus will be placed on toxicological and pharmacological studies of QDs to find new strategies with lower risks and higher benefits for public health, providing a unique technique for nanopharmaceutical applications.

## 2. Synthesis of quantum dots

In nanotechnology, cadmium is primarily utilized in the construction of nanoparticles such as QDs, which are semiconductor metalloid-crystal structures.[44–46] Due to their small size, QDs have unique electronic and optical properties which impart the nanoparticles with highly stable "size-tunable" fluorescence. The large surface area also enables ready functionalization of QDs with targeting ligands for site-directed activity. Based on these properties, QDs have potential for innovations in cancer detection and treatment, including biological imaging at the cellular level.[7,44,46–49] However, the intense interest in QDs is somewhat diluted by the fact that QDs contain substantial amounts of cadmium in a highly reactive form, while little is known about the health risks of exposure to cadmium nanoparticles.[39,40,45]

In the 1980s, CdSe QDs were prepared by top-down techniques such as lithography. However, the size variations, poor optical properties, crystal defects, and poor reproducibility of these QDs made them inappropriate for advanced applications.[50] These QDs were very hydrophobic because the nanocrystals were capped with nonpolar surfactant molecules, and these nonpolar aliphatic chains were located on the surface of the QDs.[15,51] Murray *et al.*[18] introduced the currently widespread method for the synthesis of QDs by the injection of organometallic precursors into trioctylphosphine (TOP) and trioctylphosphine oxide (TOPO) surfactants at high temperature (190 °C to 320 °C). Hydrophobically coated CdS, CdSe, and CdTe QDs could be prepared by pyrolyzing organometallic precursors of cadmium (dimethyl cadmium) and selenium in a coordinating solvent mixture composed of TOP and TOPO.[50] Peng *et al.*[52] indicated that the existence of small amounts of impurities in the TOPO (essentially phosphinic acids and alkyl phosphonic acids) may inhibit the growth of particles. However, adding a certain amount of compounds such as hexylphosphonic acid (HPA) to the reaction medium will result in QDs with homogenous size distribution while inhibiting their growth.[52] Later, dimethyl cadmium was displaced by other less toxic, non-pyrophobic, and superior cadmium precursors such as myristate,[53] acetylacetonate,[54] and oxide.[55] Therefore, size-tunable photoluminescence (PL) and better quantum confinement of colloidal QDs were obtained through this method, which attracted many researchers. Another, older method, Ostwald ripening, which results in the gradual dissolution of smaller QDs and the formation of larger ones, was achieved by separating the spontaneous nucleation process from the relatively slow nanocrystal growth process. The primary advantage of this method is that size-tunable QDs can be obtained by selecting the injection and growth temperature.[56,57] However, because this method involves a complicated procedure, it is less utilized.

The colloidal preparation of CdSe nanocrystals, which employs the TOP/TOPO and high temperature system, is one of the most extensively used methods, and QDs synthesized by this process have been extensively characterized. However, aqueous synthetic methods have been proposed that employ lower temperatures and aqueous systems.[15,58] These strategies are essentially based on the utilization of different zinc or cadmium inorganic salts and sodium hydrogen selenide or sodium sulphide precursors, both of which can dissolve in water. The thiol-containing amino acid cysteine is currently applied as a coating agent in this methodology, owing to its high solvation ability. The thiol groups are stabilized on the surface of the QDs which the amino acid groups are oriented to the exterior of the surface of the QDs, providing a net charge for the dissolution of QDs in aqueous solution.[59] Many other coating materials can also be applied for the synthesis of QDs, such as polyphosphates,[60] poly(*N*-vinyl-2-pyrrolidone),[61] 1-thioglycerol,[60,62] thioglycolic acid (TGA),[63] and 3-mercaptopropionic acid.[64,65] Meanwhile, secondary coating materials such as polyethylene glycol (PEG) and mercaptopropionic acid are applied to further improve the solubility of QDs, preventing aggregation. These coating materials can be further conjugated with targeting molecules such as receptor ligands and antibodies, enabling the QDs to preferentially target a specific organ or tissue.[17,46,66,67] The purification of QDs is usually obtained through precipitation with ethanol or methanol, centrifugation, and removal of the supernatant, which mainly contains unreacted precursors and other impurities. Some researchers have used the size-selective precipitation method, by which small amounts of polar solvents (acetone, ethanol, and 2-propanol) are employed to precipitate polydisperse mixtures of CdS QDs. The procedure is repeated until monodisperse fractions are obtained.[62] Dialysis is preferred to overcome difficulties in the dispersion of QDs, especially in the aqueous synthesis of polyphosphate-capped CdS QDs.[60]

### 2.1. Structure of quantum dots

QDs are composed of a metalloid crystalline core and a shell. The shell serves as a shield for the core and enables the bioavailability of QDs (Fig. 1). The cores of QDs usually consist of various metal complexes, such as magnetic transition metals, semiconductors, and noble metals.[7,68] Therefore, decorating the cores of QDs with protecting shell layers has been widely encouraged. Additionally, the ZnS shell layer presents more

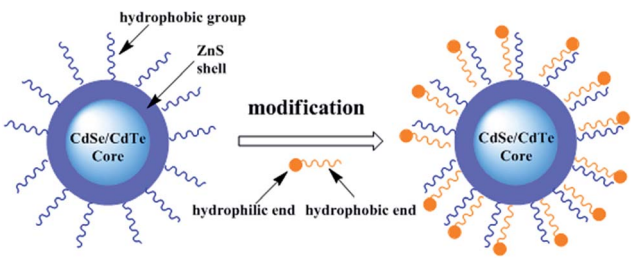


Fig. 1 The structure of a representative QD: the core, shell, and targeting ligands.

positive effects than other capping materials because it can: (i) decrease Cd toxicity by restricting the dissolution of free ions; (ii) prevent oxidation of the CdSe core; (iii) recombine the surface defects of the core; and (iv) enhance the photostability of the QDs. Simultaneously, the size of the QD core is unchanged while the ZnS shell layer is grown directly on the surface of the core; thus, the luminescence characteristics of the QDs are mainly preserved, and only a tiny shift (less than 5 nm) in the fluorescence maximum wavelength is detected.[15]

Further utilization of functional groups or biocompatible coatings can confer desired bioactivities upon core–shell QDs.[69] Newly synthesized QDs are inherently hydrophobic and unsuitable for biological use due to hydrophobic capping on the surface of the metalloid cores during their synthesis in organic solvents.[70] Generally, newly synthesized QDs are functionalized or given secondary coating materials to improve their water solubility, core durability, and suspension characteristics, rendering them biologically compatible.[70–72] For example, QD cores can be capped with hydrophilic polyethylene glycol (PEG) groups to endow the QDs with good biocompatibility and dispersity in aqueous solution; they can also be further conjugated with bioactive compounds to target cellular structural features or specific biological events.[73,74] Hence, bonding with various molecular entities can functionalize QD cores for specific therapeutic or diagnostic purposes. These functionalization methods generally include electrostatic interactions, covalent bonding, and multivalent chelation in consideration of the stability/durability and *in vivo* reactivity of QDs.

### 2.2. Concentration of quantum dots

Due to the unquantifiable number of ligand molecules that are conjugated to QDs, the concentration of QDs after the colloidal preparation process is difficult to ascertain by elemental composition or gravimetric methods. To this end, Peng's group proposed empirical equations to calculate the extinction coefficients for CdS, CdSe, and CdTe QDs; therefore, the concentrations of these QDs could be readily determined by the Lambert–Beer law.[22,52,55] However, for water soluble QDs, empirical equations could not be used because the spectrum was not only influenced by the applied coating materials, but also by the ionic strength and acidity of the working environment. Alternative optimal methods have recently been provided for the calculation of the concentration of QDs in aqueous solution, such as phage-based assays to observe mercaptoacetic acid-capped CdSe/ZnS QDs[75] and the single-particle counting of streptavidin-capped CdSe/ZnS QDs.[76]

## 3. Surface modification

As stated earlier, the high surface energy of crystalline nanoparticles can result in surface defects that quench the fluorescence properties of exposed QDs.[77–79] In addition, exposed QDs may suffer photochemical degradation and surface oxidation and may leach metal ions after long term exposure to ionic media or cellular media, resulting in metal ion toxicity.[80–82] Therefore, it is necessary to cap the surface of the QD core with stable materials to reduce their high reactivity and surface defects. ZnS is usually used as a capping material to increase the stability of the QD core and enhance the quantum yield at room temperature.[54]

QDs can be prepared by aqueous phase synthesis or by an organometallic route. In the former case, QDs can be obtained under normal atmospheric conditions without special equipment requirements. High temperature thermal decomposition of organometallic compounds is a well-confirmed method for the preparation of QDs. This method is carried out in the absence of oxygen and water to decompose the organometallic compounds into non-aqueous media at high temperature.[83] Organic QDs possess distinctly different surface properties compared to aqueous QDs. The surface of organic QDs is covered with a large number of hydrophobic ligand molecules (*e.g.*, TOP/TOPO), while the surface of aqueous QDs is capped by hydrophilic molecules (*e.g.*, 3-mercaptopropionic acid, MPA). Therefore, organic QDs require additional surface modification to enhance their water dispersibility, while aqueous QDs are inherently water dispersible without any surface modification.[84] As shown in Fig. 2, surface modification usually significantly enhances the hydrodynamic diameter of QDs as detected by dynamic light scattering (DLS). Consequently, organic QDs and aqueous QDs have similar particle sizes, as determined by transmission electronic microscopy (TEM);[85] the hydrodynamic diameter of surface modified organic QDs is larger than 5.0 nm, while aqueous QDs typically possess small hydrodynamic diameters (less than 5.0 nm).[85–87]

The polarity of the medium in which QDs are dispersed can strongly influence their luminescence properties, as it directly determines the stability of the surface capping ligands of QDs.[88] It is necessary for QDs to maintain their abilities and optical properties during transfer into a polar medium to interact with target analytes. Thus, ligand exchange is the usual method that is employed to replace the hydrophobic capping ligands on the surface of QDs. To this end, the most widely used capping ligands are thiol-based species, such as L-cysteine or glutathione (GSH) and mercaptoacetic acid (MAA) or 3-mercaptopropionic acid (MPA). Usually, exchange of the original hydrophobic

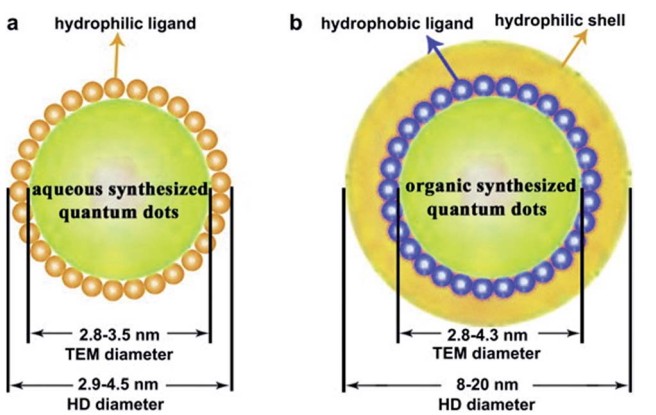


Fig. 2 Schematic of the characteristics of aqueous synthesized QDs with hydrophilic ligands and organic synthesized QDs with hydrophobic ligands.[85]

capping ligands may induce the generation of poorly stable QDs and dramatically reduce their luminescence quantum yields.[89] Another strategy to promote the solubility of QDs in aqueous media is encapsulation, thereby avoiding ligand exchange.[90] Encapsulation usually involves the use of polymer layers or silica shells to protect the QD cores efficiently while preserving the optical properties and original hydrophobic coating layers.[91] The two encapsulation methods present different advantages: the polymer layers can incorporate multifarious functionalities on the surface of QDs and thus enhance their interaction with target analytes, while the silica shells are chemically inert. Amphiphilic polymers such as calixarenes, cyclodextrins, and other similar organic cyclic species are the most widely employed polymers in the synthesis of QDs.[92,93] In addition, polyethylene glycol (PEG) derivatives, which are commercially available and involve simple encapsulation processes, have become another popular material in the synthesis of QDs. The sole drawback of micelle encapsulation is that not all nanoparticle sizes are suitable for encapsulation.[94]

### 3.1. Inorganic surface

Most binary QDs cannot meet the obligatory band gap and band alignment requirements due to the lattice mismatch between the shell and the core; thus, an overall coating for QDs is necessary. Inorganic surface modification of QDs can establish a multilayer semiconductor heterogeneous system with desirable conduction and valence bands. The main advantage of such a heterogeneous system is that it can provide extraordinary photoluminescence, higher quantum yield, increased half-life, enhanced optical properties, better structural properties and improved stability towards photo-oxidation. If an inorganic semiconducting layer is provided over core–shell QDs and its band gap is higher than that of the shell, the particle is called a quantum dot quantum well (QDQW).[95,96] Core–shell structured nanoparticles combine the favorable properties of the magnetic core with protective polymer, gold, silica, carbon or metal oxide shells. These coating materials may not only protect the chemical-active metal core from acid erosion and oxidative degradation but may also be responsible for further surface modification.[97] Coating the surface of nanoparticles with an amorphous silica layer is called silanization. As shown in Fig. 3, surface silanization generates QDs that are biocompatible for cancer diagnosis and therapy. Replacing the surface ligand with a thiol-derived silane such as mercaptopropyl tris silane is the first step of surface silanization. The trimethoxysilane groups can be well cross-linked by the formation of siloxane bonds. During further growth of the shells, other types of silicon can be added to provide functional groups and different charges on the surface of QDs. Generally, the additional materials that are used frequently are phosphor-silanes, aminopropyl-silanes, and polyethylene glycol silanes. Silanized QDs are extremely stable because the silica shells are highly cross-linked.[74] In addition, the electrochemical properties of silica make it a perfect material to improve the solubility of QDs in aqueous media.[74] Apart from silica, other metals and metal oxides can also be employed as shell materials. For example, gold as a shell material has been widely studied by many researchers.[65,98,99] Wang *et al.*[100] successfully synthesized $Fe_3O_4$@PAH@Au multifunctional QDs, which presented both magnetism and near-infrared absorption. Xuan *et al.*[99] also reported $Fe_3O_4$@PANI@Au multifunctional QDs with well-defined core–shell structures, optical properties, magnetic separability, and catalytic activity. On the other hand, the gold could also endow the QDs with biocompatibility through the modification of thiol/amine terminal groups. When the core is composed of a polymer or different copolymers, an inorganic surface modification could be applicable. Coating the polymeric core with an inorganic shell is greatly beneficial to the mechanical strength, thermal and colloidal stability of QDs and can provide resistance to oxidation and corrosion. Meanwhile, these particles also present good polymeric properties, such as flexibility and toughness, and excellent optical properties.

### 3.2. Organic surface

QDs produced by the colloidal synthetic method are mostly hydrophobic and can only dissolve in non-polar solvents such as toluene or chloroform. However, almost all the biological applications of QDs require aqueous conditions; thus, direct modifications on the surface of QDs are necessary to improve their water solubility without altering the properties of the cores. For this purpose, water-soluble QDs are obtained by introducing functional groups (hydroxyl, carboxyl, or amino) over their surfaces to achieve a total net charge. Additionally, this surface modification facilitates the conjugation of QDs with biomolecules.[15,101–103] In general, the usual method for organic surface modification is to coat the QDs with thiolate ligands during the growth period. As shown in Fig. 3, mercaptoacetate, thioglycerol, 2-mercaptoethanol, 1,4-dithiothreitol, cysteine, glutathione, and methionine have been applied as capping ligands. Amines such as *n*-butylamine, *n*-hexylamine, and hexadecylamine have also been applied for conjugation with TOP and TOPO.[74]

Ligand exchange occurred during the substitution process of hydrophilic ligands for native hydrophobic ligands through mass action.[105,106] Generally, these substituting ligands possess bifunctional groups: (a) thiols (–SH) to bind the ZnS shell on the surface of the QDs; (b) hydroxyls (–OH), carboxyls (–COOH), and amines ($–NH_2$) to enhance water solubility and provide secondary conglutination for biomolecules such as antibodies, proteins or drugs.[105,107] The main advantage of these ligands is that they can effectively prevent the QDs from aggregation and simultaneously passivate surface defects, preserving the quantum yield.[108–110] Organic ligands, which can be replaced by water soluble ligands through simple mass action, provide excellent stability and solubility for QDs to cooperate with organic non-coordinating solvents.[110] Evidence has showed that the ligands on the surface of QDs are in a dynamic equilibrium with the native ligands in solvent; thus, these two kinds of ligands can substitute each other under equilibrium conditions.[111] In general, ligand exchange can be promoted by increasing the local probability of replaceable ligands through supplying more replaceable ligands in the solution than

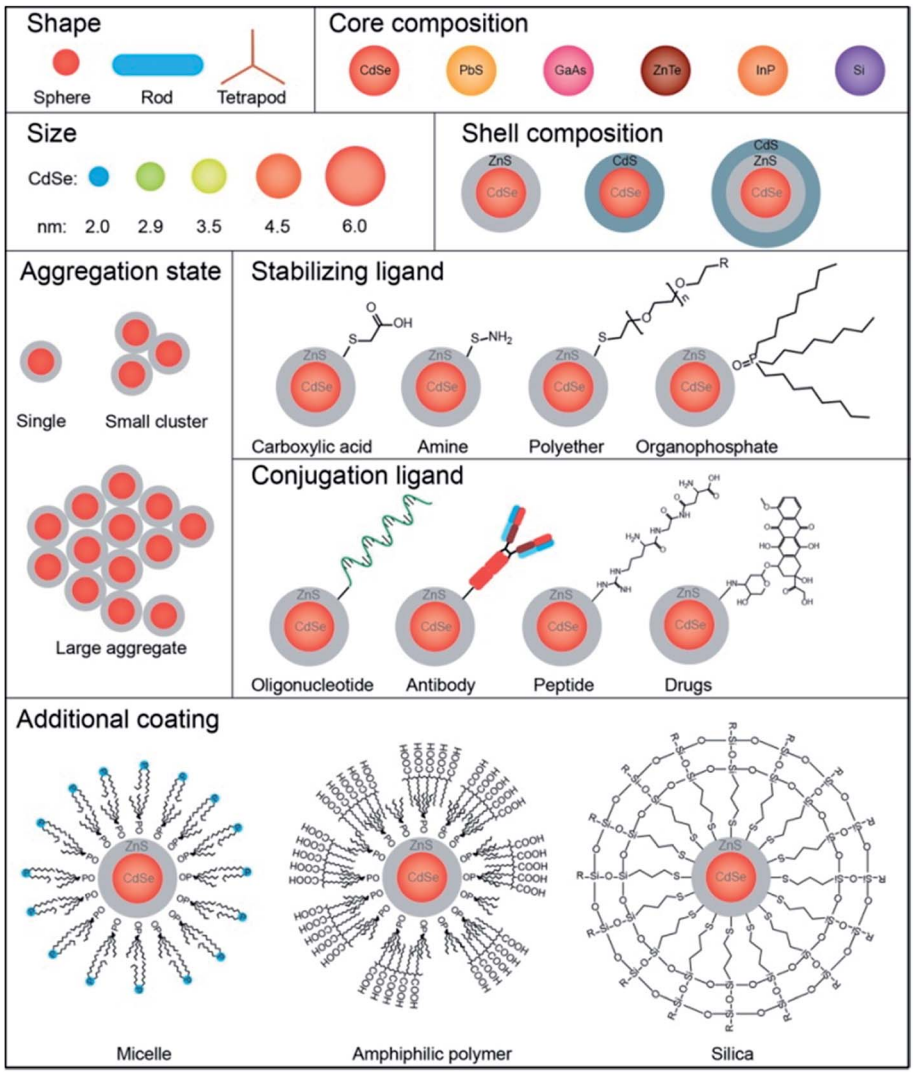


Fig. 3 Schemes of different QD surface modification methods. Additional coating can further protect the QD core from oxidation. The surface chemistry of QDs influences their propensity to aggregate, particularly in biological solutions.[104]

existing ligands when the surface affinity of the replaceable ligands is low.[112]

The surface of QDs can also be encapsulated by TOP/TOPO ligands with amphiphilic phospholipids or polymers, which can unite both hydrophilic groups and hydrophobic alkyl chains (Fig. 3). Under the circumstances, non-specific hydrophobic interactions are useful for linking the alkyl chains, including phosphine ligands and the phospholipid/polymer, while the polar functional groups located at the exterior provide water solubility to the QDs. The amphiphilic polymers are usually applied at the base of a polyester backbone (maleic anhydride) with a hydrophobic alkyl chain, including dodecyl,[113] octadecane,[114] and tetradecene chains.[115] These polymers wrap the surface of the QDs by forming an amine-type cross-linker, such as hexamethylene triamine. Other polymer coating compounds, such as alginate, polyvinyl pyrrolidone, and chitosan, have also been applied to produce water-soluble and less toxic QDs.[15]

Several studies have demonstrated that the stabilization of QDs through ligand exchange, covalent modification and other chemical surface modifications shows several drawbacks: (i) small ligands with one head group attached to the surface of QDs can easily be released and influence the stabilization process, especially when excess unbound ligands exist in the suspension; (ii) thiol-containing ligands can bind strongly to QDs; however, they should be carefully selected on the basis of the core material.[74,116] It has been well established in a variety of reports that using multifunctional ligand molecules to modify QDs not only improves their water solubility but also enhances their stabilization effects.[116,117] Interestingly, owing to the various bonding points on the particle surface, the amphiphilic molecules can prevent facile desorption of the polymer molecule during the modification of QDs. For example, the amphiphilic coating can interlink the amphiphilic molecule with its hydrophobic ligand groups by hydrophobic interactions, which neither depend on the type of ligand molecule nor the exact

 

material composition (Fig. 3). These observations are mainly based on hydrophobic interactions between the hydrocarbon chains and the polymer molecules. Meanwhile, amphiphilic molecules coated on the surface of QDs exhibit the same physicochemical surface properties, independent of the core material.[74,116]

Core–shell QDs are desirable for biological applications, as the shell can enhance their fluorescence properties and decrease their leaching ability.[118] The ligand functional group, which has electron donating and withdrawing ability, can induce trapping effects on the surface of QDs.[118] CdSe/ZnS-ssDNA fluorescent dye conjugates were applied as bioprobes by Huang *et al.*[119] to detect micrococcal nuclease with high sensitivity and specificity. Furthermore, water-soluble encapsulation CdTe/ZnS QDs were also used as a pH probe for tiopronin determination[120] and enzyme kinetics.[121] One-step DNA functionalization on QDs or core–shell QDs synthesized in aqueous media was reviewed by Samanta *et al.*[122] Polydentate-phosphine coating QDs have been employed in cancer diagnosis[123] for large animals through imaging. Additionally, capped InP/ZnS QDs have also been applied to cellular imaging.[124]

# 4. Environmental conditions for transport and fate of quantum dots in aquatic environments

As a new type of pollutant in aquatic environments, QDs will cause ecological pollution; this is closely related to the composition and chemical properties of the core–shell structure. To thoroughly evaluate the potential environmental and ecological risks of QDs, it is necessary to obtain a better understanding of the environmental transport and fate of QDs. Although a number of studies have investigated the weathering process of QDs, our knowledge about their potential mechanisms and dissolution kinetics is limited. The coexistence of heavy metals in aquatic environments could significantly enhance the toxicity of QDs, while natural organic matter would affect the adsorption and migration reaction at the QD interface. On the other hand, the pollution characteristics of QDs could be influenced by many environmental factors, such as light, pH, dissolved oxygen and ionic strength. At the same time, aquatic organisms could secrete extracellular polymeric substances (EPS) and stabilize QDs on EPS layers or subcellular structures to change the form of QDs in aquatic environments.

## 4.1. Light

When QDs are excited by incident light carrying higher photon energies than the band gap of QDs, a bound electron–hole pair that can react with the surrounding oxygen molecules is formed and produces ROS, including $^{\cdot}OH$, $^1O_2$, and $O_2^{\cdot-}$.[37,125–127] As shown in Fig. 4, two independent methods, UV-vis and scavenging experiments, were used to analyze the formation of ROS during the dissolution of QDs under UV irradiation.[31] Previous studies showed that the release rate of $Cd^{2+}$ did not change distinctly when excess $^{\cdot}OH$ and $^1O_2$ scavengers were expended, indicating that $^{\cdot}OH$ and $^1O_2$ were not the main substances formed during the generation of ROS. However, when excess $O_2^{\cdot-}$ scavengers were added before the reaction, an obvious retardation of the release of $Cd^{2+}$ was observed, suggesting that photoexcitation may lead to the generation of $O_2^{\cdot-}$, a precursor of the oxidative dissolution of QDs.[31,37] Interestingly, several studies confirmed that superoxide dismutase (SOD) could increase the release of $Cd^{2+}$ observably after irradiation, probably because SOD catalyzed the conversion of $O_2^{\cdot-}$ into $H_2O_2$, which accelerated the release of $Cd^{2+}$.[35,128] The reaction can be shown as follows:

$$2O_2^{\cdot-} + 2H_2O \xleftrightarrow{SOD} O_2 + H_2O_2 + 2OH^-$$

Therefore, $H_2O_2$ is the most likely intermediate oxidant that reacts rapidly with QDs.[129]

To explore the stoichiometric reaction of QDs, the possible ionic species were first determined after photooxidation of QDs, as shown in the reaction:

$$Cd_{5.68}SeZn_{4.1}S_x + (x-8.78)H_2O + (1.5x+6.39)O_2 \xleftrightarrow{UV}$$
$$5.68Cd^{2+} + SeO_4^{2-} + 4.1Zn^{2+} + xSO_4^{2-} + (2x-17.56)H^+$$

The photooxidation of QDs is a proton-generating process, as confirmed by the observed decrease in pH value.[59,130] The

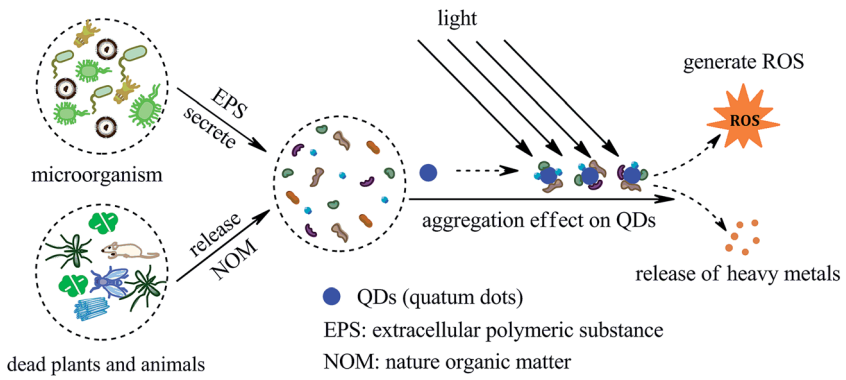


Fig. 4 Effects of light, nature organic matter, and extracellular polymeric substances on the dissolution and stability of QDs in aquatic environments.

Table 1 Supernatant concentrations of QD constituents measured at various pH values[27a]

| QD | pH treatment | Total Cd (mg $L^{-1}$) | Total Se (mg $L^{-1}$) |
|---|---|---|---|
| QD557-PMAO | Coated (pH 7) | 29.2 ± 5.3 | 23.0 ± 3.8 |
| | Weathered (pH 2) | 2853 ± 93.3 | 2760 ± 129 |
| | Weathered (pH 12) | 1511 ± 97.6 | 1617 ± 94.5 |
| QD559-PEI | Coated (pH 7) | 28.0 ± 7.3 | 21.5 ± 5.6 |
| | Weathered (pH 2) | 3362 ± 207.4 | 3029 ± 42.5 |
| | Weathered (pH 12) | 3123 ± 101.9 | 2819 ± 103.8 |
| QD655-carboxyl | Coated (pH 7) | 14.9 ± 1.2 | 5.3 ± 0.8 |
| | Weathered (pH 2) | 3528 ± 74.5 | 934 ± 106.7 |
| | Weathered (pH 12) | 3729 ± 99.0 | 1052 ± 88.3 |

[a] Note: values represent the average ± the range of 3 observations.

above chemical formula is determined on the basis of the measurement of the total element composition with ICP-MS. The photo-degradation products ($Cd^{2+}$, $Zn^{2+}$, and $SeO_4^{2-}$) may be released from the core–shell structure, decreasing the hydrodynamic size of the QDs.

### 4.2. Weathering of QDs during pH variations

In a previous study, the laboratory conditions were adjusted to pH values ranging from 2 to 12 to investigate the possible weathering process of QDs.[27] Several different processes, including QD aggregation, core–shell QD leaching, and precipitation of metal oxides, can occur under extremely acidic or alkaline conditions. Low pH values were expected to readily solubilize core–shell QDs, while high pH values may result in the chemical speciation, precipitation, and bioavailability of Cd and Se (Table 1).

It is well documented that the luminescence properties of QDs are pH-dependent.[59,130–132] Nevertheless, pH may have a dual influence on the luminescence properties of QDs because it affects their structure and the function of the capping ligands.[130] For example, pH-dependent cadmium–thiol complexes can be produced at the interface of Cd-containing QDs and capping ligands at pH > 5.[59] However, at pH < 5, protonation can result in the detachment of capping ligands from the surface of QDs and induce agglomeration, thus decreasing the luminescence intensity and lifetime.[133] Zhang *et al.*[130] have reported that the decline of the pH value from 12 to 5 could result in the agglomeration of QDs (Fig. 5), causing a change in the luminescence intensity of the QDs.

### 4.3. Dissolved oxygen

It has been demonstrated that the dissolved oxygen can induce and catalyze the oxidation of QDs.[31,134–137] For instance, several phenomena have been observed upon exposing QDs to an oxidative environment: (i) a blue-shift in the excitonic fluorescence spectra; (ii) a broad red-shift adjacent to the excitonic fluorescence peak; (iii) a progressive change in the absorbance profile of the QD solution; and (iv) a decline in the quantum yield.[32] Shifts in the fluorescence and absorbance spectra may

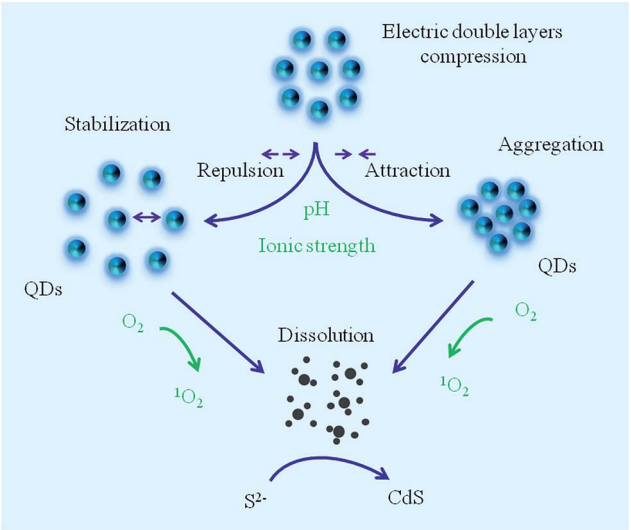


Fig. 5 Effects of pH, dissolved oxygen, and ionic strength on the dissolution and stability of QDs in aquatic environments.

result from the decrease in size of the QDs (a result of oxidative damage on surface atoms), while the broad red-shifted fluorescence peak can be attributed to the formation of lower-energy band gaps (a result of newly-formed defective structures). It has been established that $O_2$ molecules can oxidize chalcogenide atoms (S and Se) to form oxides ($SO_4^{2-}$ and $SeO_2$) on the surface of QDs (Fig. 5).[27,32] In the case of CdSe QDs, the $SeO_2$ molecules can desorb from the surface, leaving a decreased number of "dangling" Cd atoms behind. Therefore, prolonging the exposure of QDs to an oxidative environment could induce the decomposition of the nanocrystals, leading to the desorption of $Cd^{2+}$ or CdSe complexes from the QD core.[32,138,139]

### 4.4. Ionic strength

Ionic strength is an important parameter in analyzing the transport and fate of QDs in granular aquatic environments.[140,141] However, due to the limitations of available experimental techniques, the sizes of suspended QDs are difficult to determine.[142]

It has been reported that the addition of monovalent electrolytes (*e.g.*, $K^+$ and $Na^+$) will increase the ionic strength and compress the electric double layers (EDLs) of QDs (shown in Fig. 5). A plausible explanation is that the capping ligands on the surface of the QDs may extend into the electric double layers and prevent the QDs from approaching each other when the ionic strength increases.[25,143,144]

The aggregation behavior of QDs in surface water in the presence of divalent cations has also been examined in some studies. The main reason for the destabilization of divalent cations is the formation of complexes with the thioglycolate capping ligands on the surface of QDs, through which their negative charge can be neutralized. Furthermore, the complexes can bridge the gap between QDs to form aggregates. Therefore, the divalent cation complexation constants of capping ligands

 

can be used to quantify the aggregation of QDs. In this paper, we use $Ca^{2+}$ as an example. $Ca^{2+}$ complexes are formed through the combination of $Ca^{2+}$ and carboxyl groups on the surface of QDs. A $Ca^{2+}$ ion may bond to either monodentate or bidentate capping ligand sites.[145,146] The $Ca^{2+}$ complexation constants are determined by calcium titration. According to the results of previous aggregation experiments, even a low concentration of $Ca^{2+}$ can lead to the formation of $Ca^{2+}$ complexes with QD capping ligands, supported by the high complexation constants of the bound capping ligands.[25,147,148]

Similar to divalent electrolytes, trivalent electrolytes (*e.g.*, $Al^{3+}$) can also reduce the negative zeta-potentials of QDs and cause aggregation. The inconformity in the aggregation of QDs with $Al^{3+}$ at pH values between 5 and 8 is correlative to the complexation mechanism of $Al^{3+}$ with the capping ligands.[59,130] In liquid media, $Al^{3+}$ can be hydrolyzed and is present as $Al^{3+}(H_2O)_n[(OH)_{6-n}]^{n-6}$. Thus, the complexation of $Al^{3+}$ with the capping ligands may occur through a substitution reaction between $OH^-$ groups or the original water molecules and amino groups or carboxyl groups in $Al^{3+}(H_2O)_n[(OH)_{6-n}]^{n-6}$.[25,149]

### 4.5. Natural organic matter

The transport and fate of QDs in aquatic environments are not only dependent on physicochemical parameters, such as light, pH, dissolved oxygen, and ionic strength as described by the DLVO theory,[150,151] but are also related to natural organic matter (NOM). Some researchers have confirmed that the humic substances (HS) which are commonly present as NOM in aquatic environments[152,153] can affect the environmental transformations of QDs.[31,154,155] Evidence has shown that HS can alter the surface properties of QDs, thus influencing their dispersibility and aggregation state,[24] or can even transfer the originally hydrophobic QDs to aqueous QDs.[156–158] While the content of NOM in aquatic environments exceeds the charge of DLVO theory, QDs will tend to form larger aggregations, especially when the ionic strength is high.[1] NOM can either enhance the stability of QDs through coating their surfaces with negative charges by static repulsion[159] or can decrease the stability of QDs through a variety of mechanisms, including pearls-on-a-string formations[160] and bridging effects.[161] Hence, NOM can greatly affect the stability of QDs through both direct physicochemical processes and indirect chemical reactions (Fig. 4).

### 4.6. Extracellular polymeric substances

Extracellular polymeric substances (EPS) are widespread in aquatic environments and have an effect on the transport and toxicity of QDs.[154] As with many other engineered nanoparticles, quantitative information on the transport and fate of QDs in aquatic environments is confined, particularly in open waters. Owing to their amphipathy, EPS are ubiquitous in the environment and have a remarkable ability for self-assembly or assembly with other molecules, including metal ions, nanoparticles, and NOM (Fig. 4). Therefore, EPS can act as a strong agent for QDs to aggregate in aquatic environments through electrostatic and hydrophobic interactions.[1] The electrostatic interactions are based on the surface properties of QDs. For example, positively charged amine-functionalized QDs have a stronger affinity to EPS than negatively charged carboxyl-functionalized QDs[162] because the positively charged surfaces could help stabilize the affinity of QDs to EPS by enhancing cross-links in the gel networks.[1,163] Furthermore, due to the formation of aggregate networks between QDs and EPS, the release of QDs into aquatic environments can potentially disturb the aquatic biosphere and at the same time change their own biological pathways. On the other hand, EPS could reduce the stability of QDs, promote their degradation and facilitate the release of $Cd^{2+}$ into aquatic environments upon exposure to light.[164] According to some studies, the increased degradation of QDs is directly related to the ROS provided by EPS[31] as well as the composition (ratio of carbohydrates/proteins) of the EPS;[1,164] however, the mechanisms involved need to be further studied.

## 5. Toxicity of quantum dots to microorganisms

QDs are composed of a semiconductor core (*e.g.*, CdS and CdSe) and are usually encapsulated by a shell (*e.g.*, ZnS) to improve their electronic and optical properties and prevent the core metal from leaching.[32,165,166] For many applications, QDs are often coated with organic molecule ligands to enhance their dispersibility in solution and guide them to biological targets.[17,167–169] Recent advances have led to the large-quantity production of water soluble QDs. Given their wide applications, substantial production of QDs is envisioned in nature.[7,43,170,171] However, most currently produced QDs consist of heavy metal chalcogenides (*e.g.*, PbS and CdSe), which may cause a hazard to humans and microorganisms in consideration of their toxic metal release and nanoscale properties. The toxicity of QDs depends on multiple factors derived from both their inherent physicochemical properties and their acquired environmental conditions. Particle size, charge, concentration, bioactivity of the surface coatings (capping ligands and functional groups), exposure time, photolysis, oxidation, and mechanical stability are the main factors that determine the toxicity of QDs, individually or collectively. Functional capping, physicochemical characteristics, and the stability of the QD core are recognized as the significant factors in assessing the toxicity of QDs to microorganisms following real world exposure.

### 5.1. Particle size

Particle size is critical to the biological performance of nanoparticles.[172–174] Several reports have proved that particle size affects the toxicity of QDs at the intracellular level. In cellular studies, CdTe QDs with sizes within 2.2 nm had greater toxicity than particles with sizes within 5.2 nm.[35,175] Additionally, the intracellular biodistribution of QDs also showed an obvious size dependence in some studies.[84,176] Larger particles were distributed in the cytoplasm, while smaller particles were localized around and in the nucleus of the cell.[35,45,177] Hardman[7] has also found that the size of QDs can influence the subcellular distribution, in which larger cationic QDs are present in the cytosol and smaller cationic QDs are distributed in the nuclear

compartment. Endocytosis, including pinocytosis and phagocytosis, has been well recognized as the main mechanism by which QDs enter cells (Fig. 6).[178,179] Pinocytosis is further classified into at least four mechanisms (caveolae-mediated, clathrin-mediated, macropinocytosis, and clathrin/caveolae-independent endocytosis) depending on the products of the intracellular vesicles.[180,181] Additionally, the intracellular localization of QDs is also particularly important for cytotoxicity.[175,182] The confocal fluorescence images demonstrated that CdTe QDs were predominantly located in the cytoplasmic and perinuclear area.[183] However, the distribution of QDs was not uniform but presented a dotted pattern with differential intensity. Especially, high-intensity dots were concentrated in the marginal and perinuclear area of the cell.[84] This heterogeneous distribution of QDs may result in an abnormally high local concentration of $Cd^{2+}$ in the nuclei or other organelles, aggravating the damage to these organelles. The concentrated effect of $Cd^{2+}$ on organelles was responsible for the higher cytotoxicity of CdTe QDs compared to $CdCl_2$ QDs. Overall, CdTe QDs may enter subcellular organelles and directly result in loss of function of the organelles.

### 5.2. Surface coating materials

A main cause of QD toxicity is the cadmium contained in the QD core. The toxicity of uncoated CdSe and CdTe QDs has been extensively studied in several reports.[184,185] The results showed that the toxicity of QDs is closely associated with free Cd released from the QDs core into the suspensions because it was found that the cytotoxicity of QDs was consistent with $Cd^{2+}$ toxicity from the QD core.[32,34,186,187] Derfus *et al.*[32] found that the uncoated QDs could release $Cd^{2+}$ through surface oxidation when incubated with rat hepatocytes, indicating that the uncoated QD cores could be degraded in biological environments. Therefore, the $Cd^{2+}$ toxicity from QD cores is likely to be responsible for the cytotoxicity of QDs. However, CdSe and CdTe QDs are also highly charged and can be easily affected by air or photo oxidation. Hence, the generation of free radicals is considered to be another major mechanism of the cytotoxicity of QDs.[33,37,188,189] Cho *et al.*[190] found that the cytotoxicity of CdTe QDs was not related to $Cd^{2+}$ released from the QD core but to the formation of free radicals (Fig. 6). Additionally, similar to the findings we mentioned above, uncoated QDs have also been involved in further cytotoxicity. For example, in SH-SY5Y neuroblastoma cells, the damage induced by CdTe QDs was related to up-regulation of Fas expression, which may result from oxidative stress caused by the QDs.[191–193] Tang *et al.*[194] studied the neurotoxicity of CdSe QDs in hippocampal neurons and found a dose-dependent augment in neuronal death. However, the evidence showed that the influx of extracellular $Cd^{2+}$ and the release of intracellular $Cd^{2+}$ were enhanced even at low doses.

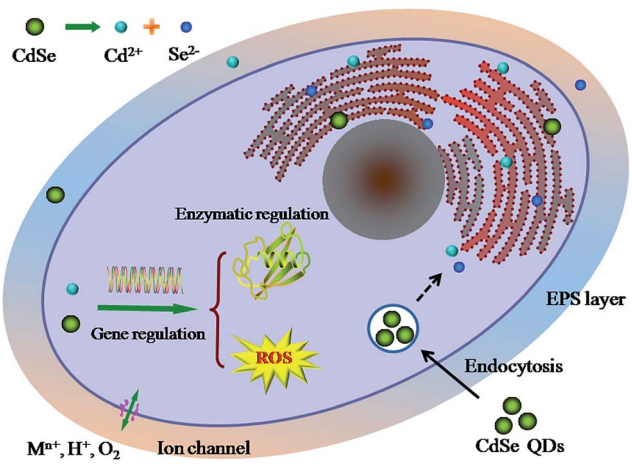


Fig. 6 Schematic of the cytotoxicity induced by CdSe QDs. When CdSe QDs are transported across the cell membrane, free $Cd^{2+}$ is released into the cytoplasm. The QD nanocrystals and free $Cd^{2+}$ induced a series of protective responses, including the up-regulation of proteins and an increase in oxidative stress.

Encapsulation of QDs with a ZnS shell or other coating materials has been shown to be an effective way to reduce the toxicity of QDs, although much work remains to be accomplished in this arena. Derfus *et al.*[32] indicated that free Cd released from CdSe QDs into aqueous media could be dramatically decreased by ZnS shells. In addition to decreasing free Cd release, the ZnS shell was also observed to reduce the generation of free radicals by protecting the QDs from air oxidation. Hence, the encapsulation of QDs with a ZnS shell or other coating materials appears to be a promising way to inhibit the release of $Cd^{2+}$ and the generation of free radicals.[195,196] However, in order to accurately assess the toxicity of shell or coated QDs, the degradation of the shell or coating materials, along with their toxicity, must also be adequately considered. Previous studies have shown that the ZnS shell did not completely eliminate the toxicity of QDs due to the effect of photo or air oxidation on the shell;[32] moreover, the CdSe/ZnS QDs could also induce the generation of free radical species.[33,189] These researchers hypothesized that the ZnS shell could protect the CdSe core from oxidation, but could not inhibit the generation of electron-induced radicals in the surrounding environment, indicating that the ZnS shell may be slowly oxidized in the presence of air or water, thus generating the $SO^{2-}$ radical.[45]

In addition, several groups have also been found to enhance toxicity when associated with coating materials such as TOPO and MPA.[46] Hoshino *et al.*[197] observed that the surface coatings of QDs such as MPA could be detached under oxidative and acidic conditions in endosomes and then released into the cytoplasm. To assess the toxicity of surface capping materials, Hoshino *et al.*[197] employed three capping materials (thioglycerol, MPA, and cysteamine) and two possible impurities (ZnS and TOPO) in the study. The result demonstrated that the removal of TOPO from the QD samples was important in decreasing cytotoxicity because TOPO was observed to be genotoxic and cytotoxic. Their findings provided obvious evidence to prove that QD-induced genotoxicity and cytotoxicity were not caused by the QD core but by the hydrophilic QD coating materials. Taken together, these reports indicated that the ingredients of the shell or capping materials must be more thoroughly assessed.

### 5.3. Photolysis and oxidation

The stability of QDs, both *in vivo* and in storage, is a significant aspect for assessing their toxicity. Some reports have indicated that the cytotoxicity of QDs may be related to photolysis or oxidation.[7,32,198,199] Under photolytic and oxidative conditions, the core–shell QD coatings were too labile to maintain the stability of the QDs; thus, the potentially toxic coating materials or intact core metalloid complexes were exposed to the environment and caused the dissolution of the core complexes. Zhang's group[200] demonstrated that the fluorescence intensity of CdSe/ZnS QDs showed a shift to blue spectra that decreased with contacting time upon exposure to living cells, indicating that the ZnS shell deteriorated intracellularly.[200,201] Hardman[7] reported that primary rat hepatocytes exposed to 62.5 μg $mL^{-1}$ MAA-CdSe QDs underwent cell death, which may be related to photolysis and oxidation of the QD capping material. Derfus *et al.*[32] deduced that toxicity of QDs was related to the environmental conditions and that lengthened exposure time to photolytic and oxidative environments could lead to the decomposition of MAA-TOPO capped CdSe QDs. Although ZnS coating materials could significantly decrease ambient air oxidation, they did not completely eliminate photooxidation, with high levels of free $Cd^{2+}$ found in solution under photooxidative conditions.[7,192] Aldana *et al.*[202] have also experimentally observed the photochemical instability of thiol-coated CdSe QDs, although not at correlative UV wavelengths (254 nm); it was noted that the photochemical stability of CdSe QDs was closely related to the packing and thickness of the ligand monolayer. Kloepfer *et al.*[203] reported that when exposing *Staphylococcus aureus* cultures to conjugated QD solution for 2 weeks, a noteworthy increase in fluorescence was observed. The change of fluorescence may be related to the intracellular oxidation of QDs, because a remarkable increase of Se was found in the cells. Therefore, the photostability of QD conjugates is a considerable issue during their preparation; at the same time, QD conjugation procedures should also be performed under little or no light conditions to avoid photolysis of the QDs. Some studies have suggested that QDs may be susceptible to photolysis and oxidation; this increases the possibility of degradation of QDs *in vivo* or intracellularly. For example, a recent study indicated that QD surface coatings and ligands were slowly degraded *in vivo*, leading to surface defects and fluorescence quenching.[204] However, several reports noted that QDs coated with a grafted 8-carbon alkyl side chain and a high molecular weight copolymer showed even greater stability *in vivo* than those with simple polymer and amphiphilic lipid coatings.[7] Hoshino *et al.*[205] observed that for CdSe/ZnS-SSA QDs in EL-4 cells, approximately 10% of the cells retained QDs after exposure for 10 days, and the fluorescence intensity of the cells was found to gradually decline and become highly concentrated in the endosomes. Likewise, a substantial loss of QD fluorescence was described by Gao *et al.*[204] upon implementing QDs in live animals.

### 5.4. Charge, concentration, and exposure time

As with pharmacological studies, QD toxicity studies confront difficulties in terms of charge, concentration, and exposure time, which underscores their requirement of rigorous physicochemical properties. Existing evidence shows that surface modifications can influence QD properties such as surface net charge, which may contribute to their cytotoxicity.[32,165] For example, uncharged (polyethylene glycol; PEG), negatively charged (carboxyl-modified; COOH), and positively charged (amino-terminated; $NH_2$) CdSe/ZnS QDs were employed to monitor the uptake, ingestion and depuration procedures of nanoparticles in *Ceriodaphnia dubia* and *Daphnia magna* over 24 h of exposure.[162] These studies proved that CdSe/ZnS QDs with a higher negative charge (QDs-COOH) were taken up to a greater extent by *Daphnia* (259.17 ± 17.70) than either positively charged (QDs-$NH_2$) (150.01 ± 18.91) or uncharged PEG-QDs (95.17 ± 9.78). To some extent, these results are also related to the surface functional groups attached to QDs.

Particle concentration is also intricately related to the toxicity of QDs because surface area is critical to nanoparticle activity. The dosage or exposure concentration of QDs has been widely reported in the literature using various units of measurement (*e.g.*, QDs per cell, molarity, micrograms per milliliter, and milligrams per kilogram body weight). However, correlative dosage studies are currently challenging. For instance, no cytotoxicity was observed during a 2 h period of acute exposure of cells to QDs.[206–208] Critical questions related to toxicological studies are relevant to the estimation of the effects of QD exposure on humans and effective methods to describe suitable concentrations of QDs for humans.

Finally, exposure time deserves further consideration. QDs appear to widely distributed in tissues and almost cannot be excreted or metabolized.[190] In consideration of the resistance of tissues, it is critical to assess the toxicological risk of QDs in long term studies. In the case of QDs, electronically active Cd nanoparticles may be excessively retained in tissues for years. In general, QDs cause toxicity by releasing $Cd^{2+}$ and generating free radicals in the environment, both of which could influence the transcription and synthesis of DNA or even change the signal transduction in long term treatment.

## 6. Conclusions and perspectives

It is critical to understand the transport and fate mechanisms as well as the toxicity of QDs for their practical biomedical and biological applications in diagnostics, therapy, and imaging. However, it is difficult to assess the overall environmental implications of QDs from current reported studies due to the complexity of their inherent physicochemical properties, environmental conditions, and analytic methods. The synthetic methods and surface modifications of QDs will greatly affect their physicochemical properties as well as their interactions with cellular membranes and their subsequent uptake into cells. Therefore, the transport and fate of QDs in aquatic environments and their toxicity to microorganisms depend on their multiple synthesis methods and surface modification methods. Light, pH, dissolved oxygen, ionic strength, NOM, and EPS have been implicated as the determining factors in evaluating the transport and fate of QDs in aquatic environments. Also, unless they are stabilized by NOM and EPS or other natural species in

the environment, QDs may ultimately be degraded in aquatic environments and serve as a source of toxic mobile Cd species. The increasing production and utilization of QD nanoparticles have raised concerns regarding the possibility of contamination of aquatic and terrestrial ecosystems. Thus, it is necessary to perform extensive toxicological and pharmacological investigations of the applications of QDs to reduce the environmental risk. Therefore, studies on the behavior of QDs in aquatic environments and the cytotoxicity of QDs are critically important, and future directions must include: (i) complete physicochemical characterization of QD structures; (ii) environmental considerations—with increasing application of Cd-containing QDs in biomedical studies and therapies, studies are required to consider the environmental risk of core–shell particles and the dissolution extent of shell materials; and (iii) increased animal toxicity studies to evaluate the biological persistence of QDs in tissues, particularly in long term studies. Research without overall assessment of these critical areas will place human health at risk and impede the progress of nanomedicine development. However, sensible further studies into these areas will undoubtedly contribute to public health and the development of pharmaceuticals for drug delivery and cancer treatment.

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