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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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Abstract: Semiconductor quantum dots (QDs) have raised great attention for their superiorly optical properties and wide utilization in biological and biomedical studies. Recently, intense concerns have been focused on the cytotoxicity assessment of QDs since most QDs are made of heavy metal ions (e.g., Cd^{2+}) which pose a threat to human beings and at the same time hamper their practical applications. This review provides an overview of the synthetic methods, surface modification, dissolution mechanism and cytotoxicity of core-shell QDs. Accordingly, how the polymer coating materials and environmental conditions affect the dissolution kinetics of polymer-coated core-shell QDs are discussed in sufficient details. For offering 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 their toxicity mechanism. 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 nanopharmaceuticals application.

Keywords

Quantum dots; Surface modification; Transport; Dissolution; Cytotoxicity; Reactive oxygen species

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 lots of consumer goods, including detergents, printings, paints, cosmetics, bactericides, coatings, computer electronics, sunscreens, tires and drug delivery systems.[1-5] QDs, also known as semiconductor crystals with outstanding photophysical properties, are a class of inorganic fluorophores that increasingly used in medical imaging and industry.[6,7] Recent studies showed that QDs have a great potential in promoting the applications of image sensor.[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 environments are poorly understood.[12-14]

QDs have highly stable "size-tunable" fluorescence since their photoluminescence emission band is easily adjustable from the UV to the IR regions.[15] These properties of QDs prepared by binary alloys have been acquired by using distinct synthesis routes with a strict control of the constituent material, shape, size, and surface chemistry.[16,17] For example, the colloidal chemistry method is the common route to synthesize QDs since the nanocrystals' surface could be functionalized during the produce process. This process enables nanocrystals ability to

interact with selected species, providing narrow size distribution as well as high luminescence efficiency.[3,18] Moreover, the QDs should also be stabilized by some materials to prevent the agglomeration while they are dispersed in a solvent. Because the QDs are very hydrophobic since many nonpolar surfactant molecules are located on the QDs' surface. Therefore, it is of significant importance to find appropriate ligand materials for the surface modification of QDs. This could not only affect the nanocrystals solution properties but also limit their potential use. Meanwhile, the selective ligand materials on the surface of QDs play a key role in the shaping of nanocrystals.[9] For example, the ligand materials can control the particle size and size distribution during the QDs synthesis as well as nanocrystals structure and stability.[16,19-22]

With the rapid development in commercial and biomedical applications, QDs may eventually enter the environment.[23-25] The residual QDs may release toxic metal ions to the environment during the weathering process, exhibiting toxicity to *Chlamydomonas reinhardtii*,[26] bacteria,[27,28] macroinvertebrate,[29] and even human being. Therefore, it is of great importance to understand the environmental transport and fate of QDs.[30,31] Meanwhile, the systematic cytotoxicity assessment of QDs is also necessary for their practical biological and biomedical applications. To date, a large number of studies on 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 directly correlated with cell death. Parak et al.[36] reported that except for the release of Cd^{2+}, the QDs precipitation on cell surface could also damage cells.

They suggested that QDs presented lower cytotoxicity while QDs only existed in the medium surrounding cells other than ingested by cells. Further, several published reports indicated that QDs could generate reactive oxygen species (ROS), which were cytotoxic and genotoxic.[31,33,34,37,38] For instance, in Green and Howman's study,[33] they speculated that DNA damage occurred because the shell ZnS was oxidized to generate $SO_2^{\cdot -}$, which then generated superoxide and hydroxyl radicals. Ipe et al.[37] also reported the 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 a mechanism of QDs cytotoxicity.[39-43] However, the dissolution kinetics and mechanisms of QDs have not been systematically investigated yet. Moreover, the environmental conditions and the inherent physicochemical characteristics as the significant factors in assessing the QDs' toxicity also have not been well documented.

The aims of this article were to overview and highlight recent works on transport and fate of QDs in aquatic environments and evaluate its toxicity to microorganisms. The effects of environmental factors (e.g., light, pH, dissolved oxygen, ionic strength, natural organic matter, and extracellular polymeric substances) and polymer coating on the dissolution kinetics of polymer-coated core-shell QDs were summarized. Finally, we also discussed the QDs' cytotoxicity to microorganisms by analyzing particle size, surface coating materials, photolysis and oxidation, charge, concentration, exposure time, and mechanical stability. To the best of our knowledge, it is the first time to discuss the effects of polymer coating and environmental factors

on dissolution kinetics of core-shell QDs in aquatic environment, as well as its cytotoxicity to microorganisms. The current knowledge of cadmium nanoparticle pharmacology and toxicology points out the directions for future research. Focus will be placed 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 nanopharmaceuticals application.

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 nanoparticle with highly stable "size-tunable" fluorescence. The large surface area also makes QDs readily to be functionalized with targeting ligands for site-directed activity. Based on these properties, QDs own the potential to innovate cancer detection and treatment, biological imaging at the cellular level.[7,44,46-49] However, fanaticism for QDs is somewhat diluted by the fact that QDs contain substantial amounts of cadmium in a highly reactive form while we know little about the health risks when exposed to cadmium nanoparticles.[39,40,45]

In the 1980s, CdSe QDs were prepared by top-down techniques such as lithography. However, size variations, poor optical properties, crystal defects, and poor reproducibility of such QDs made them inappropriate for advanced applications.[50] QDs were very hydrophobic since the nanocrystals were capped with

nonpolar surfactant molecules, and these nonpolar aliphatic chains were located on the QDs' surface.[15,51] Murray et al.[18] introduced the currently widespread synthesis of QDs by the injection of organometallic precursors into trioctylphosphine (TOP) and trioctylphosphine oxide (TOPO) surfactants at high temperature (190–320°C). The hydrophobically coated CdS, CdSe, and CdTe QDs could be prepared by pyrolyzing organometallic precursors of cadmium (dimethyl cadmium) and selenium in a mixture coordinating solvent composed by 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) may inhibit the growth of particles. However, adding a certain amount of compounds such as hexylphosphonic acid (HPA) in the reaction medium will make the QDs' size homogenously distributed while the growth of QDs was inhibited.[52] Afterwards, dimethyl cadmium was displaced by other less toxic, no pyrophobic, and more 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 more ancient method, Ostwald ripening, which resulted from the gradual dissolution of smaller QDs and the formation of larger ones, was managed by separating the spontaneous nucleation process from the relatively slow nanocrystal growth process. The primary advantage of this method is that the size-tunable QDs could be obtained by selecting an injection and growth temperature.[56,57] But the complicated procedure of the method makes it less utilized.

The colloidal preparation of CdSe nanocrystals which employs the TOP/TOPO

and high temperatures system is one of the most extensive and wrought methods, and the so-synthesized QDs have been extensively characterized. However, the aqueous synthetic methods have been proposed to 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 could dissolve in water. Thiol-containing amino acid cysteine is currently applied as coating agents in this kind of methodology owing to its high solvation ability. The thiol groups are stabilized to the QDs surface which the amino acid groups are oriented to the exterior of QDs surface, 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] thyoglycolic acid (TGA),[63] and 3-mercaptopropionic acid.[64,65] Meanwhile, the secondary coating materials such as polyethylene glycol (PEG) and mercaptopropionic acid are applied to further improve the solubility of QDs, preventing the aggregation. Such coating materials can be further conjugated with targeting molecules such as receptor ligands and antibodies, making the QDs a preferential target to a specific organ or tissue.[17,46,66,67] The purification of QDs is usually obtained through the precipitation with ethanol or methanol, centrifugation, and removal of the supernatant which mainly contains unreacted precursors and other impurities. Some researchers used the size-selective precipitation method by which small amounts of polar solvents (acetone, ethanol, and 2-propanol) were employed to precipitate polydisperse mixtures of CdS QDs.

Repeated the procedure until monodisperse fractions were obtained.[62] The dialysis is preferred to overcome the difficulties in QDs' dispersion, especially in the aqueous synthesis of polyphosphate-capped CdS QDs.[60]

2.1. Structure of quantum dots

QDs are made up 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). QDs' cores usually consist of various metal complexes such as magnetic transition metals, semiconductors, and noble metals.[7,68] Therefore, decorating the QDs' cores with a layer of protecting shells has been widely encouraged. Additionally, the ZnS shell layer presented more positive effects than other capping materials since it could: (i) decrease the Cd toxicity by restricting the dissolution of free ions; (ii) prevent the CdSe core from oxidation; (iii) recombine the surface defects of core; and (iv) enhance the photostability. Simultaneously, the size of QDs' core is unchanged while the ZnS shell layer is directly growing on the cores' surface, thus the luminescence characteristics of QDs are mainly reserved and only a tiny shift (less than 5 nm) in the fluorescence maximum wavelength is detected.[15]

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

Further assignation of functional groups or biocompatible coatings can give the core-shell QDs a desired bioactivity.[69] Newly synthesized QDs are inherently hydrophobic without biological use due to a hydrophobic capping on the metalloid cores' surface during their synthesis in organic solvents.[70] Generally, the newly synthesized QDs are usually functionalized or given secondary coating materials to improve their water solubility, core durability, and suspension characteristics, rendering the biologically compatible ability.[70-72] For instance, QDs' core can be capped with hydrophilic polyethylene glycol (PEG) groups to endow QDs good biocompatibility and dispersity in aqueous solution, and it can also be further conjugated with bioactive compounds to target cellular structural features or specific biologic events.[73,74] Hence, bonding with various molecular entities can functionalize QDs' cores for specific therapeutic or diagnostic purposes. The functionalization methods generally include electrostatic interactions, covalent bonding, and multivalent chelation in consideration of QDs' stability/durability and in vivo reactivity.

2.2. Concentration of quantum dots

Due to the unquantifiable number of ligand molecules that conjugated to QDs, the concentration of QDs after the colloidal preparation process is hard to ascertain by elemental composition or gravimetric methods. To this end, Peng's group put forward empirical equations to reckon the extinction coefficients for CdS, CdSe, and CdTe QDs, therefore the concentrations of these QDs could be readily determined by the

Lambert–Beer's law.[22,52,55] But for the water soluble QDs, the empirical equations had no availability since 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 method has been currently provided for the calculation of the QDs' concentration in aqueous solution, such as the 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 the 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 leach metal ions after long term exposure to ionic media or cellular media then result in metal ions toxicity.[80-82] Therefore, it is necessary to cap the surface of QDs' core with stable materials to reduce its high reactivity and surface defects. ZnS is usually used as a capping material to increase the stability of QDs core and enhance the quantum yield at room temperature.[54]

The QDs can be prepared by aqueous phase synthesis or the organometallic route. In the former case the QDs can be obtained under normal atmospheric conditions without special requirements of equipment. High temperature thermal decomposition of organometallic compounds is a well-confirmed method for the preparation of QDs. This method is carried out with the absence of oxygen and water to make the

organometallic compounds decomposed into a non-aqueous media at high temperature.[83] Organic QDs possess distinctly different surface properties as compared to aqueous QDs. The surface of organic QDs is covered with a large amount of hydrophobic ligand molecules (e.g., TOP/TOPO) while the aqueous QDs' surface is capped by hydrophilic molecules (e.g., 3-mercaptopropionic acid, MPA). Therefore, the organic QDs have to receive additional surface modification to enhance its water-dispersibility while the aqueous QDs are inherently water dispersible without any surface modification.[84] As shown in Fig. 2. The surface modification could usually significantly enhance the hydrodynamic diameter of QDs as detected by dynamic light scattering (DLS). Consequently, organic QDs and aqueous QDs are of similar particle sizes as determined by transmission electronic microscopy (TEM),[85] the hydrodynamic diameter of surface modified organic QDs are larger than 5.0 nm while aqueous QDs typically possess small hydrodynamic diameter (less than 5.0 nm).[85-87]

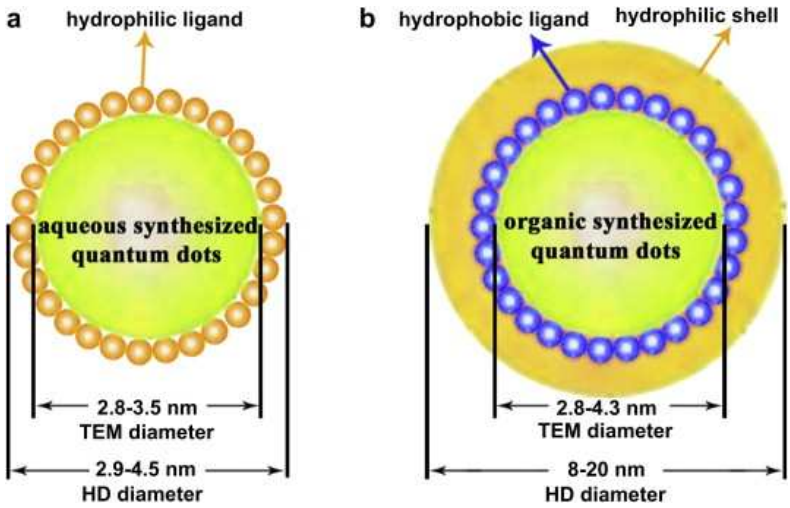


Fig. 2. Schematic characteristics of aqueous synthesized QDs with hydrophilic ligands and organic synthesized QDs with hydrophobic ligands.[85]

The polarity of the medium which applied to disperse QDs could strongly influence the QDs' luminescent properties as it directly determines the stability of surface capping ligands of QDs.[88] It is decisive for QDs to maintain their ability and optical properties during transferring into a polar medium to interact with target analytes. Thus ligand exchange is the usual method that employed to replace the hydrophobic capping ligands on the QDs' surface. 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, the exchange of the original hydrophobic capping ligands may induce the generation of poor-stability QDs and dramatically reduce the luminescence quantum yields.[89] Another strategy to promote the solubility of QDs in aqueous media is encapsulation, thereby avoiding ligands exchange.[90] Encapsulation is usually carried out in polymer layers or silica shells to protect QDs' cores efficiently with optical properties and original hydrophobic coating layers unchanged.[91] The two encapsulation methods present different advantages: the polymer layers could incorporate multifarious functionalities on the QDs' surface, and then enhance their interaction with target analytes while the silica shells are chemically inert. Amphiphilic polymers such as calaxirenes, cyclodextrins, and other similar organic cyclic species are the most widely employed polymers in the synthesis.[92,93] In addition, the polyethylene glycol (PEG) derivatives, which are commercial available and simplicity for encapsulation, become another popular material used for the QDs' synthesis. The only drawback of micelle encapsulation is that not all of the nanoparticle sizes are suitable for

encapsulation.[94]

3.1. Inorganic surface

Most of the binary QDs cannot meet the obligatory band gap and band alignment demands due to the lattice mismatch between the shell and the core, thus an overall coating for the QDs is necessary. Inorganic surface modification of QDs can establish a multilayer semiconductor heterogeneous system with relative conduction band and valence band. The main advantage of such a heterogeneous system is that it could provide extraordinary photoluminescence, higher quantum yield, increased half life time, enhanced optical properties, better structural properties and improved stability towards photo-oxidation. If an inorganic semiconducting layer is provided over the 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 favorable properties of the magnetic core with a protective polymer, gold, silica, carbon or metal oxide shell. These coating materials may not only protect the chemical-active metal core from acid erosion and oxidative degradation but 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 renders QDs biocompatible for cancer diagnosis and therapy. Replacing the surface ligand with a thiol-derived silane such as mercaptopropyltris 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

293 silicon can also be added to provide functional groups and different charge on the
294 QDs' surface. Generally, the additional materials that used frequently are
295 phosphor-silanes, aminopropyl-silanes, and polyethylene glycol silanes. Silanized
296 QDs are extremely steady since the silica shells are highly cross-linked.[74] In addition,
297 the electrochemical properties of silica make it a perfect material to improve the
298 solubility of QDs in aqueous media.[74] Apart from silica, other metals and metal oxides
299 can also be employed as shell materials. For example, gold as a shell material has
300 been widely studied by many researchers.[65,98,99] Wang et al.[100] successfully
301 synthesized Fe_3O_4@PAH@Au multifunctional QDs, which presented both magnetism
302 and near-infrared absorption. Xuan et al.[99] also reported Fe_3O_4@PANI@Au
303 multifunctional QDs with well-defined core-shell structures, optical property,
304 magnetic separability, and catalytic activity. On the other hand, the gold could also
305 endow the QDs with biocompatibility through the modification of thiol/amine
306 terminal groups. When the core is composed of a polymer or different copolymers, an
307 inorganic surface modification could be applicable. Coating the polymeric core with
308 an inorganic shell is greatly beneficial to QDs' mechanical strength, thermal and
309 colloidal stability, as well as the resistance ability against oxidation and corrosion.
310 Meanwhile, these particles also present perfectly polymeric properties such as
311 flexibility, toughness, and excellent optical properties.

312 *3.2. Organic surface*

313 The QDs produced by colloidal synthetic method are mostly hydrophobic and

could only dissolve in non-polar solvents such as toluene or chloroform. Nevertheless, almost all the biological applications of QDs demand the aqueous conditions, thus a direct modification on the QDs' surface to improve the water solubility without altering the cores' properties is necessary. For this purpose, water-soluble QDs are obtained by introducing functional groups (hydroxyl, carboxyl, or amino) over its surface to achieve a total net charge. Additionally, the surface modification makes QDs more convenient to conjugate 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 like n-butylamine, n-hexylamine, and hexadecylamine have also been applied in conjugating with TOP and TOPO.[74]

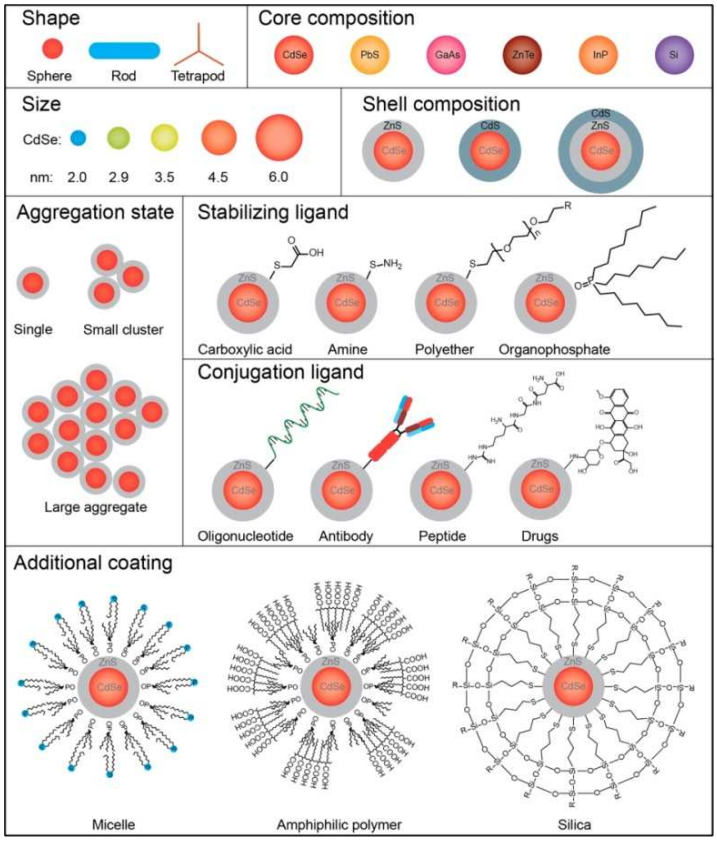


Fig. 3. Schemes of different QDs surface modification methods. An additional coating can further protect the QDs core from oxidation. Surface chemistry influences the QDs propensity to aggregate, particularly in biological solutions.[104]

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 QDs' surface; b) hydroxyls (–OH), carboxyls (–COOH), and amines ($–NH_2$) to enhance the 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 at the same time passivate surface defects, ensuring the quantum yield.[108-110] Organic ligands, which can be

replaced by water soluble ligands through simple mass action, could provide excellent stability and solubility for QDs to cooperate with organic non-coordinating solvents.[110] Evidences showed that the ligands on QDs' surface are in a dynamic equilibrium with the native ligands in solvent, thus these two kinds of ligands could substitute for each other under the equilibrium conditions.[111] In general, the ligand exchange can be proceeded by increasing the local probability of replaceable ligands through supplying more replaceable ligands in the solution than the existing ligands when the surface affinity of the replaceable ligands is low.[112]

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

Several researches have demonstrated that the stabilization of QDs through ligand exchange, covalent modification and other chemical surface modification

showed several drawbacks: (i) Small ligand with one head group attached to the QDs surface can easily be released and influence the stabilization process, especially when excessively unbound ligands exist in the suspension; (ii) The thiol-containing ligands can bind strongly to QDs, but it 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 molecule to modify QDs could not only improve their water solubility but also enhance the stabilization effect.[116,117] Interestingly, owing to the various bonding points on the particle surface, the amphiphilic molecules could avoid facile desorption of the polymer molecule during the modification of QDs. For instance, the amphiphilic coating could interlink the amphiphilic molecule with its hydrophobic ligand groups by hydrophobic interaction which neither depends on the type of ligand molecule nor exacts material composition (Fig. 3). Such observations are mainly based on hydrophobic interaction between hydrocarbon chains and the polymer molecules. Meanwhile, the amphiphilic molecules coated on QDs' surface exhibit the same physicochemical surface properties as the independent of core material.[74,116]

Core-shell QDs are more desirable for biological applications as the shell could enhance their fluorescent properties and decrease the leaching ability.[118] The ligand functional group, which has the electron donating and withdrawing ability, can induce trapping effects on the QDs' surface.[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 served as a pH probe for tiopronin determination[120] and enzyme kinetics.[121] One-step DNA functionalization on QDs or core-shell QDs synthesis in aqueous media was reviewed by Samanta et al..[122] The 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 the ecological pollution, and it is closely related to the composition and chemical properties of the core-shell. To thoroughly evaluate the potential environmental and ecological risks of QDs, it is necessary to make 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 its potential mechanisms and dissolution kinetics is limited. Coexistence of heavy metals in aquatic environment could significantly enhance the QDs' toxicity while the natural organic matter would affect the adsorption and migration reaction on QDs' 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 etc. At the same time, aquatic organism could secrete extracellular polymeric substances (EPS) and stabilize QDs on EPS layer or subcellular structure to change the form of QDs in aquatic environments.

4.1. Light

When QDs were excited by incident light carrying higher photon energies than the band gap of QDs, a bound electron-hole pair that could react with the surrounding oxygen molecules was formed and produced 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 executed 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 during the formation of ROS. However, when excess $O_2^{\cdot-}$ scavengers were added before the reaction, an obvious retardation on the release of Cd^{2+} was observed, suggesting that the photoexcitation may lead to the generation of $O_2^{\cdot-}$, a precursor of 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 the SOD could catalyze the conversion of $O_2^{\cdot-}$ into H_2O_2, which accelerated the release of Cd^{2+}.[35,128] The reaction was shown as follows:

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

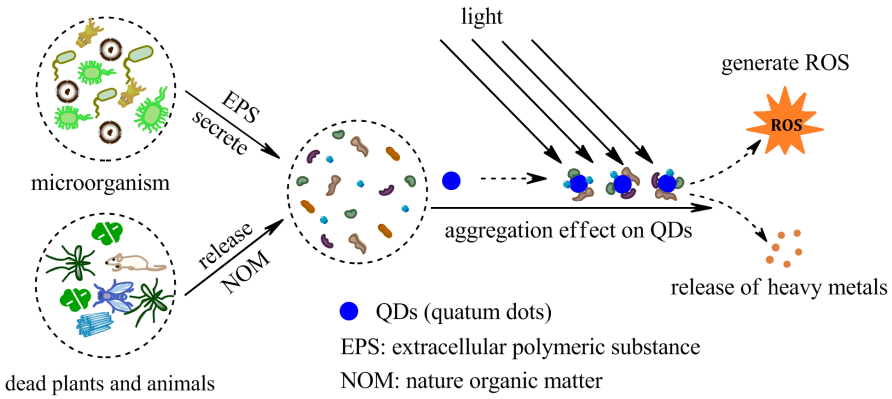
Therefore, H_2O_2 is the most likely intermediate oxidant that reacts rapidly with QDs.[129]

To explore the stoichiometry reaction of QDs, the possible ionic species are firstly determined after photooxidation of QDs, as shown in the reaction.

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

425 $4.1\ Zn^{2+} + x\ SO_4^{2-} + (2x - 17.56)\ H^+$

426 The photooxidation of QDs is a proton-generating process, as confirmed by the
427 observed decrease in pH value.[59,130] The above chemical formula is determined on the
428 basis of the total element composition measurement with ICP-MS. The
429 photo-degradation products (Cd^{2+}, Zn^{2+}, and SeO_4^{2-}) may release from the core-shell
430 structure, decreasing the hydrodynamic size of QDs.



431

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

434 *4.2. Weathering of QDs at pH variation*

435 In a previous study, the laboratory condition was adjusted to pH value ranging
436 from 2 to 12 to investigate possible QDs weathering process.[27] Several different
437 processes, including QDs aggregation, core-shell QDs leaching, and precipitation of
438 metal oxides, could be conducted under extremely acidic or alkaline conditions. Low
439 pH value was expected to solubilize core-shell QDs readily, while high pH value may
440 relate to the chemical speciation, precipitation, and bioavailability of Cd and Se
441 (Table 1).

Table 1

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

QD	pH treatment	total Cd (mg/L)	total Se (mg/L)
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

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

442 It is well documented that luminescent properties of QDs depend on pH
443 values.[59,130-132] Nevertheless, pH may have a dual influence on luminescent properties
444 of QDs since it affects QDs' structure and the function of capping ligands.[130] For
445 instance, pH-dependent cadmium-thiol complexes can be produced at the interface of
446 Cd-containing QDs and capping ligands when pH > 5.[59] But at pH < 5, protonation
447 could result in the detachment of capping ligands from QDs' surface and induce the
448 agglomeration of QDs, thus making the luminescence intensity and lifetime
449 declined.[133] Zhang et al.[130] have reported that the decline of pH value from 12 to 5
450 could result in the agglomeration of QDs (Fig. 5), causing the change of the

luminescence intensity of 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 after exposing the QDs to an oxidative environment: (i) A blue-shift in the excitonic fluorescence spectra; (ii) A broad red-shifted adjacent to the excitonic fluorescence peak; (iii) A progressive change in the absorbance profile of QDs solution; and (iv) A decline in the quantum yield.[32] Shifts in the fluorescence and absorbance spectra may result from the decline of the QDs' size (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 QDs' surface (Fig. 5).[27,32] In the case of CdSe QDs, these SeO_2 molecules could desorb from the QDs' surface, leaving the "dangling" decreased Cd atoms behind. Therefore, prolonging exposure of QDs to an oxidative environment could induce the decomposition of nanocrystal, leading to the desorption of Cd^{2+} or CdSe complexes from the QDs' 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, as limited by available

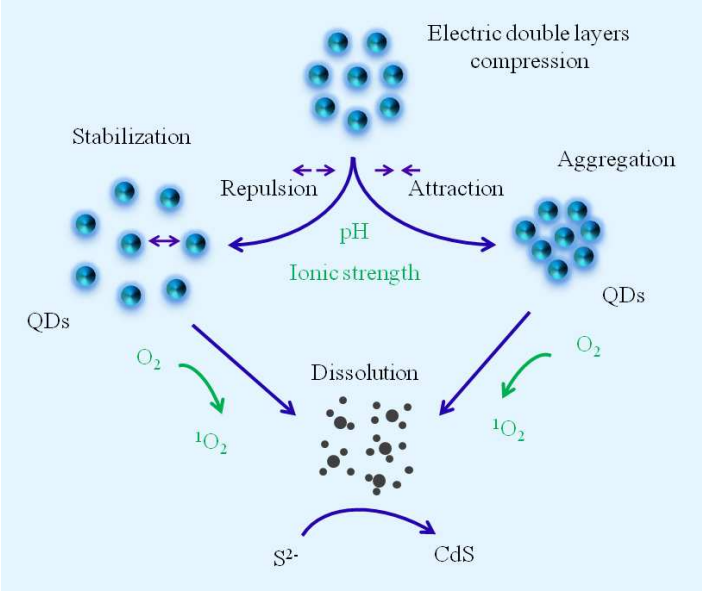
experimental techniques, the sizing suspended QDs are difficult to be obtained.[142]

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

The aggregation behavior of QDs in most surface water within 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 QDs' surface, through which the negative charge on it could be neutralized. Furthermore, the complexes could bridge the gap between one QD and the other QD to form aggregates. Therefore, the divalent cation complexation constants of capping ligands can be used to quantify QDs' aggregation. Here we set Ca^{2+} for an example in this paper. Ca^{2+} complexes are formed through the combination of Ca^{2+} and carboxyl groups on the QDs' surface. A Ca^{2+} 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+} could lead to the formation of Ca^{2+} complexes with QDs' capping ligands, supported by the high complexation constants of the bound capping ligands.[25,147,148]

Similar to the divalent electrolyte, the trivalent electrolyte (e.g., Al^{3+}) could also reduce the negative zeta-potentials of QDs and cause the aggregation. The

493 inconformity in QDs aggregation with Al^{3+} at pH value between 5 and 8 is correlative
494 to the complexation mechanism of Al^{3+} with the capping ligands.[59,130] In liquid media,
495 Al^{3+} can be hydrolyzed and present as $Al^{3+}(H_2O)_n[(OH)_{6-n}]^{n-6}$. Thus the complexation
496 of Al^{3+} with the capping ligands may occur through the substitution reaction between
497 OH^- groups or the original water molecules and amino groups or carboxyl groups in
498 $Al^{3+}(H_2O)_n[(OH)_{6-n}]^{n-6}$.[25,149]



499

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

502 *4.5. Natural organic matter*

503 Transport and fate of QDs in aquatic environment are not only dependent on
504 physicochemical parameters, such as light, pH, dissolved oxygen, and ionic strength
505 as described by the DLVO theory,[150,151] but also related to the natural organic matter
506 (NOM). Some researchers have confirmed that the humic substances (HS) which are

commonly present in aquatic environment as a kind of NOM,[152,153] could affect the environmental transformations of QDs.[31,154,155] Evidence showed that HS could alter the surface properties of QDs, thus influenced the dispersibility and aggregation state of QDs,[24] or even transferred the primitively hydrophobic QDs to aqueous QDs.[156-158] While the content of NOM in aquatic environments exceeds the charge of DLVO theory, the QDs will tend to form larger aggregations, especially when the ionic strength is high.[1] NOM can either enhance the QDs stability through coating the QDs' surface with negative charges by static repulsion[159] or decline the QDs stability through a variety of mechanisms, including pearls-on-a-string formation[160] and bridging effect.[161] Hence, NOM could 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 QDs transport and toxicity.[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 more strongly affinity to EPS than the negatively charged carboxyl-functionalized QDs[162] since the positively charged surfaces could contribute to stabilize 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 the 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 QDs' stability, promote the degradation of QDs and facilitate the release of Cd^{2+} into the aquatic environments when exposed to light.[164] According to some researchers' study, 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] but the mechanisms involved need to be further studied.

5. Toxicity of quantum dots to microorganisms

QDs are composed of semiconductor core (e.g., CdS and CdSe) and usually encapsulated by a shell (e.g., ZnS) to improve the 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 lead to the large-quantity production of water soluble QDs. Given their wide applications, substantial productions of QDs are envisioned in the nature.[7,43,170,171] However, most currently produced QDs consist of heavy metal chalcogenides (e.g., PbS and CdSe)

549 which may cause a hazard to humans and microorganisms in consideration of toxic
550 metal releases and nanoscale properties. The toxicity of QDs depends on multiple
551 factors derived from both the inherent physicochemical properties and the acquired
552 environmental conditions. Particle size, charge, concentration, bioactivity of the
553 surface coatings (capping ligands and functional groups), exposure time, photolysis,
554 oxidation, and mechanical stability are the main factors that determine QDs' toxicity
555 individually or collectively. Functional capping, physicochemical characteristics, and
556 the stability of QDs' core are recognized as the significant factors in assessing the
557 QDs' toxicity to microorganisms in real world exposure.

558 *5.1. Particle size*

559 Particle size is critical for the biological performances of nanoparticles.[172-174]
560 Several reports have proved that particle size affects QDs toxicity at the intracellular
561 level. In cellular studies, CdTe QDs within 2.2 nm had greater toxicity than the
562 particles within 5.2 nm.[35,175] Additionally, the intracellular biodistribution of QDs also
563 showed an obviously size-dependent in some studies.[84,176] Larger particles were
564 distributed in the cytoplasm while smaller particles were localized around and in the
565 nucleus of the cell.[35,45,177] Hardman[7] has also found that QDs size could influence the
566 subcellular distribution, in which larger cationic QDs presented in the cytosol and the
567 smaller cationic QDs distributed in the nuclear compartment. Endocytosis, including
568 pinocytosis and phagocytosis, has been well-recognized as the main mechanism for
569 QDs to enter the cells (Fig. 6).[178,179] The pinocytosis is further classified into at least

four mechanisms (e.g., caveolae-mediated, clathrin-mediated, macropinocytosis, and clathrin/caveolae-independent endocytosis) depending on the product of intracellular vesicles.[180,181] Additionally, the intracellular localization of QDs is also particularly important for the 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 in dotted pattern with the differential intensity. Especially, high-intensity dots were concentrated in the marginal and perinuclear area of the cell.[84] Such heterogeneous distribution of QDs might cause 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 than $CdCl_2$. All in all, CdTe QDs may enter the subcellular organelles and directly result in a functional loss of the organelles.

5.2. Surface coating materials

A main cause of the QDs toxicity is the cadmium contained in the QDs core. The toxicity of uncoated CdSe or CdTe QDs has been extensively studied in several reports.[184,185] Results showed that the QDs' toxicity is closely associated with the free Cd released from QDs' core into the suspensions since it was found that the cytotoxicity of QDs was consistent with Cd^{2+} toxicity from the QDs' core.[32,34,186,187] Derfus et al.[32] found that the uncoated QDs could release Cd^{2+} through the surface oxidation when incubated with rat hepatocytes, indicating that the uncoated QDs

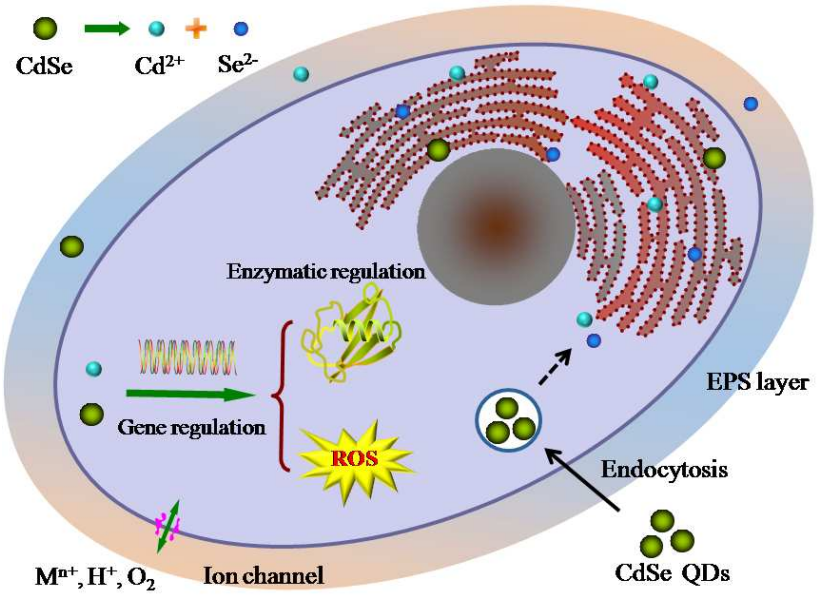
591 cores could be degraded in biological environment. Therefore, the Cd^{2+} toxicity from
592 QDs' cores is likely to be responsible for QDs' cytotoxicity. However, CdSe or CdTe
593 QDs are also highly charged and can be easily affected by air or photo oxidation.
594 Hence, the generation of free radical is also considered as another major mechanism
595 for QDs' cytotoxicity.[33,37,188,189] Cho et al.[190] found that the CdTe QDs cytotoxicity
596 was not relevant to the Cd^{2+} released from the QDs' core, but related to the formation
597 of free radical (Fig. 6). Additionally, similar to the findings we mentioned above, the
598 uncoated QDs have also been involved in other cytotoxicity. For example, in
599 SH-SY5Y neuroblastoma cells, the damage CdTe QDs induced was relevant to
600 up-regulation of Fas expression, which may result from the oxidative stress caused by
601 the QDs.[191-193] Tang et al.[194] carried out the neurotoxicity of CdSe QDs in
602 hippocampal neurons and found a dose dependent augment in neuronal death.
603 However, evidences showed that the influx of extracellular Cd^{2+} and release of
604 intracellular Cd^{2+} were enhanced even at low doses.

605 Encapsulation of QDs with a ZnS shell or other coating materials has been
606 testified as an effective way to reduce the QDs' toxicity, although much work remains
607 to be accomplished in this arena. Derfus et al.[32] indicated that free Cd released from
608 CdSe QDs into the aqueous media could be dramatically declined by ZnS shell. In
609 addition to decreasing the free Cd release, ZnS shell was also observed to reduce the
610 generation of free radical by protecting the QDs from air oxidation. Hence, the
611 encapsulation of QDs with a ZnS shell or other coating materials appears to be a
612 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 shell or coating materials, along with the toxicity must also be considered adequately. Previous studies showed that the ZnS shell did not completely eliminate the QDs' toxicity due to the effect of photo or air oxidation on the shell[32] and on the other hand, the CdSe/ZnS QDs could also induce the generation of free radical species.[33,189] These researchers hypothesized that the ZnS shell could prevent the CdSe core from oxidation, but it could not inhibit the generation of electron-induced radical in the surrounding environment, indicating that the ZnS shell might be slowly oxidized in the presence of air or water, thus generating the SO^{2-} radical.[45]

In addition, several groups have also found to enhance the 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 QDs samples was important in decreasing cytotoxicity since the TOPO was observed to be genotoxic and cytotoxic. Their findings provided obvious evidence to prove that the QDs induced genotoxicity and cytotoxicity were not caused by the QDs core but by the hydrophilic QDs' coating materials. Taken together, these reports indicated that the ingredient of a shell or capping materials needs to be more

635 thoroughly assessed.



636

637 **Fig. 6.** Schematic illustration of the cytotoxicity induced by CdSe QDs. When CdSe
638 QDs are transported across the cell membrane, free Cd^{2+} is released into the
639 cytoplasm. The QDs nanocrystal and free Cd^{2+} induced a serious of protective
640 responses including the up-regulation of proteins and an increase in oxidative stress.

641 *5.3. Photolysis and oxidation*

642 QDs' stability, both in vivo and storage, is a significant aspect for assessing their
643 toxicity. Some reports indicated that QDs' cytotoxicity may relate to photolysis or
644 oxidation.[7,32,198,199] Under photolytic and oxidative conditions, the core-shell QDs
645 coatings were too labile to maintain the stability of QDs, thus the potentially toxic
646 coating materials or intact core metalloid complexes were exposed to the environment
647 and caused the dissolution of the core complexes. Zhang's group[200] demonstrated that
648 the fluorescence intensity of CdSe/ZnS QDs showed a shift to blue spectra and was

649 reduced with contacting time when exposing to the living cells, indicating that the
650 ZnS shell was deteriorated intracellularly.[200,201] Hardman[7] reported that the primary
651 rat hepatocytes exposed to 62.5 μg/mL MAA-CdSe QDs appeared cell death, which
652 may relate to photolysis and oxidation of the QDs' capping material. Derfus et al.[32]
653 deduced that QDs' toxicity was relevant to environmental conditions, and lengthened
654 exposure time of QDs to photolytic and oxidative environments could lead to the
655 decomposition of MAA-TOPO capped CdSe QDs. Although ZnS coating materials
656 could significantly decrease the ambient air oxidation, it did not completely eliminate
657 the photooxidation, with high levels of free Cd^{2+} found in solution under
658 photooxidative conditions.[7,192] Aldana et al.[202] have also observed the photochemical
659 instability of thiol-coated CdSe QDs in the experiment, although not at correlative UV
660 wavelengths (254 nm), it was noted that the photochemical stability of CdSe QDs was
661 nearly related to the packing and thickness of the ligand monolayer. Kloepfer et al.[203]
662 reported that when exposing *Staphylococcus aureus* cultures to conjugated QDs
663 solution for 2 weeks, a noteworthy increase in fluorescence was observed. The change
664 of fluorescence may relate to the intracellular oxidation of QDs since a remarkable
665 increase of Se was found in cells. Therefore, the photostability of QDs' conjugates is a
666 considerable issue during the preparation, and at the same time the QDs' conjugation
667 procedures should also be performed under little or no light condition to avoid the
668 photolysis of QDs. Some studies suggested that QDs may be susceptible to photolysis
669 and oxidation, thus the possibility of QDs' degradation in vivo or intracellular could
670 be increased. For example, recent study indicated that QDs' surface coatings and

ligands were slowly degraded in vivo, leading to the 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 even showed a greater stability in vivo than those with simple polymer and amphiphilic lipid coatings.[7] Hoshino et al.[205] observed CdSe/ZnS-SSA QDs in EL-4 cells within approximately 10% of the cells reserving QDs after exposure for 10 days, and the fluorescent intensity of the cells was found to gradually decline and highly concentrate in endosomes. Likewise, a substantial loss of QDs' fluorescence was declared by Gao et al.[204] upon implement of QDs to live animals.

5.4. Charge, concentration, and exposure time

As with pharmacological studies, QDs' toxicity studies confront the same difficulties in terms of charge, concentration, and exposure time, which underscore the requirement for their rigorous physicochemical properties. Existed evidences showed that surface modifications could influence QDs' properties such as surface net charge, which may contribute to QDs' 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] Their studies proved that CdSe/ZnS QDs with higher negative charge (QDs-COOH) were taken up to a greater extent by *Daphnia* (259.17 ± 17.70) than either positive charge (QDs-NH_2)

692 (150.01 ± 18.91) or uncharged PEG-QDs (95.17 ± 9.78). To some extent, these results
693 are also relevant to the surface functional groups attached to QDs.

694 Particle concentration is also intricately related to the QDs' toxicity since surface
695 area is critical for nanoparticle actions. QDs' dosage or exposure concentration has
696 been widely reported in the literature using various units of measurement (e.g., QDs
697 per cell, molarity, micrograms per milliliter, and milligrams per kilogram body
698 weight). However, correlative dosage studies are currently challenging. For instance,
699 no cytotoxicity was observed during a 2 h acute exposure of cells to QDs.[206-208]
700 Critical questions related to toxicological researches are relevant to how to estimate
701 the effects of QDs' exposure on humans and what will be the effective way to describe
702 the express concentration of QDs to humans.

703 Finally, exposure time deserves further consideration. QDs appear to widely
704 distribute in tissues and almost cannot be excreted or metabolized.[190] In consideration
705 of the tissues' resistance, it is critical to assess the toxicological risk of QDs in long
706 term researches. In the case of QDs, an electronically active Cd nanoparticle may be
707 excessively reserved in tissues for years. In general, QDs cause the toxicity by
708 releasing Cd^{2+} and generating free radicals to the environment, both of which could
709 influence the transcription and synthesis of DNA or even changed the signal
710 transduction in long term treatment.

711 6. Conclusions and perspectives

712 It is critical to understand the transport and fate mechanism as well as the

toxicity of QDs for its practical biomedical and biological applications in diagnostics, therapy, and imaging. However, it is difficult to assess the overall environmental implications of QDs from present reported studies due to the complexity of inherent physicochemical properties, environmental conditions, and analytic methods. The synthetic methods and surface modifications of QDs will greatly affect its physicochemical properties and its interaction with cellular membrane and the subsequent uptake into the cells. So the transport and fate of QDs in aquatic environment and their toxicity to microorganisms depend on the multiple synthesis methods and surface modification ways. 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 environment. And unless stabilized by NOM and EPS or other natural species in the environment, QDs may ultimately be degraded in aquatic environment and serve as a source for toxic mobile Cd species. The increasing production and utilization of QDs nanoparticles caused the concerns for the possibility of the contamination in the aquatic and terrestrial ecosystems. Thus it is necessary to make extensive investigations on the toxicological and pharmacological for the applications of QDs to reduce the environmental risk. Therefore, studies on the QDs' behavior in aquatic environment and the cytotoxicity of QDs become critical important, and future directions need to include: (i) complete physicochemical characterization of QDs structure; (ii) environmental considerations—with increasing application of Cd-containing QDs in biomedical study and therapy, researches are required to consider the environmental risk of core-shell particles and the dissolution

735 extent of shell materials; and (iii) increase animal toxicity studies to evaluate
736 biological persistence of QDs in tissues, particularly in long term studies. Research
737 without overall assessing these critical areas will make human health at risk and
738 impede the progress on nanomedicine development. However, sensible further
739 researches into these areas will undoubtedly contribute to the public health and
740 development of pharmaceuticals for drug delivery and cancer treatment.

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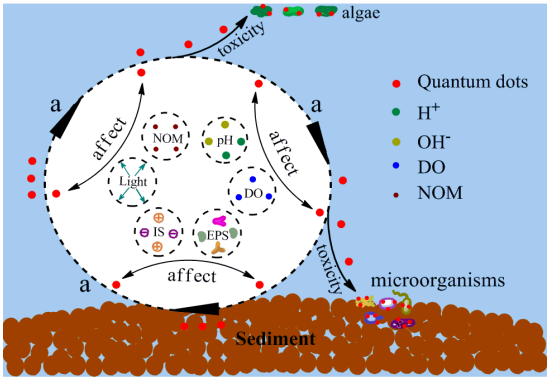

Aquatic Environment

a:migration and transformation; NOM:natural organic matter; DO:dissolved oxygen; EPS:extracellular polymeric substances; IS:ionic strength.

The fanaticism for metal-based QDs is somewhat diluted by the fact that it causes risks in aquatic environment.