

A Review of in vivo Toxicity of Quantum Dots in Animal Models

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Abstract: Tremendous research efforts have been devoted to nanoparticles for applications in optoelectronics and biomedicine. Over the past decade, quantum dots (QDs) have become one of the fastest growing areas of research in nanotechnology because of outstanding photophysical properties, including narrow and symmetrical emission spectrum, broad fluorescence excitation spectrum, the tenability of the emission wavelength with the particle size and composition, anti-photobleaching ability and stable fluorescence. These characteristics are suitable for optical imaging, drug delivery and other biomedical applications. Research on QDs toxicology has demonstrated QDs affect or damage the biological system to some extent, and this situation is generally caused by the metal ions and some special properties in QDs, which hinders the further application of QDs in the biomedical field. The toxicological mechanism mainly stems from the release of heavy metal ions and generation of reactive oxygen species (ROS). At the same time, the contact reaction with QDs also cause disorders in organelles and changes in gene expression profiles. In this review, we try to present an overview of the toxicity and related toxicity mechanisms of QDs in different target organs. It is believed that the evaluation of toxicity and the synthesis of environmentally friendly QDs are the primary issues to be addressed for future widespread applications. However, considering the many different types and potential modifications, this review on the potential toxicity of QDs is still not clearly elucidated, and further research is needed on this meaningful topic.

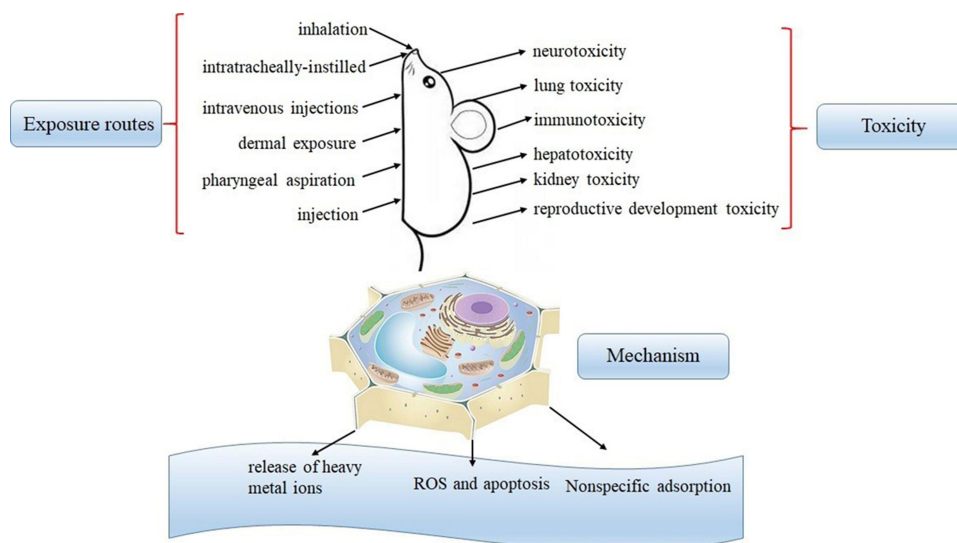
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Introduction

As a new type of nanomaterials, quantum dots (QDs) have attracted wide attention all over the world due to their unique optical and electrical properties. QDs are semiconductor nanoparticles composed of II–VI elements (eg, CdTe, CdSe, CdS, ZnS, ZnSe, or ZnTe), group III–V elements (eg, InP or InAs), group I–III VI₂ elements (eg, CuInS₂ or AgInS₂), group IV–VI elements (eg, PbSe, PbS, or PbTe) and group IV elements (eg, Si, C, or Ge).¹ The structure of QDs usually consists of a semiconductor material and second semiconductor materials outside. Usually, the core determines the optical properties of QDs, while the shell enhances the optical stability of QDs. More importantly, QDs can also be coated with a special material for hydrophilic or functionalized modification in order to meet specific biomedical applications.^{2,3}

In recent years, with its excellent fluorescence properties, QDs have been applied to many biotechnologies including immunofluorescence, cell tracking and in vivo imaging.^{4,5} The most successful biomedical application in the early days was cellular or tissue labeling. In 1998, Bruchez and his partners labeled 3T3 mouse fibroblast cells using two different size biotinylated CdSe/ZnS core-shell nanocrystals for the first time. Selection of fluorescent probe emission wavelengths in the near-infrared wavelength range of in vivo imaging can obtain the best tissue penetration and high-quality optical signal.⁶ In addition, QDs are also widely used for targeting tumor markers.⁷ The basic principle is that recognition of specific antigens on the surface of a tumor cell as a target. Antibody-conjugated QDs were injected into the animal body to achieve in vivo tumor targeting and imaging according to the specific bright fluorescent of QDs. These findings are of great significance for promoting complex, highly sensitive imaging and diagnosis of tumor targeting in vivo. In addition

Graphical Abstract



to the above studies, QDs have also been used for a variety of other purposes. So far, researchers have successfully described the multicolor and multi-strength fluorescent encoded spheres with different sizes of QDs encapsulated in polymer microspheres at different ratios,⁸ and successfully achieved the specific marking and discrimination of target DNA.^{9,10} QDs have also been used to track RNA interference¹¹ and vasculature imaging.¹²

However, along with the increasing production and application of QDs, the risk of unintentional occupational or environmental exposure to QDs is growing. The potential harm of QDs to environment and human health has gradually attracted the attention of researchers.^{13,14} From 2004, many research teams have studied the toxicity of QDs and obtained some QDs toxicological data.^{15,16} Most toxicology is evaluated by using *in vitro* or *in vivo* models, and *in vitro* toxicity studies are evaluated using a variety of cell models.¹⁷ To some extent, these studies have made an evaluation of the toxicity of QDs. However, because of the diversity of QDs and the complex characteristics of biological samples, it is difficult for us to analyze and evaluate the obtained data. Current research results showed the toxicity of QDs is not only related to its physical and chemical properties, such as preparation methods and surface properties and particle size,^{18,19} but also influenced by cell type, treatment environment and administration route.^{20,21} At the same time, their toxicological research methods are not unified and systematic, making the work of evaluating and comparing the biosafety of QDs extremely complex and difficult. Many QDs emitting in the NIR limit their applications (for instance, in biomedical labeling) because of their toxic Cd (II), Hg (II), Pb (II), As (III) and other elements.^{22,23} Previous research evidence shows that even if the Cd²⁺ containing QDs are wrapped in a tight outer membrane that inhibits the release of Cd²⁺, the intracellular ROS content of QDs is still significantly increased.²⁴ So QDs that do not contain Cd (non-Cd QDs) have been prepared as an alternative to the Cd-based QDs. These newly developed non-Cd QDs exhibit improved blood half-life and minimal reticuloendothelial system (RES) uptake.²⁵ QDs toxicity has also been studied by using different animal models, such as zebrafish,²⁶ xenopus,²⁷ mouse,²⁸ rat^{29,30} and macaque.³¹

The toxicity of QDs depends on multiple physicochemical factors including composition, size, shape, surface chemistry, dosage, and route of exposure.³² Cd²⁺ QDs can release toxic Cd²⁺ ions, while other QDs may induce toxicity through mechanisms like oxidative stress. Smaller QDs tend to have higher cellular uptake and toxicity compared to larger ones.³³ Positively charged QDs are more toxic than neutral or negatively charged ones.³⁴ Surface coatings like silica can reduce QD toxicity by preventing ion leaching and aggregation.³⁵

Despite promising applications, concerns remain about potential health and environmental hazards of QDs, especially with long-term exposure. Most toxicity studies have been short-term *in vitro* evaluations. There is still limited

understanding of QDs toxicity mechanisms, bioaccumulation, organ-specific effects, and impacts on organisms in real-world exposure scenarios.

This review summarizes current knowledge on the *in vivo* toxicity of QDs in animal models. A particular focus is QDs effects on major organs like liver, kidneys, lungs, brain, and the immune system. The review also examines parameters affecting QDs toxicity such as composition, size, surface modification, dose, exposure route, and duration. By reviewing recent literature, this paper aims to provide insights into QDs toxicity mechanisms, gaps in current understanding, and strategies to develop safer QDs for biomedical and environmental applications.

In vivo Imaging

QDs are semiconductor engineering nanomaterials (ENM) with tiny luminescent particles at the nanoscale (typically 2–10 nm in diameter) and are considered as an important choice for traditional fluorescent dyes in biomedical applications.³⁶ The most classical and common QDs are mainly cadmium containing QDs, such as CdTe, CdS, and CdSe. However, the inherent toxicity of heavy metals Cd limits their practical applicability because they contain dangerous and expensive raw materials.³⁷ Therefore, it is essential to develop environmentally friendly Cd²⁺ free QDs in practical applications.³⁸ In the last two decades, a series of Cd²⁺ free QDs based on indium phosphide (InP),³⁹ copper indium sulfide (CuInS₂),⁴⁰ silver indium sulfide (AgInS₂),⁴¹ silver sulfide (Ag₂S),⁴² doped Zn chalcogenides⁴³ have been successfully developed. These QDs share a strong resemblance to the optical properties and colloidal stability of the conventional Cd-based QDs.⁴⁴

QDs transmit fluorescence signals in a wavelength range by varying their sizes and composition, thus providing wide excitation profile and high absorption coefficient. Compared with traditional fluorescent dyes (1–10 ns), they have a narrow and symmetry emission spectrum, thus having longer excited state lifetimes (20–50 ns).⁴⁵ Their quantum yield is 40% to 90% and has a high extinction coefficient. They are more stable than the traditional organic dyes. They can be coated and covered with hydrophilic materials to conjugate with biomolecules.⁴⁶ In addition, the near-infrared (NIR) fluorescence (700–1000 nm) QDs have the characteristics of low optical damage to organisms, strong tissue penetration and low autofluorescence interference, so it has an important application prospect in the field of biological cell imaging, especially in the field of cancer diagnosis and cell tracking.^{47,48}

Compared with conventional imaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography (PET) and X-ray computed tomography (X-ray CT), *in vivo* animal imaging provides more cost-effective and high resolution in clinical diagnosis. However, compared with *in vitro* cell imaging, challenges arise with the increasing complexity of multicellular organisms. Unlike monolayer cells, the thickness of biological tissue is a major concern, because biological tissue can restrict the transmission of visible light and weaken the QDs signal for fluorescence imaging. Up to now, many *in vivo* animal imaging applications using functionalized QDs have been confirmed, such as *in vivo* cell tracking,⁴⁹ tumor imaging,⁵⁰ vascular system imaging,⁵¹ and so on. The greatest advantage of functionalized QDs in *in vivo* animal imaging applications is that their emission spectra can be adjusted in the whole near-infrared wavelength range by changing their size and composition, thus producing light-stable fluorescent groups in the biological environment. For *in vivo* animal imaging using QDs, systemic intravenous delivery into the blood will be the main mode⁵². When QDs are exposed to blood, they may be rapidly absorbed by opsonin, leading to phagocytosis, platelet coagulation, stimulation of complement system and activation of immune system. In view of various factors that may affect the implementation of QDs, including particle size, charge, shape, surface ligands, the two most important parameters that may affect the biological distribution are particle size and preference for serum protein adsorption.⁵³ Although many studies on the pharmacokinetics and biological distribution of QDs are still controversial, it has been considered that QDs are absorbed by reticuloendothelial system (RES), such as liver, spleen, kidney and lymphatic system.^{54,55}

In vivo Toxicity of QDs

The evaluation of the *in vitro* toxicity test of QDs depends on the cytotoxicity of QDs. The biocompatibility and safety of QDs must be studied before QDs are applied *in vivo*. Because cytotoxicity research can pre-determine the potential toxicity of QDs and the existing mechanism of drug production before animal exposure, it is very important to study the

cytotoxicity of QDs. Previous studies have found that QDs caused different degrees of cytotoxicity, such as decreasing cell viability⁵⁶, altering cell morphology,^{57,58} inducing autophagy,^{59,60} and inducing cells to produce living oxygen substances⁶¹ and changing the expression of genes⁶² and so on.

In addition, the researchers also explored the cytotoxic mechanism of QDs using some immortalized cell lines. A number of research teams have reported the nonspecific intracellular uptake of QDs.⁶³ Most QDs enter the cell through endocytosis, and cells regulate the endocytosis process through many ways including G protein coupled receptors. Although understanding the mechanism of QDs and cell reaction has a positive effect on inhibiting non-specific endocytosis, cell endocytosis is a complex process, which is regulated by multiple factors and levels. At present, the research on QDs endocytosis has just started, and researchers need to do more work in this area. The substance that enters the cell by endocytosis will be transported to different parts of the cell as needed to perform its function. The present results show that QDs are transported to the lysosome mainly through the early endosomes and late endosomes after entering the cell. Considering that the lysosome is an acidic organelle, QDs are highly likely to degrade under such low pH conditions, inducing cell organelle damage and cell function damage. Unfortunately, Experiments have proved that QDs caused a series of cell organ pressure, such as cell membrane defect, nuclear shrinkage,⁶⁴ lysosome swelling,⁶⁵ mitochondrial lipid oxidation and membrane potential decline.^{66,67} Although the cell has a certain self-repair function, when the organelle pressure exceeds a certain threshold, the cell will go to the irreversible process of death. The high concentration of QDs further activate the apoptosis pathway on the basis of organelle damage, leading to the cell apoptosis; or induce cells to trigger programmed death-autophagy.⁶⁸ At the body level, QDs may induce adverse effects on some organs and systems, such as respiratory, cardiovascular, nervous, immune and endocrine systems.

Dynamics of QDs

With the continuous improvement of the preparation of functional QDs, multi-functional QDs with targeting, tracer, diagnosis and treatment are constantly emerging. It is necessary to carry out the commonness and individualized toxicological evaluation of the functional QDs. Due to a wide variety of functional QDs and different synthetic processes, there is a great difference in their toxicological evaluation, so there is a lack of comparability among the results of the toxicological studies in each experiment. Potential cytotoxicity mechanisms are still at the early exploration stage. It has been reported that QDs are able to disrupting cellular structures and attenuating cellular function in a number of different cell lines, including human HepG2 cell lines,⁶⁹ lung epithelial A549 cells,⁷⁰ and so on.

The toxicity of QDs in vitro cell cultures must be highly valued, but in vivo animal models, the QDs are not toxic or very weak in a short period of time. For toxicological testing and evaluation, information on the dynamics of QDs, including adsorption, distribution, metabolism and excretion, is essential.⁷¹ The pharmacokinetics of the QDs in vivo has been described in Figure 1. After QDs entering the physiological environment, whatever the entry routes (oral, injection, etc), they enter the fluid circulation through the blood flow, and then enter the tissue fluid and lymph through the internal circulation.⁷² QDs that enter the biological fluid are rapidly wrapped by natural organic substances, carbohydrates, lipids, especially proteins, thus forming the “protein corona”.^{73,74} On the one hand, the formation of protein corona changes the structure, dynamic behavior and functions of QDs, and further changes the distribution, accumulation, degradation, clearance, intracellular recognition, signal transduction and toxicity of QDs in vivo.^{75,76} On the other hand, the protein corona can be used to regulate the uptake of QDs in vivo and improve the biocompatibility between QDs and organisms.⁷⁷

The distribution of QDs in vivo has a certain target and accumulates in some organs or tissues. As the QDs are very small, they can pass through the blood retinal barrier,⁷⁸ the blood-brain barrier,⁷⁹ it is possible to accumulate and cause toxic effects. However, the damage of tissues and organs is related to its special metabolic reaction and repair ability, and the mechanism of its damage remains to be discussed separately. Distribution and metabolism of QDs vary with the type, dose, particle size and surface coating.⁸⁰ For example, Chan et al studied the short-term (<7 days) and long-term (>80 days) toxicity of different concentrations of QDs to SD mice. No tissue damage or inflammatory reaction related to QDs was observed during the experimental period and the tissue function and serum markers of liver, spleen, kidney and other organs in experimental animals were normal. However, the QDs accumulated in liver, spleen, kidney and other organs, and later had the trend of transferring from liver and spleen to kidney.⁸¹

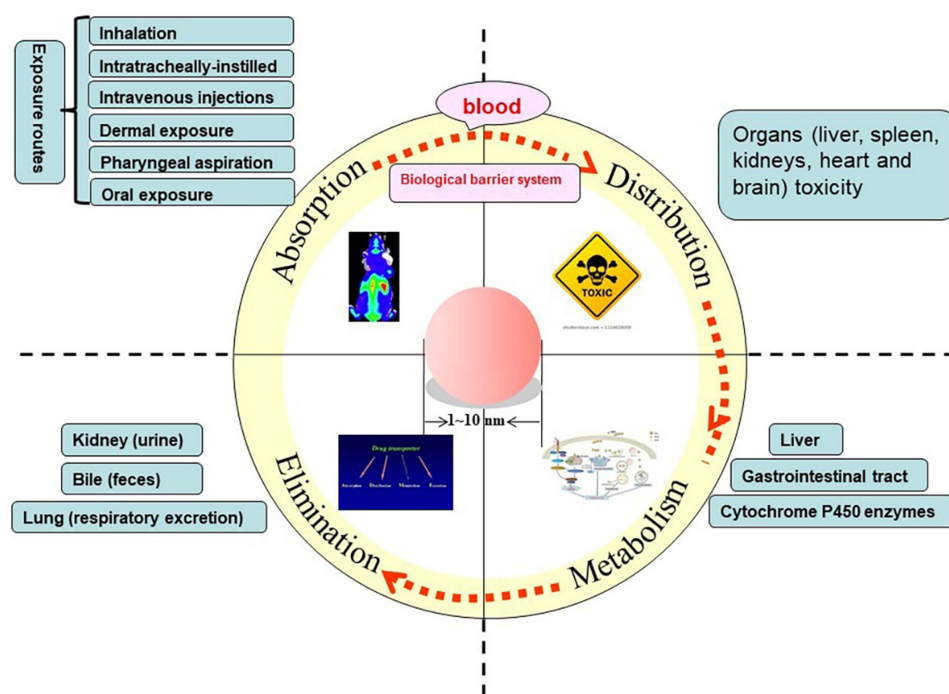


Figure 1 The pharmacokinetics of the QDs in vivo.

Biodegradation and excretion are also key considerations for the use of QDs in vivo. Researchers have found that <5.5 nm in hydrodynamic diameter led to rapid and effective urinary excretion and elimination of QDs from the body, whereas those greater than 8 nm are retained in blood circulation.⁸² The renal pathway depends on glomerular filtration in the kidney, and the filtration threshold of glomerular capillary wall of globular particles is 6–8 nm (in this range, size, charge, and surface chemistry dependence), which indicates that renal excretion is limited to substances with ultra-small hydrodynamic diameter.⁸³ Ge et al also demonstrated that Ag₂Se QDs (<3 nm) could be rapidly removed from the kidneys of mice at 168 h without long-term organs accumulation.⁸³ In addition to renal clearance, due to the binding of serum proteins, some hydrophobic enhanced QDs are excreted from the body through the liver pathway (including liver metabolism, bile excretion and feces excretion).^{84,85}

However, so far, no QDs have been prepared which can be completely excreted from the living body.

Immunotoxicity

Immune system is an important system for the body to perform immune response and immune function, mainly containing innate and adaptive immune.⁸⁶ It is the most effective weapon against the invasion of pathogens, which detects and removes factors such as foreign bodies and pathogenic microorganisms. As one of the important systems of the organism and the potential target organs of QDs, the immune toxicity of QDs has attracted the attention of some researchers. After the body is exposed to QDs, immune enhancement, immunosuppression and other immunotoxicity in the immune system often appear early.

The accumulation of QDs in the spleen may lead to inflammatory reaction, which may lead to unnecessary effects and toxicity. It has been confirmed that smaller QDs have stronger toxic effects on the immune system as they are more likely to pass through immune cells in vivo.⁸⁷ It is also worth noting that surface coating is an effective strategy to change the toxicity of QDs in vivo. For example, after 6 weeks of oral exposure of adult Sprague Dawley rats with AgNPs, the spleen is one of the main tissues with significantly increased Ag and increased immune response.⁸⁸ However, no harmful effects were found in treated animals when AgNPs were coated with polyethylene pyrrolidone (PVP-AgNPs).⁸⁹ Spleen size and weight in Wistar rats increased significantly on the 28th day after intravenous injection of 20 nm and 100 nm

silver QDs.⁹⁰ The authors suggested that the increase in T, B and NK cell numbers might be the reason for the weight increase of spleen.

Cytokines are crucial to determining the type of immune response. The activation of Toll-like receptor 4 (TLR4) and subsequent stimulation of NF- κ B and monocyte chemotactic protein-1 (MCP-1) pathway could ignite proinflammatory cytokines and simultaneously trigger immune responses after QDs exposure.^{91,92} It has been reported that after QDs enter biological environments, QDs gather “protein corona” to induce cytokines release.⁹³ Our group has reported that exposure to PEGylated Cd-free CuInS₂/ZnS QDs increased the levels of IL-4 on day 1 and enhanced the levels of IL-10 and IL-13 on day 28 in mice (Figure 2).⁹⁴

Cells involved in the immune response or related to the immune response can be divided into a variety of cells, including lymphocytes, dendritic cells, mononuclear/macrophages, granulocytes, mast cells, and so on. However, the immunotoxicity of QDs to mast cells and bone marrow hematopoietic stem cells is rarely reported. The effect of QDs on the migration tendency of immune cells and the allergic reactions are not involved.

Hepatotoxicity

The liver is the largest and most important organ, which plays a major role in maintaining life and health. The functions of the liver include filtration of blood, biosynthesis of enzymes and bile, degradation of fat, storage of glycogen and regulation of blood sugar. After QDs absorbed through the gastrointestinal biofilm pass through the portal vein into the liver, some of them can be metabolized and inactivated, thus reducing the dose of systemic circulation. The process is called “first pass elimination”. On the other hand, the liver has detoxification function and detoxification-related enzymes, such as P450, so the liver can complete most of the organism’s metabolic process.⁹⁵ Hepatocytes are the most abundant cells in the liver, which have metabolic, endocrine and secretory functions.⁹⁶ Kupper cells are specialized macrophages, which exist in the liver and easy to absorb exogenous substances and cause liver damage.⁹⁷ Therefore, the

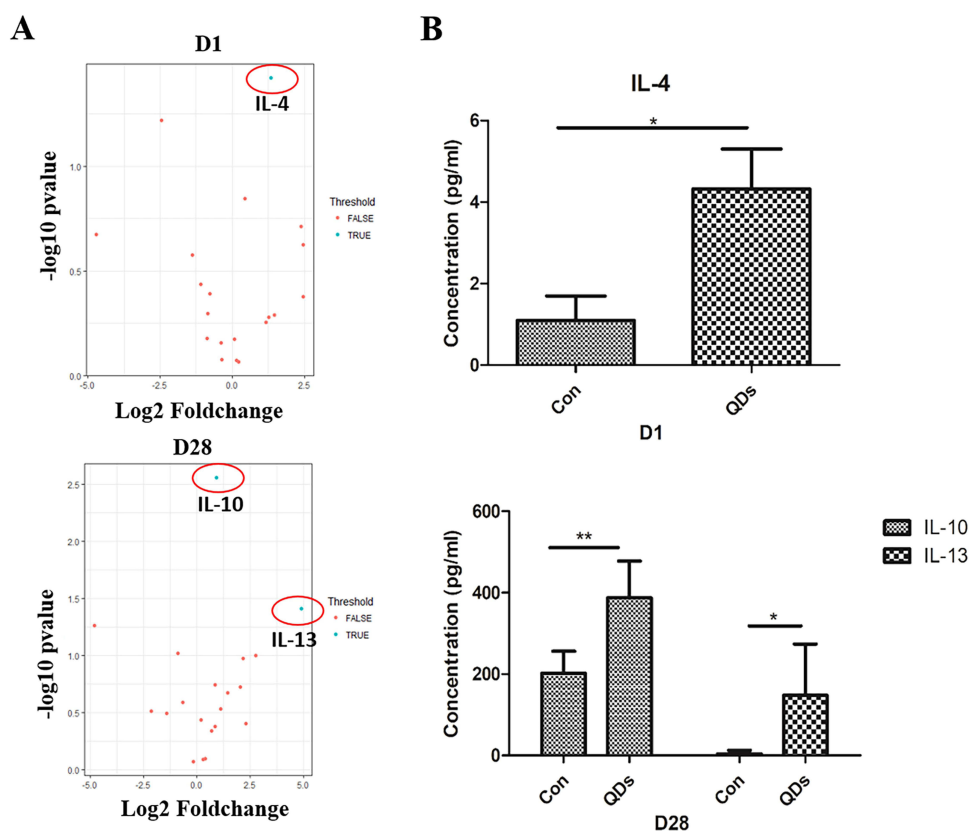


Figure 2 In vivo cytokine release in the serum detected by cytokine array. **(A)** Levels of cytokines are detected by cytokines antibody array. **(B)** The amount of IL-4, -10, and -13 was quantified by ELISA (* $P < 0.05$, ** $P < 0.01$). Copyright 2020 Nanotoxicology.

liver is one of the first organs to experience the effects of exogenous substances. When the high dose or high toxic QDs affect the body, the hepatocytes will be apoptotic or necrotic, and the body will lose the steady state. A large number of enzymes in the liver migrate to body fluids, resulting in significant changes in the function of amino acids, carbohydrates and hormones in the body fluids.⁹⁸

The liver is the main enrichment organ of QDs, so the liver is very susceptible to toxic effects due to QD exposure.⁹⁹ Furthermore, more than 60% of the Cd^{2+} administered to rats accumulates in the liver and liver is a major target of Cd injury.¹⁰⁰

The main mechanism of liver damage caused by Cd^{2+} in vitro is the binding of sulfhydryl groups in key mitochondrial proteins, resulting in functional inactivation of these proteins, leading to oxidative stress, DNA impairment, mitochondrial dysfunction, autophagy induction, inflammatory cell infiltration and fibrosis.^{101,102} Alarifi et al demonstrated that after human hepatic carcinoma HuH-7 exposure to CdTe QDs, ROS content increased, intracellular antioxidant system damaged, intracellular glutathione (GSH) reduced and superoxide dismutase (SOD) activity increased.¹⁰² In addition, the latest research suggests that Cd^{2+} enhances mitochondrial autophagy and hepatotoxicity by upregulating mitochondrial calcium uniporter (MCU).¹⁰³

Contrary to the cytotoxicity study of QDs, the reports on toxicity of QDs to organisms vary widely. Wei Liu et al found that mice exposed to CdSe QDs for 2 days (acute) and 6 weeks (chronic) caused hepatotoxicity.¹⁰⁴ In contrast, Ken-Tye Yong et al injected phospholipid-micelle-encapsulated Cd-based QDs into macaques and observed the clinical features over 90 days without any abnormalities.¹⁰⁵ Daily injection of Mn-doped ZnS QDs and polyethylene glycol-coated QDs via tail vein (1 mg/kg and 5 mg/kg) for 7 days did not cause obvious damage to the liver,¹⁰⁶ which indicated that the toxicity of QDs in vivo was minimal under appropriate formulations and doses.

The underlying mechanism in vivo indicated that the QDs induced liver inflammation, pyroptosis and dysfunction via NLRP3 activation and mitochondrial reactive oxygen species (mtROS) production and Ca^{2+} mobilization in hepatocytes.¹⁰⁷ Serban et al also reported the exposure of Si/SiO₂ QDs caused oxidative stress in carp liver and was in the state of proinflammatory response. The oxidative stress marker recovered to normal level after 3 weeks, indicating that the liver of carp successfully counteracted the toxic effects of the accumulation of QDs. The study also showed that oxidative damage caused by QDs exposure to the liver is likely to promote inflammation.¹⁰⁸ Moreover, METTL3-mediated m6a modification also plays a crucial role in hepatotoxicity caused by long-term exposure to Cd.¹⁰⁹

Although the important mechanism of QDs induced hepatotoxicity is ROS production and metabolic enzyme activity damage, the effect of QDs on the metabolic function of normal drugs in the liver has not yet been studied.

Nephrotoxicity

Kidney plays an important role in maintaining the balance of body fluid and acid-base balance, so it is the main target organ for drug poisoning. Because of the large amount of kidney blood supply, large area of the endothelial surface, large area of contact with drugs, high concentration of drugs or excretion in kidney, high sensitivity of the kidney to drugs, high metabolic rate, high oxygen consumption and relatively insufficient blood supply in the medullary examination unit of renal tubulointerstitial area, the kidney is vulnerable to drug damage.¹¹⁰ When external substances reach the renal tubules, it is easy to cause high concentration accumulation by urine concentration. So as the main excretory organ of the exogenous chemicals in vivo, the QDs entering the body are easy to cause injury to the kidney.

It is generally believed that the particle size less than 5.5 nm QDs can be cleared through the kidneys. However, recent studies have shown that QDs within this size range accumulate in the kidneys for a long time without excreting urine, which may be attributed to differences in surface charges on QDs.¹¹¹ In the study of pharmacokinetics and toxicology of heavy metal-free indium-based QDs in BALB/c mice and Wistar rats, Elnaz Yaghini et al found that after 5 mins to 3 months, the QDs of the liver, spleen and kidney gradually cleared without organ damage.¹¹² An in vivo study showed that Balb/C mice injected with different surface modification of InP/ZnS QDs for 1, 3, 7, 14, 28 d, resulting in the rapidly distribution in the liver and spleen.¹¹³

Cd^{2+} is a well-known nephrotoxicant.¹¹⁴ The proteinuria of renal tubules caused by Cd^{2+} is irreversible. Continued exposure to Cd^{2+} can lead to renal tubular dysfunction, resulting in glomerular damage and decreased glomerular filtration rates. Cd^{2+} has a long biological half-life and accumulates particularly in the kidney and bone.¹¹⁵ Pregnant

CD-1 mice were inhaled 230 $\mu\text{g}/\text{m}^3$ cadmium oxide (CdO) QDs to investigate the potential nephrotoxicity in mated and their newborn offspring by detecting the renal injury biomarkers, including kidney injury molecule-1 (Kim-1) and neutrophil gelatinase-associated lipocalin (NGAL).¹¹⁶ The results showed that Kim-1 and NGAL expression levels increased significantly both in maternal and in their offspring. Furthermore, histological analyses revealed proximal renal tubules pathology. Similarly, CdTe QDs induced time-dependent toxicity with elevated Cd^{2+} from the degradation of QDs and $\bullet\text{OH}$ production in the liver and kidneys in male ICR mice.¹¹⁷ Severe glomerular and tubular damage and apoptotic phenomena were observed in kidneys of male Sprague-Dawley rats exposed to cadmium-containing silica nanoparticles (Cd-SiNPs) and bare SiNPs, respectively.¹¹⁸

Therefore, it is of great significance to find a way to reduce Cd^{2+} accumulation in vivo. The previous results showed that betulinic acid (BA) pretreatment can reduce the residual level of Cd^{2+} in liver, kidney and testis, increase the excretion of Cd^{2+} in urine, and reduce the damage of cadmium chloride (CdCl_2) to tissues. Therefore, BA can inhibit the apoptosis of kidney and liver cells induced by CdCl_2 .¹¹⁹

However, similarities and differences of excretion of different physical and chemical QDs in vivo, the pathway of QDs excretion under different exposure conditions and the effect of QDs on renal excretion have not yet been clearly reported.

Respiratory Toxicity

Respiratory system has the most frequent contact with external environment in various systems of human body, and the contact area is large. Respiratory system is firstly exposed directly to the outside world and attacked alongside the inhalation of particles. On one hand, respiratory system contacts with all the blood volume of the heart, the QDs entering the vein will be discharged into the lungs through the heart. On the other hand, pulmonary respiratory membrane is very important. Type I alveolar cells are the gas exchange sites, which are non-proliferative and therefore nonrenewable. Type II alveolar cells have the ability to bio transform and are easy to produce metabolic activation.¹²⁰ The oxygen content in the lung is high, which is easy to cause oxidative damage.

The QDs that enter the organism through the respiratory tract are still easy to accumulate in respiratory system due to its small size effect. Its main toxicity on respiratory system is pulmonary inflammation and tissue damage. Several studies have shown that the deposition of QD in lung organs leads to lung injury.^{121,122} For example, cadmium oxide (CdO) QDs can stimulate lung inflammation, cell injury, tissue remodeling and other related pathways, and change the immune function.¹²³ Philku Lee used Sprague-Dawley rats as the research object through inhalation exposure for 28 days. Soluble Ag QDs can be dissolved in Ag ions and transferred to extrapulmonary organs and can be quickly cleared from most organs except for the brain and olfactory bulb. However, insoluble Au QDs continue to migrate to extrapulmonary organs without rapid elimination, which may have toxic effects on some organs.¹²⁴ In addition to the inherent toxicity of component materials, the toxicity of QDs also depends on other factors, including surface charge, concentration, size, outer coating as well as experimental conditions like mouse strains. Both C57BL/6J and A/J mice were exposed to 6 $\mu\text{g}/\text{kg}$ Cd equivalents of amphiphilic polymer-coated Cd/Se core, ZnS shell QDs via pulmonary respiration. However, researchers have found that QDs induced acute changes in lung mechanics are mouse strain dependent. QDs induce lung inflammation in C57BL/6J and A/J mice, and A/J mice are more susceptible to the effects of QDs in lung mechanics.¹²⁵ Tang et al observed that positively charged QDs using cationic polydiallyldimethylammonium chloride (PDMA) as outer coatings were more toxic due to pulmonary embolism. Compared with positive or negative, PEGylated QDs showed the slightest chronic damages in the long-term toxicity.¹²⁶ However, the effect of QDs on the function of lung-derived cells (such as type I cells), respiratory membrane function and the ability to penetrate blood gas barrier at different physical and chemical QDs needs to be further studied.

Neurotoxicity

Neurotoxicity refers to the toxic effects of foreign substances on the nervous system, including the central nervous system (brain and spinal cord) and the peripheral nervous system. It has been proved that QDs were able to cross the blood-brain barrier and entered the central nervous system.¹²⁷ In addition, it was found that QDs are mainly transported from nose to brain through olfaction and transported through axons.¹²⁸

Blood–brain barrier is highly selective and protective, which can prevent some foreign bodies from entering the central nervous system (CNS). However, because the diameter of QDs is very small, it is usually only 1–10 nm and has small size effect, it can cross the blood–brain barrier or move along neural pathways, and enter the CNS and cause certain toxicity. It is reported that QDs exposure can induce abnormal inflammatory responses, increase oxidative stress generation, alter neuronal function and morphological alterations, and elevate cytoplasmic Ca^{2+} levels and autophagy in adult animals.¹²⁹ The common adverse effects of nervous system related to morphological changes include neuropathy, axonal lesion, myelin sheath lesion and gliopathy.

In vivo experiments are essential to investigate the neurotoxicity of QDs, as they allow the study of the entire organ system, which cannot be modeled in vitro. Up to now, most of the data in vivo have been produced in rodents to report neurobehavioral defects, neuroinflammation and some neurodegenerative changes. Wu et al have studied the toxic effects of different concentrations of 3-MPA-CdTe QDs on the hippocampus of Wistar rats. Low dose of QDs inhibited the excitation, but the inhibitory phosphorylation of AKT and ERK1/2 and the decrease of c-FOS transcription level in high-dose group indicated that QDs induced spatial recognition and memory impairment.¹³⁰ What's more, CdTe QDs exposure could also alter genome-wide gene expression pattern in a size-dependent manner of rat hippocampus.¹³¹ CdTe QDs also cause neuroinflammatory responses in mice by activating the NLRP3 inflammasome through excessive ROS generation, resulting in proinflammatory factor release in the hippocampus.¹³² Mammalian experimental models are limited by logistics, finance and ethics. In recent years, *Caenorhabditis elegans* (*C. elegans*) has become a promising alternative for toxicological studies due to easy of cultivating, short life cycle, more offspring and so on.¹³³ Most importantly, this model organism has a well conserved and fully described nervous system that makes it ideal for neurotoxicity assessment. 0.1–1 $\mu\text{g/L}$ of CdTe caused neurotoxicity on both development and function of RMEs motor neurons due to oxidative stress, cell identity, and bioavailability. However, ZnS coating reduces the toxicity effects of CdTe QDs in *C. elegans*. Moreover, CdTe/ZnS could not be translocated into the RMEs motor neurons through the intestinal barrier.¹³⁴

Both oxidative stress and neurotoxicity are huge challenges to human health, and effective methods and agents for resisting these adverse effects are limited, especially in vivo. QDs penetrate the blood–brain barrier mostly in vitro cell models and cannot simulate the process of QDs penetrating blood–brain barrier in vivo. The effect of QDs on blood–brain barrier permeability and function has not been clearly studied. Whether QDs in the brain could cause toxicity to other organs through body distribution has not been studied. Finally, yet importantly, the neurotoxicity of QDs has been mostly observed in experimental animals. Because of the difference between humans and animals, it is a great challenge to extrapolate these data to human beings.

Reproductive and Developmental Toxicity

With the continuous change of the industrial environment and the ecological environment, the problem of the decline of human reproductive health is becoming more and more prominent. The disease of reproductive system will be the third major social disease following the cardiovascular disease and malignant tumor. Reproductive and developmental dysfunction is one of the major public health problems that seriously affect human health at present. In recent years, it has been found that QDs, such as nano silica and nano silver, may accumulate in the testis through blood circulation and blood–testis and placental barriers, causing certain cytotoxicity to the Leydig cells and the damage of the reproductive system.^{135,136} The effect of some QDs on the female reproductive system may lead to ovarian dysplasia or infertility, increasing the spontaneous abortion rate, dysplasia of the progeny and decreasing fertility, etc.¹³⁷ Therefore, it is of great significance to identify the QDs with reproductive toxicity and explore the mechanism of its toxicity, which is of great significance to the prevention and control of the reproductive system caused by the QDs.

In the development of Chinese rare minnow embryos in China, InP/ZnS QDs caused teratogenic effect and death, but InP/ZnS QDs did not cause significant genetic toxicity in the development.¹³⁸ *C. elegans* owing to its short generation time and transparent body is becoming a well-studied model organism for toxicological problems. The short-term exposure of *C. elegans* at high concentrations of MPA-CdTe QDs was not significantly toxic, while long-term exposure could produce late toxicity, such as fertilization difficulties and injury of fertilized egg shells. At the same time, the toxicity of the positive QDs (immature larvae) was significantly greater than the QDs with negative electricity. Compared with mature nematodes

treated with MPA-CdSe/ZnS and MPA-CdTe QDs, it was found that QDs toxicity with ZnS shell protection was significantly reduced.¹³⁹ In addition, MPA-CdTe QDs (≥ 50 mg/L) affected *C. elegans* to reduce the cell number in the pachytene and terminal stages, leading to reproductive capacity defects, dysregulation of proliferation and differentiation, and oogenesis imbalance. The toxicity mechanism was mediated by SPO-11 and PCH-2, as well as the protective mechanism was mediated by GLP-1/Notch.¹⁴⁰ In BALB/c mice, all the exposed mice had CdTe QDs accumulation in the testes, and there was no significant effect on the quantity of sperm. However, the high-dose group significantly decreased the sperm quality on day 60, the levels of the 3 major sex hormones (testosterone, Luteinizing hormone and follicle-stimulating hormone) in the serum were also disturbed.¹⁴¹ Amiri et al have studied the reproductive toxicity of different concentrations of CdSe/ZnS (10, 20, 40 mg/kg) on BALB/c mice by intraperitoneal exposure. Testicular histological studies showed that 40 mg/kg dose had a high toxic effect, reduced the lamina propria, damaged mesenchyme, produced seminiferous tubules, and reduced spermatogonia, spermatocytes and spermatids. The whole group (adult and embryo groups) of epididymal studies showed that the amount of sperm in the epididymis of the adult group at 40 mg/kg dose decreased considerably.¹⁴² Another study has demonstrated that high doses of PVP-AgNPs showed higher abnormalities in sperm morphology, while their effects on sperm motility and viability were not significant. These results indicated that oral sub-chronic doses of PVP-AgNPs have slight toxicological effects on rat sperm parameters.¹⁴³ Our group has studied the reproductive toxicity of CdSe/ZnS QDs on the male reproductive system and offspring health in mice. We have found that high dose QDs induced apoptosis of Leydig cells in the testes at early timepoints, but did not cause significant histopathological changes overall. However, QDs did have effects on offspring from exposed males, including slower growth, changes in organ weights, and abnormalities in some blood parameters (Figure 3).¹⁴⁴

In summary, most of the toxicological studies of QDs have toxic effects on cells or organisms, but their specific toxicity mechanisms are relatively slow. In future research, the research on the reproductive toxicity of QDs should be more specific, and more attention should be paid to the study of the toxicity of QDs. Its general direction is: A, in depth understanding of the physical and chemical properties of QDs, fully understand the absorption, distribution, metabolism and excretion process. B, the toxicity of QDs was refined, and the toxicity of each component (such as Cd, S, Si, Ti, Se) was studied. The toxicity of QDs to the reproductive system was also studied. C, Reproductive toxicity of QDs needs more animal experiments, especially for animals with chronic toxicity. D, reproductive toxicity should take into account the effects of QDs on the formation of eggs and sperm, and a series of effects on fertilized eggs, embryonic development, young growth, young offspring reproduction and so on. E, the toxicity mechanism of QDs and the toxic effects on reproductive system were comprehensively investigated from individual, cellular, molecular and genetic levels.

Genotoxicity

Genotoxicity refers to the ability of exogenous chemicals to damage genetic materials. Genotoxicity experiment is an essential part of toxicology safety evaluation, as it may lead to birth defects and malignancies.¹⁴⁵ So in the past 20 years, scholars have preliminarily described and evaluated the genotoxicity of QDs through various experiments. The genotoxicity of QDs is mainly caused by DNA damage and chromosomal aberration caused by oxidative stress, while Ames test (gene mutation) is mostly negative. For example, Li Jin et al exposed the parents and offspring of rare minnow to ZnSe/ZnS QDs, DNA damage was still present in the F1 generation 96 hours after fertilization, and the toxicity may be due to the release of Zn^{2+} from QDs, leading to abnormal development of hatching glands.¹⁴⁶ Katsumiti et al exposed mussel blood cells to CdS QDs, comet assay showed DNA damage.¹⁴⁷ Aye et al treated rats with lipoamphiphile-coated CdSe/ZnS QDs by intraperitoneal injection and analyzed the comet assay with different organs. The results showed that significant DNA damage could be observed in brain, liver and testis, but not in kidney and lung.¹⁴⁸ It indicates that QDs can accumulate in specific sites and produce corresponding toxic effects. Meanwhile, QDs can pass through biological barrier and damage target tissues after modification. Borm et al have noted that, to reach the threshold of genotoxic effect, at least 5 times of crystalline silica (CS) dose of pro-inflammatory effect in vivo is required.¹⁴⁹ Thus, the main mechanism of CS genotoxicity is inflammation-driven secondary genotoxicity. Chromosome aberration (CA) is a serious genetic damage. CAs were analyzed in bone marrow cells of Sprague-Dawley rats treated through the oral route for once a day for five days with different doses. The results suggested Ag have the potential to induce genotoxicity.¹⁵⁰

A series of studies on the toxicity of QDs in recent years are summarized in Table 1.

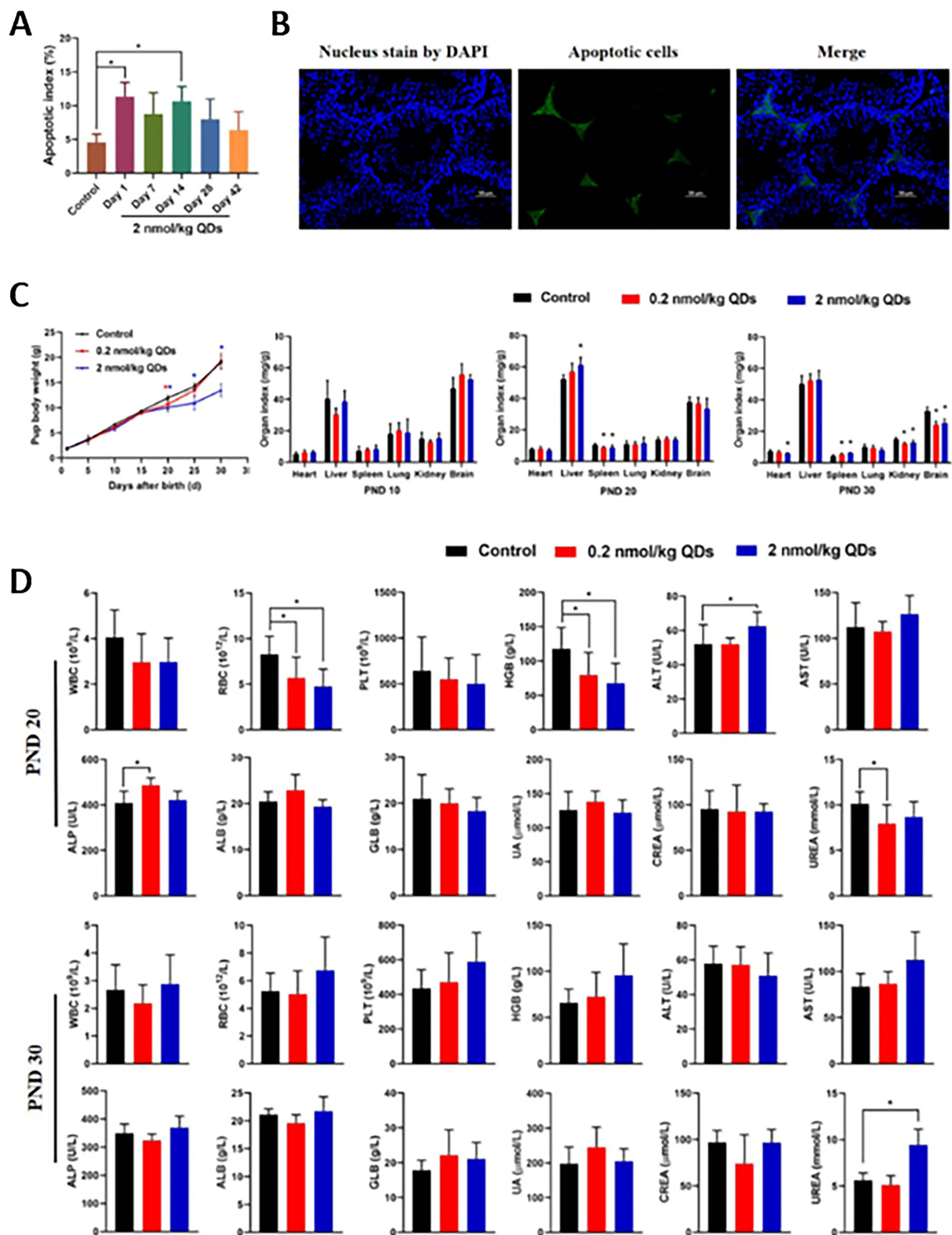


Figure 3 The reproductive toxicity of CdSe/ZnS QDs on the male reproductive system and offspring. **(A)** Apoptotic index percentage. **(B)** Representative TUNEL images of testicular tissue of mice on Day 14 treated with 2 nmol/kg BW CdSe/ZnS QDs. **(C)** Changes in pup body weight within 30 days after birth and organ index of offspring mice. **(D)** Hematology and serum biochemical data of offspring mice on PND 20 and 30 (* $P < 0.05$). Copyright 2021 Ecotoxicology and Environmental Safety.

Table 1 A Study of Some Reported QDs Toxicity

QDs	Model	Dose	Method	Toxicity Findings	References
CdSe	Wistar male rats	10, 20, 40 and 80 mg/kg	Biochemical assays, hematological parameters	Caused oxidative stress	[29]
	Chickens	1.00 mg/kg	Histopathological assay, oxidative stress, ERS and programmed necrosis	Se antagonized the toxicity of Cd	[151]
CdSe ((PEG)n-COOH, MPA, GSH, CA,)	Zebrafish	1, 10, 50 and 100 nM	Mortality, hatching rate, heartbeat and malformation assessments	(PEG)n- COOH-CdSe showed the most severe toxicity	[18]
CdSe/ZnS	Tetrahymena thermophila	0.1, 0.4, 2.4 and 9.6 µg/mL	Metabolomics experiments	Inhibited cell proliferation and induced ROS production along with cell membrane damage	[152]
CdSe/ZnS-COOH	Salmo trutta fario L.	156.86 nM	Molecular, cellular, physiological and whole-organism levels	Affected gut microbiota	[153]
3-MPA-CdTe	C57BL/6 mice and RAW264.7 macrophages	0.1 mL/20g or 0.1, 0.5 and 1 µM	Fluorescent probe FerroOrange	Induced ferroptosis	[154]
	Normal human liver cells and human liver cancer cells	0–100 µM	Annexin V-FITC/PI analysis and ROS and GSH content measurement	Induced ER stress-mediated autophagy and apoptosis	[155]
	Drosophila melanogaster	0.2–100 µM	Organism' survival, development, reproduction, and behavior	Affected the survival, development and reproduction along with increased ROS and cell death	[156]
InP/ZnS	Rare minnow	0, 5, 10, 20 and 40 nM	Histological analysis, AST, ALT, AKP activity, bile acid content detection and RNA-seq data analysis	Caused hepatic cell nuclear lysis, abnormal cytoplasmic staining, and mitochondrial cristae reduction, swelling and fragmentation	[67]
3-MPA-InP/ZnS	Chinese rare minnow	0, 50, 100, 200, 400 or 800 nmol/L	Developmental toxicity assays and gene expression analysis	Led to deformation and death of rare minnow embryos, did not affect genetic toxicity	[138]
	Male rare minnow	0, 100, 200, 400, 800 nmol/L	Sperm quality analysis, oxidative stress and content determination, gene expression analysis	High-concentration exposure damaged the integrity of the blood-testis barrier and caused reproductive damage	[157]
CdS	BALB/c mouse	1.0 µg/mL	Weight measurements	No toxicity of CdS was observed in vivo	[158]

Parameters Affecting the Toxicity of QDs

Chemical Composition

In fact, the fundamental factor of QDs toxicity is composition. From the classical metal QDs to the new inorganic non-metal QDs, it is the main component that determines the biocompatibility of QDs. By far, the most commonly used QDs are Cd-based QDs, such as CdS, CdTe, and CdSe. The composition of the Cd element raises concerns about the toxicity produced by the release of heavy metal Cd^{2+} . Cd^{2+} has been identified as a carcinogen by the International Cancer Research Center and is recognized as a toxic heavy metal.¹⁵⁹ Although the QDs have undergone surface modification and reduced their toxicity before entering the organism, after a long period of degradation and biological oxidation after entering the organism, the shell is likely to fall off to form the bare core structure and expose the core Cd^{2+} . Su et al studied the relationship between Cd^{2+} and QDs toxicity. The control group was CdCl₂ solution and the experimental group was CdTe QDs. The Cd^{2+} concentration in the cells of each group was the same after the experimental treatment. It was found that the toxicity of QDs exposed group was much greater than that of CdCl₂ solution group, indicating that the toxic effect of QDs was indeed related to Cd.²⁺¹⁶⁰ Some research groups have been dedicated to using new insights, such as flow cytometry or all-inclusive microscopy system, to investigate the relationship between Cd^{2+} and cytotoxicity.¹⁶¹ Data from Soenen et al showed that when QDs were exposed to the intracellular structure of a lower pH, it took endocytosis to result in partial degradation and release of Cd^{2+} , thereby reducing its fluorescence intensity and increasing the toxicity of particles.¹⁶² To address this problem, environmental benign non-Cd QDs are recently developed, such as III–V InP,¹⁶³ II–VI ZnSe,¹⁶⁴ I–III–VI Cu–Ga–S (CGS) QDs¹⁶⁵ and I–III–VI₂ CuInS₂.¹⁶⁶

Particle Size

Because QDs are very small in size, once they are absorbed by the human body accidentally, they will enter blood circulation rapidly, distribute into most organs of the human body, and even penetrate various biological barriers, such as the blood–testosterone barrier and blood–brain barrier. Previously, it has been reported that the toxicity of QDs is dependent on their size. Normally, the smaller QDs have the greater toxicity.¹⁶⁷ For example, Chang S et al have demonstrated that the MPA CdTe QDs of different sizes have obvious cytotoxicity. Under ultraviolet light, small size QDs show more obvious damage to the cells of larger size QDs.¹⁶⁸ The possible reasons responsible for the greater toxicity caused by smaller QDs are: (A) the smaller the particle size of QDs, the larger the surface area, the more Cd exposed to the surface, and more opportunities to form the free Cd^{2+} to produce the toxicity; (B) many pathways in the body and cells are particle size dependent, allowing only small particle size QDs, such as the placental barrier, the nuclear pore, and so on. However, unlike in vitro cultured cells, Wang Q et al pointed out that the distribution of QDs in organs and tissues was related to the clearance time and the size of QDs. Small QDs can quickly be removed from the circulation system, while large QDs will take a long time to clear them. Therefore, large QDs generate more severe toxicity.¹⁶⁹ Consistently, Su et al found that the QDs with larger sizes are more quickly to accumulate in the spleen; on the contrary, the smaller QDs are more easily to be absorbed by kidney.¹⁷⁰

Different Surface Modification

Surface modification of QDs makes them better with controllable biocompatibility and stability. QDs commonly undergo different surface modifications that involve conjugating recognition biomolecules, resulting in specific biological functions. Previously, the surface modification of QDs has been proved to affect its toxicity to some extent. Firstly, core-shell QDs are normally less toxic than bare QDs.¹⁷¹ A layer of semiconductor shell is usually rewrapped on the surface of QDs to improve its fluorescence performance. This package can improve the fluorescence properties of QDs while preventing the Cd^{2+} from the medium in the environment, reducing the leakage of Cd^{2+} and the formation of free ions, and reducing the toxicity. Secondly, the appropriate ligands on the surface of QDs help to reduce toxicity. Jiang Z et al have encapsulated CdSe with water-soluble poly (ethylene glycol)-graft-chitosan (PEG-g-CS). The in vitro cytotoxicity studies showed that PEG-g-CS as ligand displayed very low cytotoxicity.¹⁷² Thirdly, different surface functional groups (eg COOH, NH₂ or OH) also affect their biological behavior and toxic effects. Zheng N et al utilized zebrafish embryos to compare the toxicity in vivo of CdSe/ZnS QDs modified with carboxyl (–COOH) and amino (–NH₂) groups. Both CdSe/

ZnS QDs reduced the survival rate, hatching rate, and embryonic movement of zebrafish, ultimately leading to pericardial edema and cardiac dysfunction. This indicated that the properties of QDs and the release of Cd^{2+} contribute to developmental toxicity. Moreover, two types of CdSe/ZnS QDs exhibited developmental toxicity and affected heart development, while carboxyl QDs exhibited greater toxicity, possibly due to their higher affinity and release to embryos and larvae.¹⁷³ So many factors of surface modification are responsible for QDs toxicity, but their impact on toxicity varies. Rashi et al¹⁷⁴ systematically investigated the toxicity of CdSe QDs with different particle size, functional group and surface charge on human bronchial epithelial cells. They rank the contribution of each property of QDs toxicity: charge > functionalization > size. Specifically: (A) positively charged QDs are more toxic than the negative QDs; (B) QDs with long ligands are more toxic than those functionalized with the shorter chain; (C) the toxicity of QDs with small particle size is larger than that of the large particle size.

Exposure Route

For the toxicity of QDs, the researchers are also concerned with its exposure route, which is of great importance to the target of understanding the toxicity of QDs. It is generally believed that the preparation of personnel, researchers and clinical patients may be exposed to QDs and other nanomaterials through environmental transmission, workplace exposure and disease diagnosis and treatment. We could divide the potential exposure routes of QDs into two different basic pathways: workplace and laboratory studies.¹⁷⁵

At present, QDs as *in vivo* imaging probe or drug tracer are usually injected into the experimental animal by intravenous injection. Therefore, there is no doubt that QDs through the blood vessels are exposed to the human body, which follows is the potential damage to the blood vessels of QDs, and even because of the circulation of the blood, QDs will threaten more tissues and organs.¹⁷⁶ In addition, QDs may also be in contact with the skin, the respiratory system, or the digestive tract, and other parts of the contact during the actual use.^{177–179} The skin is the largest organ which covers the whole body to prevent physical, chemical and pathogenic microorganisms from invading the body tissues and organs. The traditional idea is that the complete skin is a tight barrier, and the general material cannot penetrate it. The penetration of QDs to the skin only occurs when the skin is damaged or there is mechanical stress. However, Doge et al utilized a 2-photon microscope (2PM) and a total internal reflection microscope (TIRFM) to find that QDs aggregated in the upper part of the stratum corneum (SC) and villous hair follicles (HFs) through the skin barrier.¹⁸⁰ Moreover, Research has also indicated that water-soluble CdSeS QDs could penetrate into the dermal layer through hair follicles and then get into blood circulation.¹⁸¹ It is indicated that QDs with different physical and chemical properties can penetrate intact skin into the body at working concentration. It also suggests that the skin may also be a major way for QDs to enter the human body. It should also be taken into consideration when investigating the health risks of QDs. QDs less than 100 nm have been confirmed to be distributed in nasal cavity, trachea and alveoli of experimental animals, and these QDs will also be transported to the extrapulmonary parts of liver and brain.^{182,183}

Exposure Time and Dose

The toxicity of QDs is dependent on exposure time and dose.^{184,185} Basically, the longer is the exposure time, the higher is the dose, and the more obvious is the toxicity of QDs. For example, the activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in the liver and kidneys of mice exposed to CdTe QDs increased in a dose-dependent manner. The time course study showed that the oxidative stress markers activities of SOD, CAT and GPx in the liver and kidneys in the exposure group increased on the first day, then decreased, and gradually returned to normal on the 28th day.¹⁸⁶ In addition, Stan MS et al have found that Si/SiO₂ QDs caused 2.2 and 2.6-fold higher compared to control for 25 $\mu\text{g/mL}$ and 50 $\mu\text{g/mL}$ treated group after 24 h incubation respectively, and 3.4-fold higher for the 200 $\mu\text{g/mL}$ treated group. At longer exposure times, the increased ROS generation was 5.5 times (200 $\mu\text{g/mL}$, 48 h) and 7.0 times (200 $\mu\text{g/mL}$, 72 h) higher compared with control group.¹⁸⁷

Although dosages are important for the evaluation of the toxicity of QDs, it is difficult to make effective comparison of the doses adopted by different researcher because of wide variety of QDs and the concentration of the QDs cannot be precisely quantified. The inconsistency of the concentration units used by each research groups leads to the incomparability of the mutual results, which has become one of the major obstacles to the study of the toxicity of QDs. In addition,

the exposure time of QDs toxicity study also lacks a unified standard. Most toxicity studies on QDs are still focused on short-term acute toxicity effects, long-term toxicity of QDs toxicity is still very scarce and needed to be further investigated.

Toxicity Mechanism

QDs are widely used as fluorescent nanomaterials with superior performance, but the toxic problems are also concerned. It is known that the toxicity studies of QDs begin at the cellular level. At present, a large number of experiments have been conducted to observe the effects of QDs on cell growth, viability, structure and survival. Most results showed that the QDs are toxic in a dose-dependent manner,^{188,189} but it was also found that QDs did not affect the behavior of stem cells and were suitable for in vivo fluorescence tracking and diagnosis.^{190,191} The toxicity of QDs is a complex process, including the interaction with body, cells and molecules. The toxicity is determined by itself and environmental factors. In recent years, some research groups have discussed the mechanism of QDs from different perspectives. Its cytotoxic mechanism can be summed up as the following three points (Figure 4):^{192,193} (A) The core of QDs interacts with the medium to degrade and release of heavy metal ions such as Cd^{2+} ¹⁹⁴ and Ag^{+} ¹⁹⁵ (B) Increase intracellular oxidative stress by producing ROS and induce apoptosis.¹⁹⁶ (C) Nonspecific adsorption to the surface of the cell, binding with the protein, destroying the structure, and affecting the normal function of the cell.^{197,198} It is well known that toxicity of QDs is largely dependent on many physical and chemical characteristics, such as their chemical composition, size, surface charge, the presence or absence of a shell and active groups on the surface. In addition, the toxicity of QDs is also determined by exposure conditions, including time, dose and administration route.

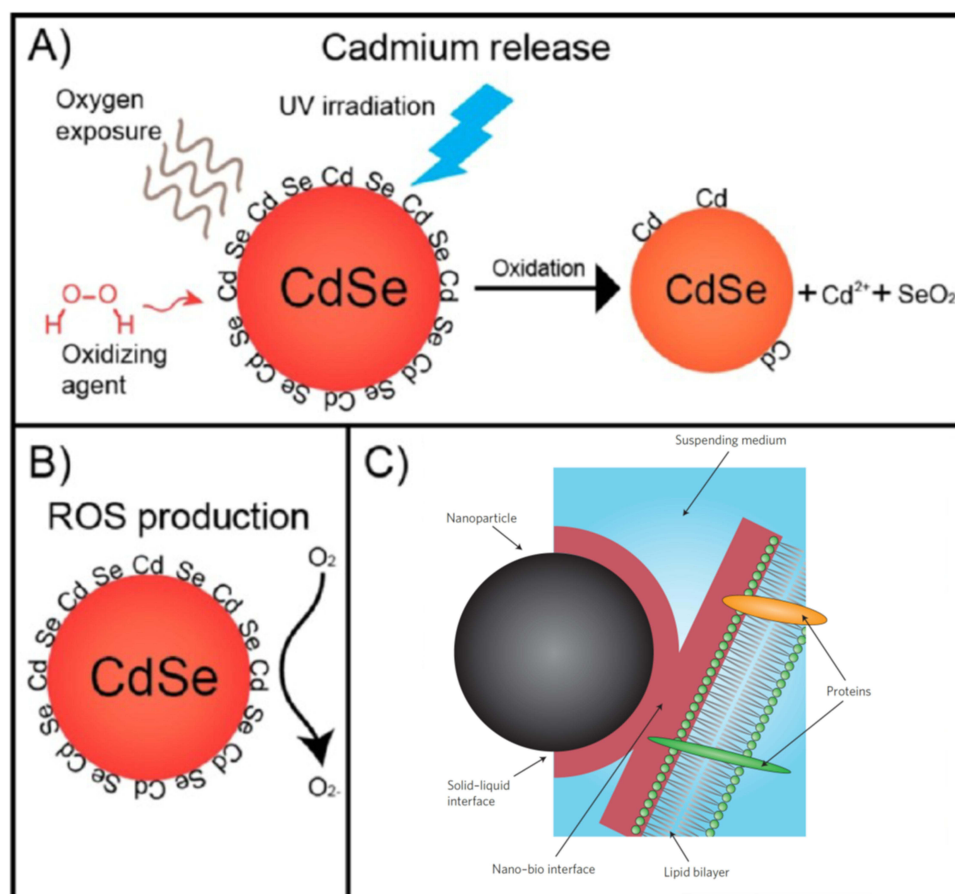


Figure 4 Cytotoxic mechanism following three points: (A) The core of QDs degradation with release of heavy metal ions such as Cd^{2+} . (B) Producing reactive oxygen species (ROS) and induce apoptosis. (C) Interacts with components in the surrounding medium. Copyright 2013 Acc Chem Res and 2009 Nat Mater.

ROS Generation

Oxidative stress (OS) is recognized as a major mechanism triggered by QDs, as it can intrinsically produce ROS or induce the intracellular production of ROS and anti-oxidant depletion upon interacting with cells.¹⁹⁹ OS refers to the imbalance between oxidation and antioxidant system. The body tends to oxidation state due to excessive accumulation of ROS. ROS usually have adverse effects on cell functions, such as oxidative damage of DNA and protein, damage of biomembrane, etc.^{200,201} At the same time, there are also protective antioxidant systems, including antioxidant enzymes, catalase, Superoxide dismutase (SOD) and some non-enzyme molecules such as thioredoxin, glutathione (GSH), vitamin C and vitamin E.²⁰² In the physiological environment, the oxidation and antioxidant systems are in a dynamic equilibrium state.²⁰³ When the active oxygen species continuously stimulated by foreign organisms exceed the speed of internal clearance, the imbalance between oxidation and antioxidant system in vivo has influence on the tissue damage and pathogenesis of serious diseases.²⁰⁴ For example, Si/SiO₂ QDs can increase the ROS and malondialdehyde (MDA) levels with lower glutathione content, which leads to the disorder of redox system in cells, thus affecting the sensitive signal pathway of redox system.¹⁸⁷ At present, the research on ROS produced by QDs mainly focuses on DNA damage,²⁰⁵ apoptosis²⁰⁶ and autophagy.²⁰⁷

Heavy Metal Ions Release

The release of QDs core can explain the toxic mechanism of QDs to some extent. Among them, Cd-based QDs are the most widely used, as they have higher toxicity than others. Due to the complex internal environment of the organism, QDs are corroded, degraded or oxidized by the microenvironment of the organism after entering organism. For example, under the condition of low pH, such as gastric juice, the core-shell dissociation occurs after the connection of the protonation, which makes the QDs reduce stably, release metal ions, and produce damage to the cells. Derfus et al found that the CdSe QDs coated with tri-n-octylphosphine oxide (TOPO), reacted with the cells 30 minutes after oxidation in the air and then modified with mercaptoacetic acid (MAA). The cell activity decreased significantly from 98% to 21%.²⁰⁸ It can be concluded that the cytotoxicity may be caused by the oxidation reaction on the surface of CdSe. In order to test this hypothesis, the researchers used UV-light source to accelerate the oxidation process of CdSe. The results showed that the cell activity decreased significantly with the increase of oxidation time, and there was a significant time effect relationship. Through the release of free Cd²⁺ concentration in the system, it is found that the Cd²⁺ concentration of non-oxidized MAA-QDs was 6 ppm under the same conditions; the concentration of Cd²⁺ of air-oxidized QDs system was 126 ppm; the concentration of Cd²⁺ in the QDs system was 82 ppm after UV catalytic oxidation. Therefore, the toxicity mechanism of QDs is proposed: the oxidation of CdSe nuclear surface leads to the release of Cd²⁺. Kirchner et al discussed the effect of different surface modifications on cell absorption and further studied the relationship between the toxicity of CdSe and CdSe/ZnS QDs and the release of free Cd²⁺ ions. They evaluated the proliferation toxicity of QDs by the number of adherent cells before and after exposure and determined the concentration of free dissolved Cd²⁺ in the system by plasma optical emission spectroscopy (ICP-OES). The results showed that the cytotoxicity increased with the increase of Cd²⁺ concentration in the system, which was consistent with the conclusion of Derfus.²⁰⁹ After that, researchers focused on the toxicity caused by the release of Cd²⁺.^{173,210} Cd²⁺ can inactivate mitochondrial protein and affect mitochondrial biochemical function through interaction with sulfhydryl group.²¹¹ Cd²⁺ can react directly with DNA, such as binding with phosphoric acid and base in DNA, which is very harmful to organism.²¹² The release of Cd²⁺ ion in the system is an important but not the only factor causing cell damage, and other mechanisms affecting its toxicity need further study.

Disturbance of Organelles

After QDs treatment, it interacts with cells and enters the cell, which mainly causes mitochondrial dysfunction, endoplasmic reticulum (ER) stress and lysosomal disruption, thus affecting cell growth, inducing apoptosis and necrosis and ferroptosis. The QDs are small in size, high in surface activity and easy to pass through the cell membrane. On the one hand, it may interfere with the hydrophobic interaction or double bond oxidation of polyunsaturated fatty acids in the lipid bilayer of the cell membrane, thereby disturbing fluidity, permeability and ion gradient distribution of the

membrane, causing damage to the cell membrane; on the other hand, it may interact with the organelle and affect the structure and function of the organelle.²¹³

The main function of cell membrane is to prevent extracellular substances from entering the cell freely, maintain the relative stability of the cell environment, and make various biochemical reactions orderly. The toxic effect of QDs on the cell membrane is mainly manifested in the damage of the integrity of the cell membrane and the change of the permeability of the cell membrane.^{214,215} The amount of LDH in cell culture medium can reflect the damage degree of cell membrane. Zhang et al incubated L929 cells with 2.2 nm CdSe QDs of different concentrations (0–14 µg/mL) for 24 hours. The results showed that the amount of LDH in the experimental group was significantly higher than that in the control group with a dose-dependent relationship.²¹⁶ Wang et al²¹⁷ incubated human umbilical vein endothelial cells (HUVECs) with 0–100 µg/mL silver nanorods (AgNR) for 24 hours, and the results showed that oxidative stress, intracellular MDA levels and proinflammatory cytokine secretion increased, suggesting cell membrane structure disruption.

The mitochondrial toxicity caused by QDs includes morphological change, increase of ROS production, change of calcium level, loss of mitochondrial membrane potential, inhibition of enzyme activity, inhibition of electron transport chain, inhibition of cell respiration, reduction of ATP synthesis, etc., resulting in insufficient function and affecting cell activity.^{98,218} Dong et al found that the silver metal nanocluster coated with bovine serum albumin (Ag-BSA NC) caused mitochondrial dysfunction mainly by inducing the mitochondrial membrane permeability transition (MPT) and ROS production, damaging mitochondrial respiratory chain, damaging mitochondrial respiratory function, causing oxidative phosphorylation disorder, insufficient ATP synthesis, and decreased cell viability.²¹⁹ Paesano et al found that low-dose CdS QDs did not cause significant damage to mitochondrial DNA, and stress caused an increase in ROS production, activated mitochondrial mediated endogenous apoptosis pathway, and induced cell death, which was mainly cell apoptosis.²²⁰ In this process, mitochondrial membrane potential lost mitochondrial ATP synthesis dysfunction, resulting in insufficient cell function.²²¹ It has been shown that the mitochondrial autophagy induced by cadmium exposure is the main cause of mitochondrial reduction in human normal hepatocyte lines and mouse liver, while the mitochondrial autophagy induced by cadmium is initiated by the mitosis dependent on dynamic 1-like.²²² At the same time, some studies have also shown that cadmium induces mitochondrial autophagy through the activation of PINK1/parkin pathway in the kidney and brain of mice. In this process, ROS induced by cadmium plays a role in the upstream of PINK1/parkin pathway and regulates mitochondrial autophagy.²²³

In addition to mitochondria, endoplasmic reticulum (ER) is also very sensitive to QDs. The changes of ER caused by QDs include morphological changes, functional disorders, ER stress, such as ER swelling, metabolic disorders, protein misfolding, protein synthesis increase or decrease, etc. Yu et al showed that TiO₂ induced the swelling and rupture of ER, the increase of expression level of ER stress-related proteins such as GRP78/BiP, chop and ire-1α in mouse lung cells in a TiO₂ dose-dependent manner.²²⁴ ER stress is considered to be one of the early sensitive indexes of QDs induced cytotoxicity. Chen et al found that when human umbilical vein endothelial cells (HUVECs) were incubated with 120 µM ZnO, the CCK-8 test results showed that there was no significant cytotoxicity. The level of ER stress was determined by the detection of xbp-1s mRNA. Under this dose measurement, the expression of xbp-1s mRNA in 8 hours was higher than that in 4 hours and 12 hours, which means that ER stress was at the highest level at this time point, but there was no significant cytotoxicity at this time.²²⁵ ER stress also participates in the autophagy process induced by QDs,^{60,226} and the damage of QDs to target organs through ER stress pathway may be permanent.²²⁷

QDs enter lysosome mainly through passive diffusion or endocytosis, causing lysosomal structure change. Condello et al showed that ZnO enters lysosome mainly through endocytosis. In the process of interaction with acid environment, it causes lysosome morphological damage, releases a large amount of Zn²⁺, and the part of Zn²⁺ entering the cytoplasm is captured by mitochondria, triggers ROS production, and causes mitochondrial dysfunction and apoptosis.²²⁸

Gene Expression Profile Alterations

QDs can reach the nucleus through the cell membrane.²²⁹ The influence on the nucleus is mainly the influence on genetic material, such as destroying the shape of nucleus, damaging DNA, affecting gene expression, etc.²³⁰ Kumer et al showed that TiO₂ can cause chromosome and DNA damage and induce apoptosis by up regulating Bax/Bcl-2 ratio, mitochondrial membrane potential loss and cytochrome c release.²³¹ Wu Z et al showed that FeAuNPs induced up regulation of Hsp70

protein expression, DNA double-strand break and apoptosis, which is consistent with the above conclusions.²³² Pasquali et al showed that QDs enter the cell by regulating several key nuclear genes, such as TOM5 and FSKI, resulting in an increase in the level of intracellular ROS, a decrease in the ratio of reduced vs oxidized glutathione (GSH/GSSG), a decrease in oxygen consumption, an impact on the morphology and function of mitochondria and cell growth.²³³

At present, the mechanism of gene expression-level change caused by QDs is that histone is an alkaline protein binding to DNA in eukaryote nucleus, and its role in epigenetic regulation, such as gene expression regulation, DNA damage repair, chromatin state regulation, cell differentiation and so on, has been paid more and more attention. The surface of the unmodified QDs is negatively charged, which can accumulate rapidly in the nuclei and nucleoli of living human cells, and preferentially combine with the positively charged core histone to form QD/protein adduct. The formation of adducts may affect the regulation of histones, thus activating, inhibiting genes or changing gene expression level.^{234,235}

Summary and Outlook

At present, QDs have been widely used in in vitro labeling and have a wide range of applications in the field of biomedicine. However, the application of QDs in vivo is still a long process. How to solve the QDs, especially the biocompatibility of the most efficient Cd²⁺ QDs, has become the bottleneck restricting the clinical application of the nanomaterials, and its research has attracted wide attention. Due to the wide variety of QDs, cell lines, and analytical methods, it is difficult to draw a consistent conclusion from the present study. The main reasons are: (1) The synthesis and surface modification of QDs will affect their physical and chemical properties to a great extent and affect their interaction with the cell membrane and the degree of entry into the cells; (2) The sensitivity of different kinds of cells to QDs is different, so the threshold of cytotoxicity is different; (3) At present, cytotoxicity is carried out by detecting cell number, growth curve, degree of apoptosis, cell morphology or metabolic activity. (4) There are many kinds of QDs. At present, the toxicity research is still focused on a few QDs, especially Cd²⁺ QDs. The toxicity study of non-cadmium QDs, such as ternary QDs CuInS₂, is still in its infancy. (5) Data on toxicity of susceptible persons, such as elderly and small, are not complete. (6) A little study on the toxicity of QDs under the disease model. (7) In vivo metabolism and excretory path of QDs are unclear. (8) The influence of QDs on specific biological barrier function needs further study. It also causes great difficulties for different research results, making QDs toxicity research more complicated.

Above summaries have shown that the difference of QDs surface modification, particle size, exposure time and concentration, and the amount of cell intake and the changes in the external environment will lead to the change of QDs toxicity. Therefore, the biological safety evaluation of QDs is needed to consider many factors, and cannot simply be defined as “toxic” or “non-toxic”.

Here is a detailed summary of the current improvements and drawbacks related to the toxicity of quantum dots (QDs), based on recent publications. Improvements: (1) Development of non-toxic QDs: There has been progress in developing heavy metal-free QDs such as carbon dots, graphene dots, silicon dots, and indium phosphide dots, which show lower toxicity. These provide alternatives to toxic Cd- and Pb-based QDs. (2) Surface modifications: Coating QDs with biocompatible polymers, lipids, proteins, or silica can reduce toxicity by preventing leaching of metals, reducing aggregation, and improving stability. Strategies like PEGylation have shown promise. (3) Lower doses: Using lower doses of QDs for bioimaging has helped reduce toxicity. However, the long-term impacts of lower chronic exposures need further study. (4) Organ targeting: Functionalizing QDs to target specific organs or tissues may lower systemic toxicity. But organ clearance and accumulation require more research. Drawbacks: (1) Toxicity mechanisms: The mechanisms underlying QDs toxicity, whether from metal release, reactive oxygen species, aggregation, etc. are still not fully elucidated. (2) Biopersistence: Most current QDs are not biodegradable and remain in the body long-term. Their long-term fate and chronic toxicity remain concerns. (3) Organ accumulation: QDs accumulate in organs like liver, spleen and kidneys. The impacts of long-term retention in organs require further investigation. (4) Variability: QDs toxicity depends on many variables like composition, size, shape, coating, dose and exposure route. More systematic toxicity analyses are needed. (5) Extrapolation to humans: Since most toxicity data come from cell cultures and animal models, extrapolating QD toxicity to humans remains a challenge.

In summary, important progress has been made in improving QD toxicity, but limitations around biopersistence, organ accumulation, variability, and human health impacts mean further research is needed for safer QD-based technologies. The applications versus toxicity are summarized in Table 2.

Table 2 QDs Applications versus Toxicity: Pros and Cons

Pros	Properties	Applications
	Excellent optical properties like bright fluorescence, high quantum yield, and photostability. Tunable fluorescence emission from visible to near infrared. Versatility to conjugate with biomolecules for targeted imaging and delivery. Ability to traverse biological barriers like blood-brain barrier. Potential for multiplexing using different colored QDs.	Ultrasensitive fluorescence imaging, multiplexed biomarker detection, long-term in vivo monitoring. Multiplexed imaging, deep tissue imaging. Cancer imaging, drug delivery, immunoassays. Imaging and drug delivery to brain. Tracking multiple cell populations simultaneously.
Cons	Properties	Toxicity
	Concerns about long-term toxicity, especially for Cd-based QDs. Accumulation and persistence in organs like liver, spleen, kidneys. Non-biodegradability may affect long-term clearance. Release of heavy metal ions (eg Cd ²⁺) induces oxidative stress. Variability in toxicity outcomes. Chronic low-dose exposures and impacts remain unclear. Limited large animal studies and human epidemiological data.	Cd ²⁺ is a known toxic heavy metal. Indicates poor clearance from body. Inorganic QDs harder to break down and clear. Ion leakage major toxicity mechanism. Makes comparisons challenging. Most studies short-term high dose. Extrapolation to humans difficult.

Disclosure

The authors report no conflicts of interest in this work.

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