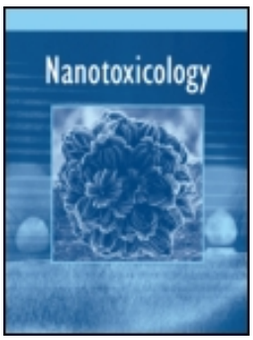

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Comparative tissue distributions of cadmium chloride and cadmium-based quantum dot 705 in mice: Safety implications and applications

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Abstract
Cadmium (Cd) is a component in quantum dot 705 (QD705). Whether QD705 behaves similar to Cd *in vivo* is of great concern. We compared the distributional kinetics of cadmium chloride ($CdCl_2$) and QD705 in mice after intravenous injection. QD705 showed a longer plasma and body retention than $CdCl_2$ and could be detected in the brain during early exposure. While both the liver and spleen demonstrated a constant Cd concentration for 28 days after QD705 injection, it is likely that this represents intact QD705 stored in mononuclear phagocytes. The kidneys showed a time-dependent accumulation of Cd in the QD705-exposed animals. By day 28, Cd in the kidneys from QD705 was 3-fold that of $CdCl_2$. QD705 and $CdCl_2$ have very different kinetics in distribution and metabolism. The long body retention of QD705 in the kidneys may mean that QD705 has even more renal toxicity than $CdCl_2$.

Keywords: *Tissue distribution, quantum dot 705, cadmium, plasma*

Introduction

Quantum dots (QDs) are nanocrystals made of semiconductor materials with unique fluorescent properties. They have a fine particular size (core diameter approximately 2–10 nm) and consist of a metalloid core with an outer cap or shell (Dabbousi et al. 1997). Coatings with different polymeric materials can be applied to the surface of QDs to optimize bioavailability or targeting toward specific sites. Due to the superior photophysical properties of QDs (Akerman et al. 2002), they have great potential as useful tools for biomedical applications. One potential application of QDs is use as optimal fluorophores for *in vivo* biomedical imaging (Larson et al. 2003; Morgan et al. 2005). Other proposed applications include biological labeling and cell targeting (e.g., labeling neoplastic cells) following conjugation with specific bioactive moieties (Voura et al. 2004; Cai et al. 2006).

QDs consisting of a cadmium (Cd) and zinc (Zn) metallic core are most frequently used for biomedical imaging. Currently, the most popular and commercially available QDs are those comprised of cadmium-tellurium (CdTe) or cadmium-selenium (CdSe) cores with outer zinc sulfide (ZnS) shells (Lim et al. 2003). These nanocrystals can be further coated with polyethylene glycol to enhance biological compatibility. Although QDs have attractive and promising usages in many medical applications, limited information is available on the disposition (absorption, distribution, metabolism, elimination) and health consequences of QDs in animals and humans (Hardman 2006; Nel et al. 2006).

Previously, Fischer et al. (2006) reported the pharmacokinetics and tissue sequestration and distribution of QDs in rats with metal analysis (Fischer et al. 2006). The results showed that the half-lives for two kinds of QDs were 39–59 min and the plasma clearance between 0.59 and 1.23 ml/min/kg (Fischer et al. 2006). The uptake of QDs by the liver was 40–90% in 90 min with little retainment in other tissues after dosing (Fischer et al. 2006). The near-infrared (NIR) fluorescence emitted by QD705 may render it useful as a NIR probe for detecting tumor vasculature in

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living subjects (Cai et al. 2006). Recently, we investigated the time-course-related tissue distributions of QD705 *in vivo* for up to six months (Yang et al. 2007; Lin et al. 2008). The inductively coupled plasma mass spectrometry (ICP-MS) analytical technique was used as the basis for tracing and quantifying the Cd component of QD705 in plasma and tissues after a single injection (Yang et al. 2007; Lin et al. 2008). We found that QD705 showed early, rapid accumulation in the spleen and liver. This accumulation is believed to be the result of phagocytotic actions of phagocytes (macrophages in the spleen and Kupffer cells in the liver) in these organs (Douglas et al. 1987). However, the kinetics of QD705 in the kidneys is very different. The distribution of QD705 in the kidneys was slow in the first three days, but dramatically increased with time from 7–28 days. The content of QD705 in the kidneys was high through the six-month study (Lin et al. 2008). The mechanism for the unique kinetics in the kidneys remains unclear.

In another study, we demonstrated that small portions of QD705 in the kidneys actually disintegrated as early as one week after injection (Lin et al. 2009). Therefore, it appears that Cd measured in the tissues of QD705-treated mice via the ICP-MS technique actually represents the sum of free Cd^{2+} and non-disintegrated (intact) QD705 particles. However, Cd^{2+} and QD705 particles are very different in size, surface charge, solubility, and tissue/protein binding capability. Furthermore, their toxicities and mechanisms for tissue distribution are probably very different. It is therefore important to assess and compare the differential kinetics of Cd^{2+} and QD705 particles *in vivo*. In our present study, we compared the plasma and tissue kinetics of cadmium chloride ($CdCl_2$) and QD705 up to 28 days after intravenous injection into the tail vein. This information will be very useful for further understanding the mechanisms of tissue distribution and potential toxicity of intact QD705 *in vivo*.

Materials and methods

The nanoparticles, QD705, used in our experiments are commercially available from Invitrogen (Hayward, CA, USA) as Qtracker 705 non-targeted Quantum Dots. Each particle has a CdTe core and ZnS shell with methoxy-PEG5000 coating. The proportions of each element in QD705 varied slightly in different lots. The test material of QD705 used in the present study contained 42–46% (g/g) Cd, 4–11% (g/g) Se, 0.5–1% (g/g) Te, 14–17% (g/g) Zn, and 11–12% (g/g) S, respectively. The diameter is about 18.5 nm and the molecular weight is 1.5×10^6 g/mole. The fluorescence of QD705 is in the range of 650–750 nm with a maximum emission around 700–715 nm. Each tube of this product contains 200 µl of a 2 µM solution in 50 mM borate buffer, pH 8.3. Cadmium chloride ($CdCl_2$) was purchased from Sigma Co. (St Louis, MO, USA).

Six-week old male ICR mice were used and were purchased from BioLASCO (Taipei, Taiwan). All mice were acclimated for two weeks in the animal facilities at the National Health Research Institutes (NHRI). All animal treatments and the experimental protocol for this study were subjected to the review and approval of the Animal Control Committee at NHRI. Thus, animal handling was in accordance with standard animal husbandry practice and regulations; animals were treated humanely and with regard for alleviation of suffering throughout the study.

All mice in this study were under a 12-h light/dark cycle, at 23 ± 1°C, and 39–43% relative humidity; water and food were available *ad libitum*. At the start of the experiments, the mice were approximately eight weeks old and weighed between 32.9 and 38.7 g. Four mice were randomly selected for each time point in our kinetic studies for QD705 and $CdCl_2$. Three mice were used as controls for the immunohistostaining study. We injected each mouse, via the tail vein, with either 12 µg QD705 or 8 µg $CdCl_2$ in saline; the injection volume was 100 µl/mouse. The amounts of Cd elements in 8 µg $CdCl_2$ and 12 µg QD705 were similar (4.9 µg and 4.6–5.5 µg, respectively). Serial sacrifices (under pentobarbital anesthesia) took place at 1, 4, and 24 h, and 3, 7, 14 and 28 days after dosing. Blood was collected from cardiac puncture at each time point and other tissue samples collected included the liver, lungs, kidneys, spleen, muscle, brain and carcass. We measured and recorded body weights as well as organ weights of each animal. Subsequently, we analyzed and quantified Cd in the plasma as well as tissues. In anticipation of possible further analyses, we saved the carcass individually with proper identification. QD705 analyses were conducted on the basis of quantification of Cd (Mass = 111) utilizing ICP-MS (PerkinElmer, Elan6100, Norwalk, CT, USA) as previously described (Yang et al. 2007).

For immunohistochemical staining, tissues were fixed with formalin and embedded in paraffin. Tissue blocks were cut into sections of 3 µm thickness by a Shandon Finesse 325 Microtome (Thermo, Waltham, MA, USA). Paraffin was removed from the sections by xylene, and the sections were then rehydrated with ethanol and finally distilled water. Sections were microwaved in a citrate buffer (pH 6.0) for 10 min, cooled for 20 min at room temperature and then washed with distilled water. To block endogenous peroxidase activity, sections were incubated with 3% hydrogen peroxide in distilled water for 15 min.

After incubation with anti-metallothionein (MT)-1/2 (DakoCytomation, Carpinteria, CA, USA) overnight at 4°C, a streptavidin-biotin peroxidase method was carried out according to the manufacturer's instructions (BioGenex, San Ramom, CA, USA). Finally, these sections were counterstained with hematoxylin. All tissue sections were examined, evaluated and photographed by a pathologist with a research microscope.

Results

QD705 distribution *in vivo* was quantified by measuring the Cd elements with ICP-MS. The proportions of Cd in QD705 varied slightly in different lots (42–46% g/g). The amounts of Cd elements in 8 μg $CdCl_2$ and 12 μg QD705 were 4.9 μg and 4.6–5.5 μg, respectively. We found that Cd (QD705) in the plasma from QD705-injected mice was detectable at 1 h after injection and gradually decreased with time. No QD705 (as Cd) was detectable after three days (Table I). In contrast, Cd (from $CdCl_2$) in the plasma of $CdCl_2$-injected mice although highly elevated at 1 h, also declined very rapidly. No detectable Cd was found in the plasma 4 h after injection (Table I). The estimated terminal half-life of QD705 in the plasma was calculated to be 16.2 h. However, because of the rapid decline of Cd in the plasma of $CdCl_2$-injected mice, an accurate half-life for $CdCl_2$ in plasma could not be calculated. It has been reported that Cd^{2+} has high affinity to MT in red blood cells (RBC) (Schultz et al. 1996). Therefore, we also compared the distribution of Cd^{2+} and QD705 in the plasma versus that in the RBCs. As presented in Table I, Cd (QD705) was detected in the RBCs of QD705-injected mice for only the first 24 h, but Cd from $CdCl_2$ was persistently detectable in the RBCs of $CdCl_2$-injected mice up to 28 days. It appears that free Cd^{2+} from $CdCl_2$ in the blood has a high binding affinity to RBCs but QD705 (measured as Cd) has a preferential distribution in the plasma.

We further compared the time-dependent distributions of $CdCl_2$ and QD705 in various tissues within 28 days. The liver and kidneys consistently showed the highest accumulations of Cd among all organs in both $CdCl_2$ and QD705-injected mice (Figure 1). Hepatic Cd concentrations in $CdCl_2$-injected mice were approximately two-fold that in QD705-injected mice (Figure 1). While the kinetics for hepatic Cd accumulation was similar between $CdCl_2$ and QD705 administration (initial increase with fairly steady maintenance throughout the 28-day period), the kinetics for renal accumulation of Cd was very different for $CdCl_2$- and QD705-injected animals. Renal Cd concentrations remained constant between 1 and 28 days after $CdCl_2$ injection, but there was a rapid and time-dependent increase in Cd distribution to the kidneys. A three-fold higher level of Cd in the kidneys was noted on day 28 compared to day 3 of exposure (Figure 1). The Cd elements remained low in the lung and muscle of $CdCl_2$-injected as well as QD705-injected mice (Figure 1). However, the Cd elements persistently accumulated in the spleen of QD705-injected mice, but not in $CdCl_2$-injected mice (Figure 1), suggesting that it probably remained as bound Cd within intact QD705 rather than as free Cd^{+2}. Furthermore, the Cd elements were detectable in the brain of QD705-injected mice on the third day after injection. This localization of Cd was not found in the brains of $CdCl_2$-injected mice (Figure 1). This observation also denoted a significant difference between $CdCl_2$ and QD705 in distribution to the central nervous system (CNS).

The liver is a major organ for Cd accumulation in both $CdCl_2$ and QD705-injected mice. Cd concentration reached a plateau within one day. It is well known that free Cd^{2+} induces MT expression in the liver (Tanaka et al. 1987). In our study, MT protein was only slightly elevated in QD705-exposed animals (Figure 2B) compared with controls (Figure 2A). MT protein expression, however, was significantly induced in the liver of $CdCl_2$-injected mice (Figure 2C). It appears therefore that the accumulation of detectable

Table I. Cadmium (Cd) concentration in plasma and RBC of $CdCl_2$ or QD705-injected mice.

	Time after injection (days)						
	0.0416	0.1666	1	3	7	14	28
In plasma (μg/ml)							
QD705	3.188 ± 0.206	3.025 ± 0.191	1.116 ± 0.086	0.048 ± 0.017	ND	ND	ND
$CdCl_2$	53.347 ± 5.504	ND	ND	ND	ND	ND	ND
In RBC (μg/g)							
QD705	0.186 ± 0.027	0.109 ± 0.019	0.212 ± 0.021	ND	ND	ND	ND
$CdCl_2$	0.015 ± 0.005	0.007 ± 0.004	0.010 ± 0.001	0.011 ± 0.004	0.012 ± 0.001	0.008 ± 0.001	0.011 ± 0.003

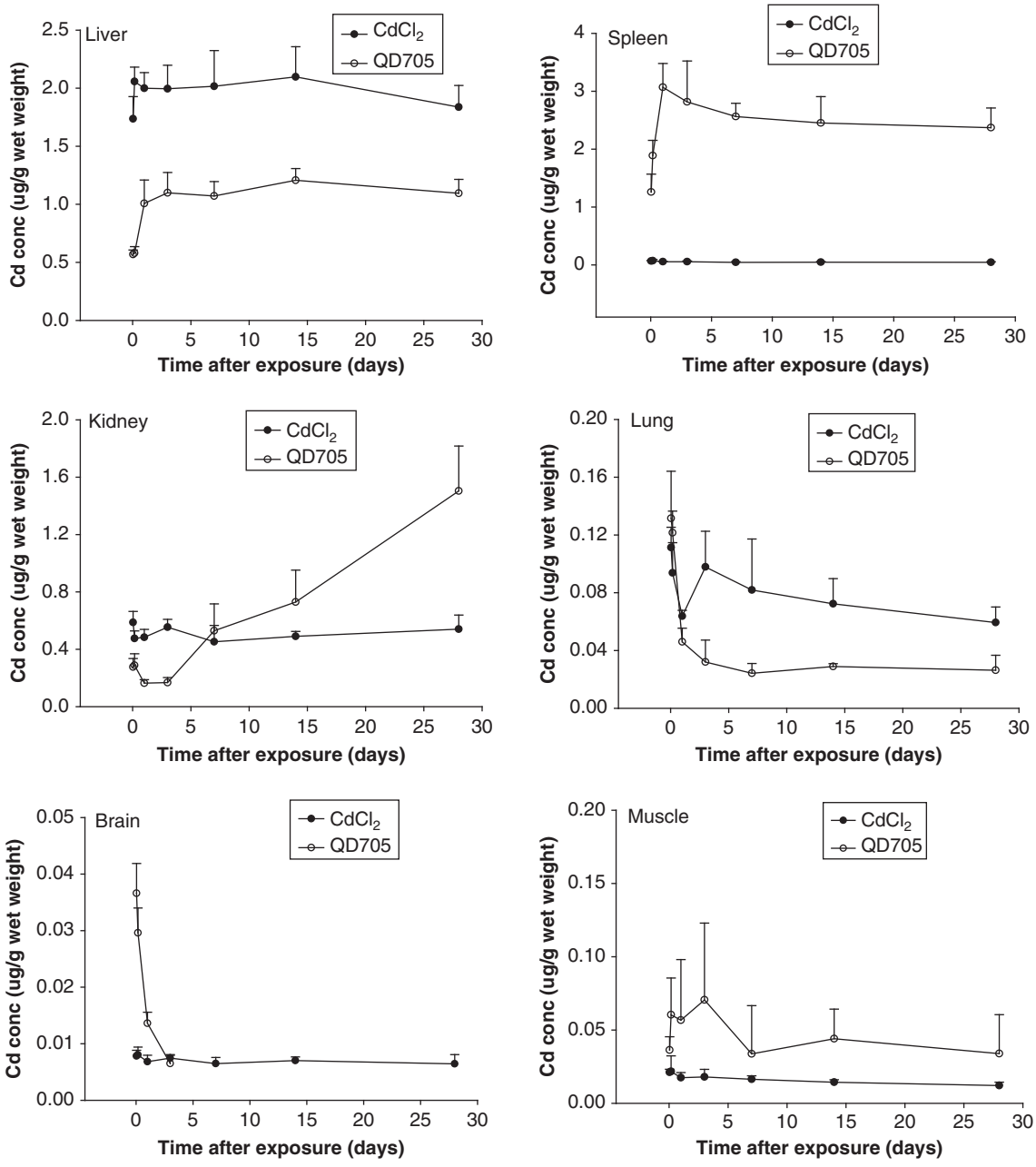

Figure 1. Concentration versus time curves of cadmium (Cd) concentrations in tissues of $CdCl_2$- and QD705-injected mice ($n = 4$ at each time point).

Cd in the liver, as in the spleen, was in the form of bound Cd within the QD705 complex and not free Cd^{2+}.

We also calculated the percentages of Cd elements in individual tissues on the 28th day after injection of $CdCl_2$ or QD705. As shown in Table II, all the injected Cd elements (100.69%) were retained in the bodies of QD705-injected mice. On the other hand, only 55.63% of Cd elements were retained in the bodies of $CdCl_2$-injected mice (Table II). This observation also denotes that Cd can be effectively eliminated (almost 50%) from the body in 28 days. Similar results have been reported that show that approximately 60% of intravenously or intraperitoneally injected Cd^{2+} are retained in the bodies of mice within 1–2 weeks after injection (Liu and Klaassen 1996; Liu et al. 1996). Complete and long retention of QD705 constitutes reasonable concerns about eventual Cd leakage or release from retained QD705, leading to undesirable risks.

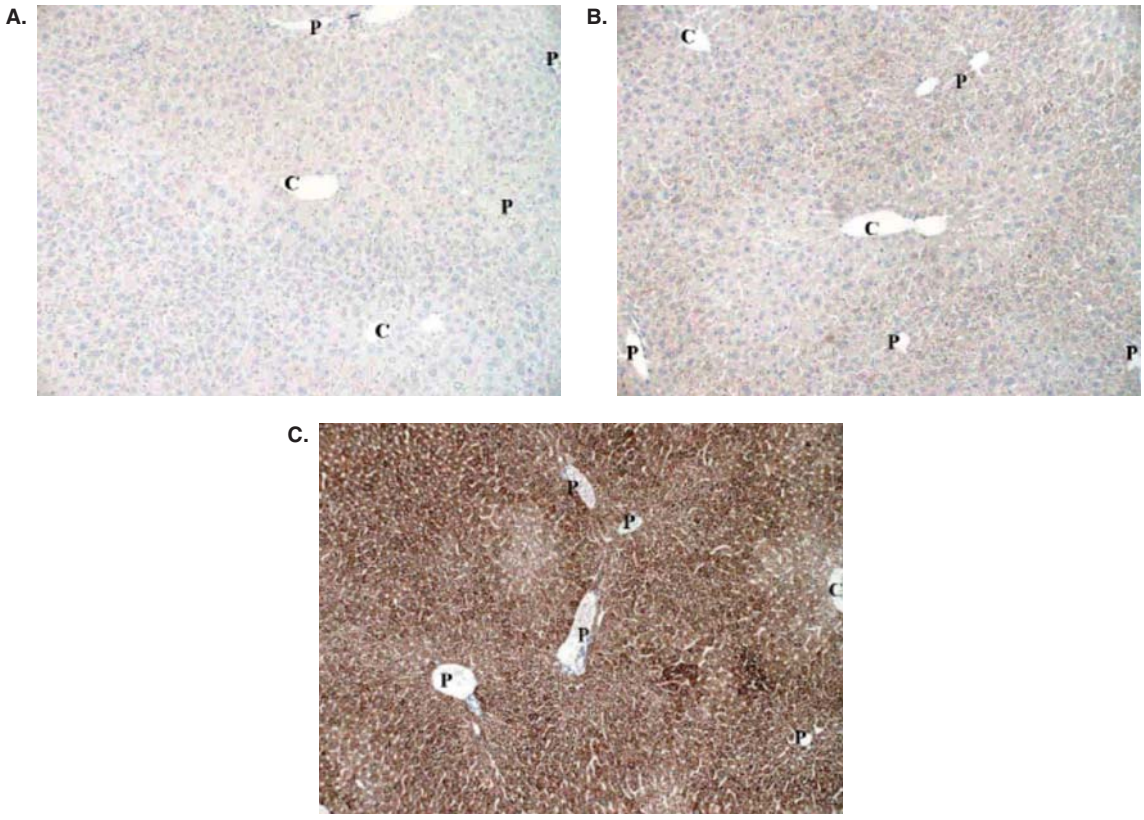

Figure 2. Immunohistostaining for metallothionein protein in the liver. (A) Control, (B) QD705 and (C) $CdCl_2$-injected mice on day 1. P, portal vein; C, central vein.

Table II. The proportion of Cd elements in tissues of $CdCl_2$- or QD705-injected mice at day 28.

	(Percentage of injected dose)	
Tissues	QD705	$CdCl_2$
Kidney	16.55 ± 1.25	3.75 ± 0.57
Liver	36.69 ± 3.89	43.49 ± 3.80
Spleen	5.46 ± 0.78	0.06 ± 0.01
Brain	0.00 ± 0.00	0.04 ± 0.01
Lung	0.11 ± 0.03	0.16 ± 0.03
Plasma	0.01 ± 0.00	0.00 ± 0.00
RBC	0.02 ± 0.01	0.22 ± 0.07
Carcass	41.68 ± 4.03	7.92 ± 0.73
Urine*	0.14 ± 0.01	0.00 ± 0.00
Feces*	0.00 ± 0.00	0.00 ± 0.00
Total recovery	100.69 ± 1.84	55.63 ± 2.80

*Urine and feces were collected between day 27 and 28.

Discussion and conclusion

QDs were developed as novel nanomaterials with promising biomedical applications (Akerman et al. 2002; Larson et al. 2003; Morgan et al. 2005). Various studies have been conducted to better understand the usefulness of QDs in pharmacological applications and to characterize their pharmacological behavior *in vivo* (Medintz et al. 2005; Popescu and Toms 2006). While different approaches have been attempted to determine QDs qualitatively or quantitatively *in vivo*, ICP-MS, which tracks the Cd elements in QDs, remains the most sensitive method to quantify their biological fate (Yang et al. 2007). However, since ICP-MS tracks Cd in general, it is still unclear if the Cd tracked is Cd in intact QDs or free Cd^{2+} leaked out to the tissues. It is therefore important to better define the comparative kinetics between free Cd^{2+} and Cd in QDs. This information will help to differentiate the nature of Cd (as a free ion or bound compound) which is distributed or accumulates in various tissues and organs. The liver is the major organ for accumulation of both Cd^{2+} and QD705, although the mechanisms may be different. Cd^{2+} is known to induce expression of MT in hepatocytes. The rapid and high induction of hepatic MT in animals treated with $CdCl_2$ certainly reflects that free Cd^{+2} is generated from $CdCl_2$ which in turn induces MT production in the hepatocytes (Klaassen

and Liu 1997). The accumulation of Cd elements from QD705 exposure, on the other hand, does not induce any significant amount of MT production, signifying that little free Cd^{+2} ions are present in the liver from QD705 exposure. In our previous study, we reported that the red fluorescence of intact QD705 was primarily located in the lining of the hepatic sinusoids where Kuppfer cells (hepatric marcophages) are located (Yang et al. 2007). Particulates with an average size below 7 μm are known to be readily taken up by macrophages in the mononuclear phagocytic system (MPS) (Lenaerts et al. 1984). Therefore it is reasonable to believe that accumulation of Cd in the liver is primarily due to the uptake and accumulation of QD705 by the hepatic macrophage system. Since intact or degraded QD705 might retain in macrophages, no induction of MT in the hepatocytes is solicited. Likewise, the spleen is also enriched with sinusoidal flows (Groom et al. 1991) and the MPS where the QD705 can be easily trapped and engulfed by macrophages. Indeed, rich autofluorescence of QD705 (intact QD705) has been reported in the spleen after intravenous injections of QD705 (Yang et al. 2007). This macrophagic 'storage' of QDs will retain these particles within the macrophages for a prolonged period of time without elimination.

The kidneys present the most interesting distributional kinetics for QDs. The accumulation of Cd in the kidneys via $CdCl_2$ exposure in our study was consistent with that described in the literature. The Cd accumulated in the kidneys is believed to be primarily via liver transfer as Cd-MT complex (Klaassen 2008). However, the kinetics of QD705 accumulation in the kidneys appeared to be biphasic: early reduction followed by tremendous time-dependent accumulation. In the first phase (1 h to 3 days), QD705 slightly decreased with time, which coincided with the reduction of plasma Cd during this time period. The second phase constituted active distribution or redistribution of QD705 to the kidneys. The 'Cd' in the kidneys may come from three possible sources: (1) Increased primary distribution of intact QDs from the plasma or redistribution of intact QD705 from other bodily tissues with time; (2) transfer of Cd as Cd-MT complex from the liver (Klaassen 2008); and (3) increased free Cd^{2+} released from QD705 within the renal tissue (Lin et al. 2009). Since most QD705 is believed to be 'stored' in the macrophages and the Cd level in the liver remained quite constant throughout our study with a significant rise in Cd content in the kidneys, transfer of Cd from the liver is unlikely. Our previous study indicated that there was a reduction of Cd elements (probably as QD705) in other body parts coinciding with the increase of the renal Cd level (Yang et al. 2007; Lin et al. 2009), so gradual redistribution of QD705 from other tissues to the kidneys is likely. Furthermore, our recent study showed an increase in MT expression in the renal tissues with time, which also indicates that the QD705 distributed to the kidneys may be degraded in the renal tissues with release of free Cd^{2+}. All these findings further affirm that the kidneys are the target organ for QD705 accumulation and possible toxicity.

The short-lasting elevation of Cd elements in the brain after QD705 exposure is also an intriguing observation. It is well known that free Cd^{2+} (from $CdCl_2$) does not cross the blood brain barrier (BBB). The extremely low levels of Cd detected in the brains of our $CdCl_2$-treated animals may only represent RBC-bound Cd within the cerebral vasculature. However, QD705, because of its nano size or organic coating, apparently may retain on the intra-luminal side of the brain vessels. The short-lasting distribution of QD705 in the brain (only 72 h) is interesting and may have important implications. Cai et al. (2006) indicated the potential application of QD705 in targeting tumor vasculature *in vivo*. The short-lasting entrance of QD705 into the vessels of the brain may allow QD705 to be useful in these applications with minimal toxicity to the nervous system. This potential use of QD705 deserves further investigation.

In summary, our present study has provided a comparative examination of the blood and distributional kinetics of Cd in various tissues from $CdCl_2$ and QD705 exposure. It is clear that $CdCl_2$ and QD705 behave very differently in the biological system. One certainly cannot equate the metabolism, biological fate, and toxicity of QD705 with those of $CdCl_2$. Our study further affirms that the kidney is the target site of QD705 accumulation and potential toxicity. On the other hand, the distribution of QD705 to the CNS with a short retention time (within 3 days) is a potentially inspirational finding. Cai et al. (2006) demonstrated that subcutaneously inoculated glioblastoma tumors could be visualized with peptide-labeled QD705 via NIR fluorescence imaging. Thus, QD705 may become useful for vascular imaging in the CNS. With its short retention time, QD705 would probably remain intact without toxicity to the CNS. Nevertheless, our present study provided the first comparative *in vivo* study of QD705 and $CdCl_2$. Information provided in this study should be valuable for the safety assessment of QDs as well as selective alternative applications of QDs.

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