

## Supplementary information

# Quantum dots cause acute systemic toxicity in lactating rats and growth restriction of offspring

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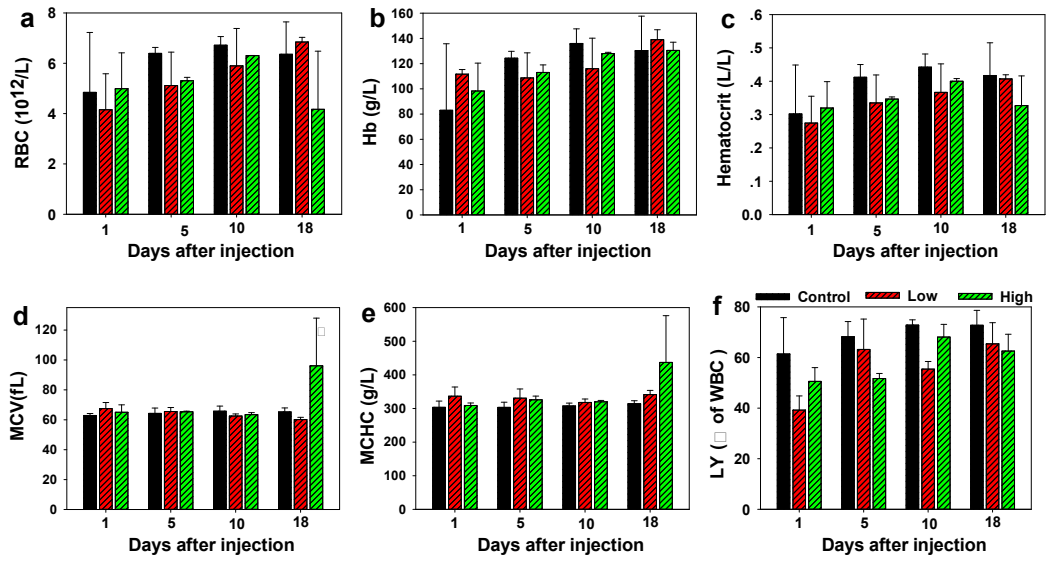


Fig S1 whole blood tests of maternal rats treated with 5 nmol (high) or 1 nmol (low) QDs and vehicle control. a-h) results exhibit mean and standard deviation of red blood cells count, RBC (a); hemoglobin, Hb (b), Hematocrit (c), mean corpuscular volume, MCV (d), mean corpuscular hemoglobin concentration, MCHC (e); lymphocyte, LY (f). n=3.

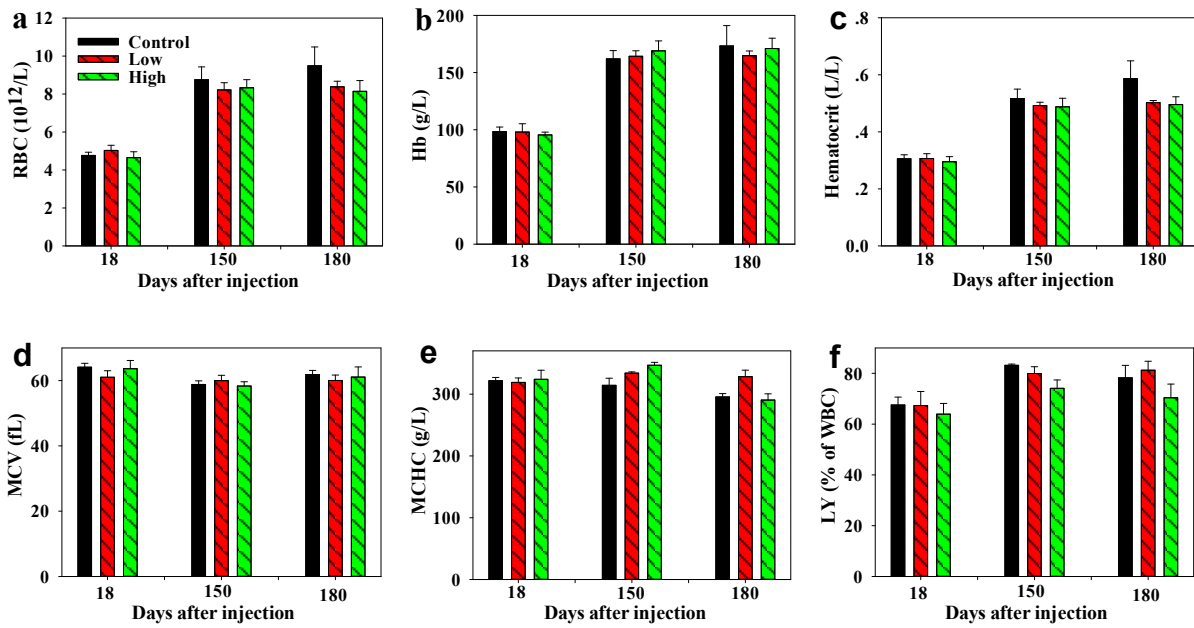


Fig S2 Whole blood tests of offspring in 5 nmol QDs group (high) or 1 nmol QDs group (low) and vehicle control at 18, 60, 120, 150 and 180 dpi. a-f) results exhibit mean and standard deviation of red blood cells count, RBC (a); hemoglobin, Hb (b), Hematocrit (c), mean corpuscular volume, MCV (d), mean corpuscular hemoglobin concentration, MCHC (e); lymphocyte, LY (f). n=3.

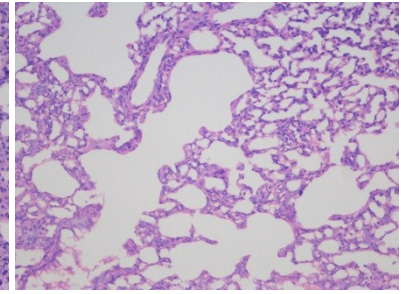
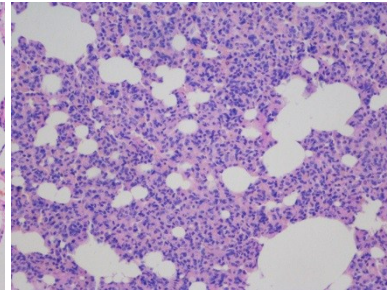
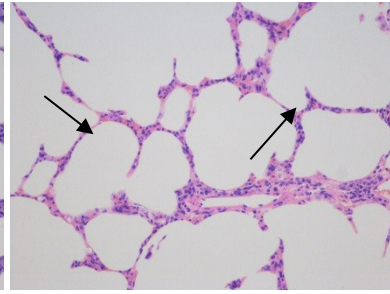
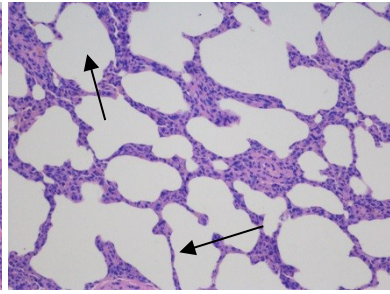
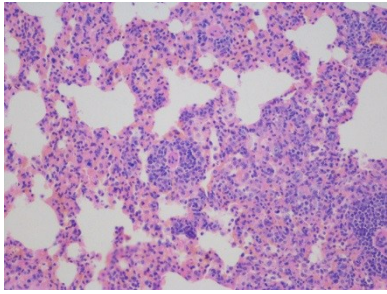
Control

D1 (Low)

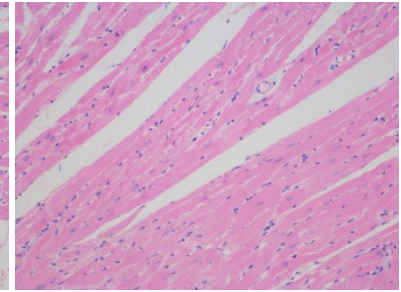
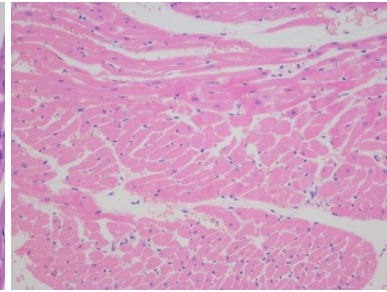
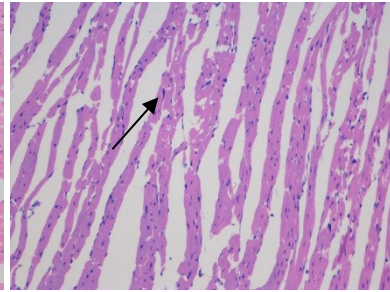
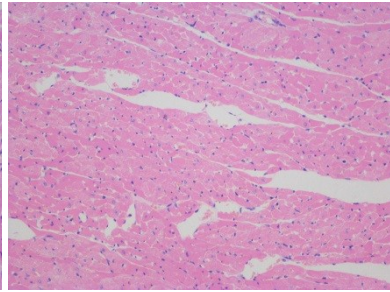
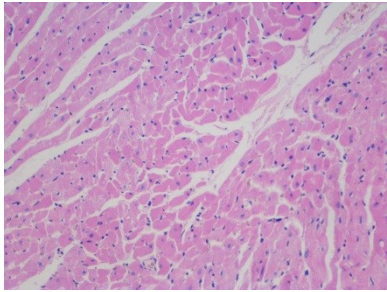
D1 (High)

D18 (Low)

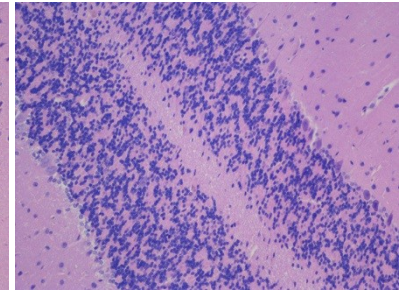
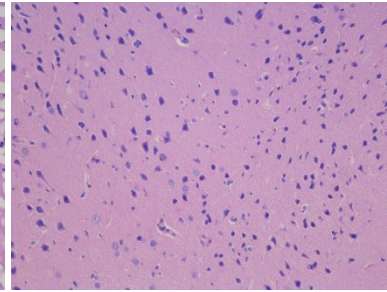
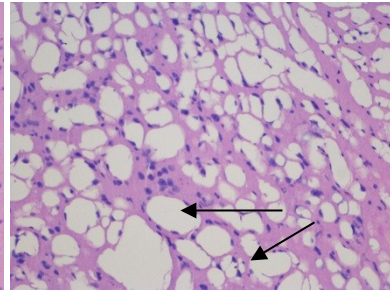
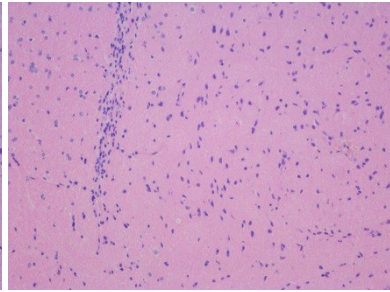
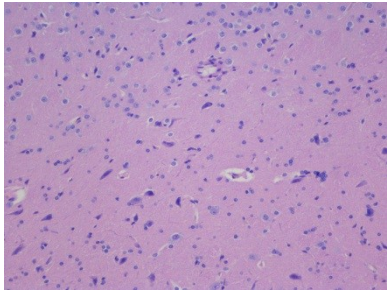
D18 (High)



Lung



Heart



Brain



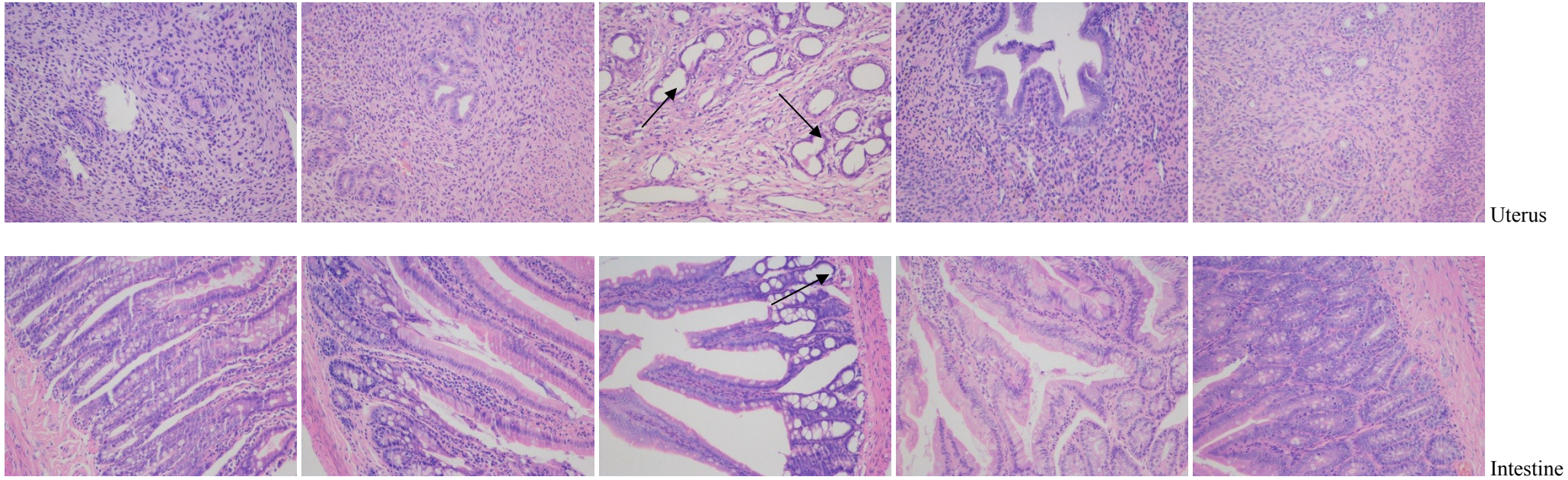


Figure S3 Histological images of maternal rat's lung, heart, brain, uterus, and intestine on 1 (D1) and 18(D18) dpi. Arrows indicate structural damages on both treated rats organs.

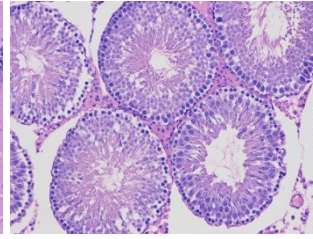
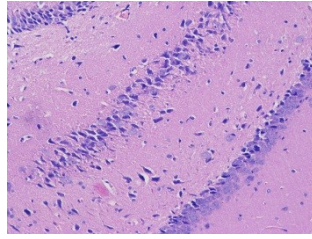
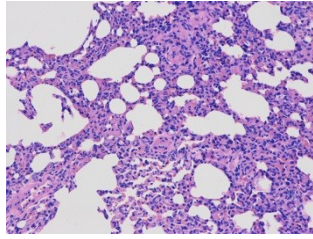
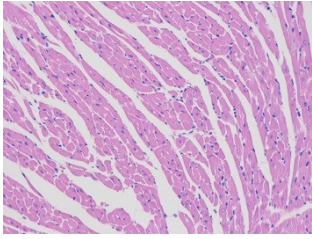


Heart

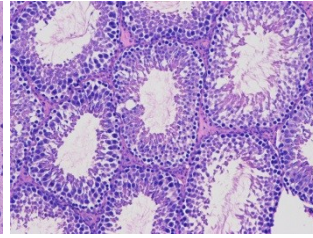
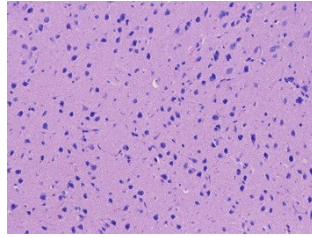
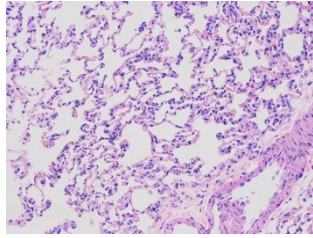
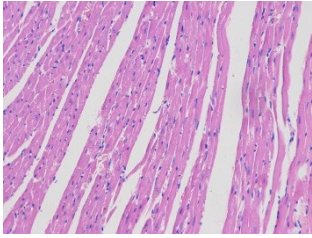
Lung

Brain

Testis



Control 60 d



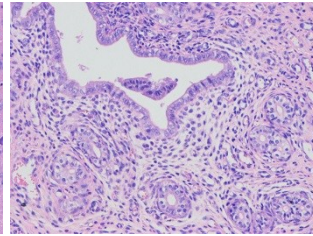
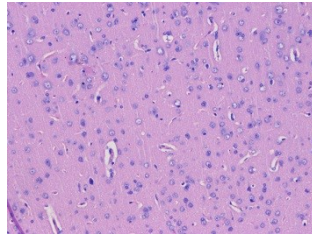
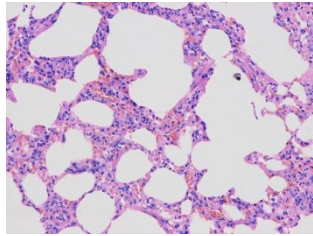
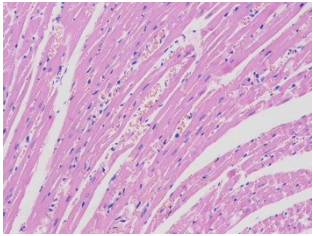
Low 60 d

Heart

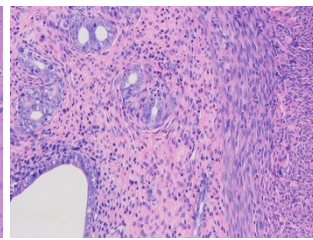
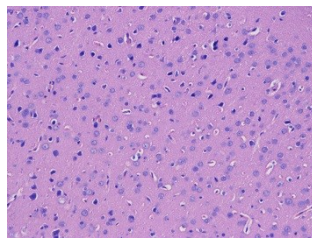
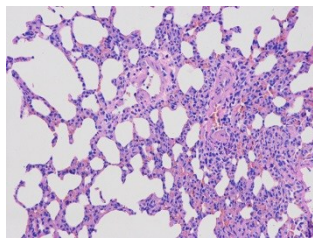
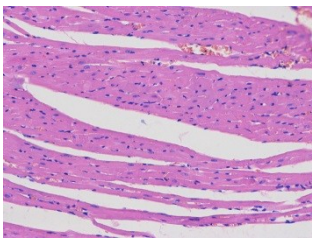
Lung

Brain

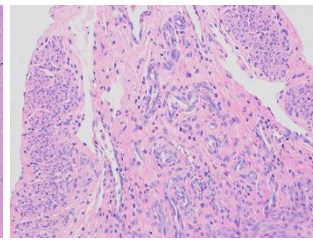
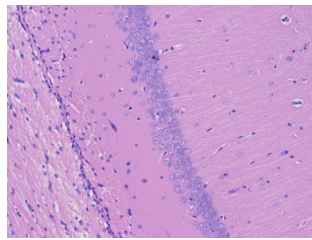
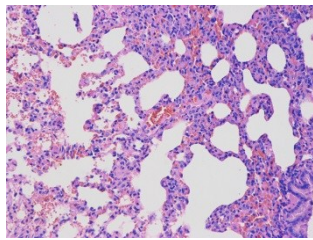
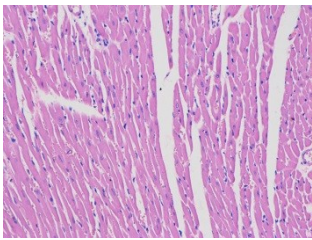
Uterus



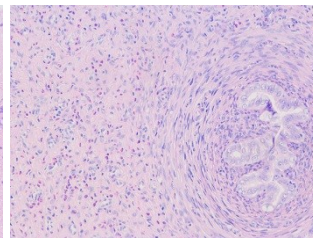
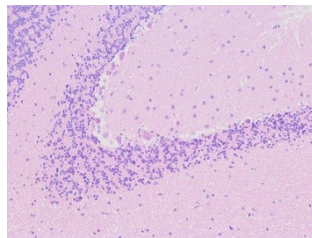
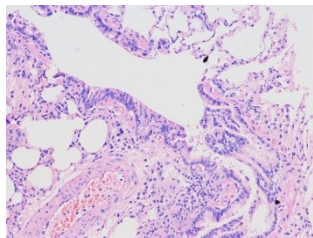
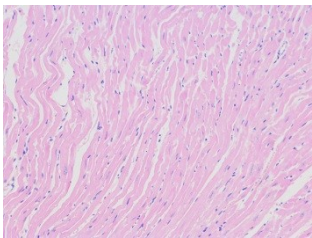
Control 120 d



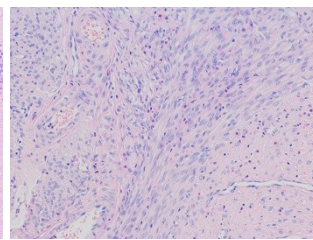
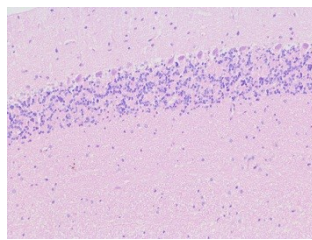
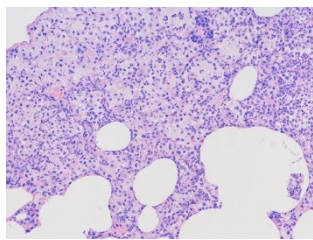
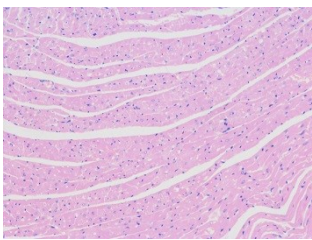
Low 120 d



High 120 d

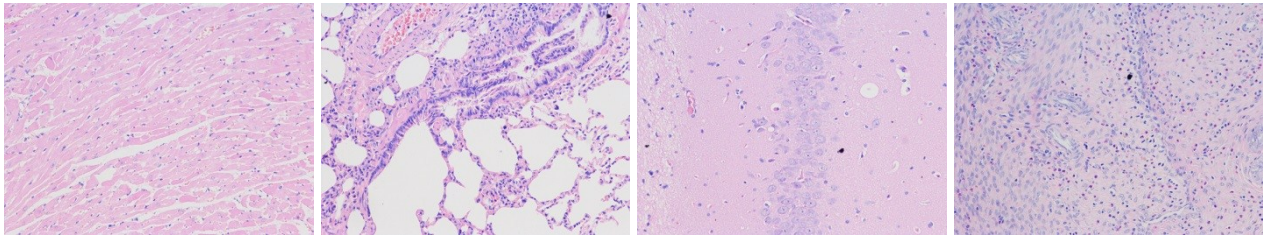


Control 180 d



Low 180 d





High 180 d

Figure.S4 Histological images of offspring's heart, lung, brain, testis and uterus on 60, 120 d, and 180 d post injection.

Table S1 Summary of the applied doses and delivered doses of QDs in classical QDs toxicological studies in animals over the past decade except one silver study as it is very relevant to our study.

NPs	Sizes (nm)	models	Administrated routes and doses	Examined organ/tissues	Delivered doses in organ/tissues	References (Journal and year)
CdSe/ZnS Quantum dots (QDs)	4.36-8.45	Rats	i v. 3 nmol/rat	Liver, spleen	4.5-26.5% of injected dose (ID) in liver, 0.5-6.3% ID in spleen.	Nature Biotechnology 2007 [1]
CdSe/ZnS QDs	12	Mice	0.48 nmol = 8.5 mg/kg (170 µg Cd)	Liver and spleen	Fluorescence examination	Nano Letter 2009 [2]
CdSe/ZnS QDs	13-21 nm	Rats	i v. 2.5 nmol, 5 nmol and 15 nmol per rat	Liver and spleen	920-1690 ng/g in liver 500-2100 ng/g in spleen.	Small 2010 [3]
CdTe QDs	1.67-4.20	Pregnant mice	i v. Containing 20, 50, 80, and 125 µg Cd QDs	Liver and spleen	5849 ng/g in liver, 4900 ng/g in spleen	Small 2010 [4]
CdSe/CdS/ZnS QDs	7-8	rhesus macaques	i v. 25 mg/kg	Liver and spleen	18000 ng/g in liver, 63000 ng/g in spleen	Nature Nanotechnology 2012 [5]
CdTe QDs	2	Mice	i v. 0.2 and 2 nmol per mouse	Testes	100-750 ng/g in testes	Biomaterials 2016 [6]
Sliver NPs	100, 50, 10	Lactating mice	i v. 1.5 mg/kg	Breast milk and blood	100-300 ng/g in milk, 100-400 ng/g in blood.	ACS Nano 2016 [7]
CdSe/CdS/ZnS QDs	7-8	Mice	i v. 25 mg/kg	Not mentioned	Not mentioned	Nanotheranostics 2017 [8]
CdSe/ZnS QDs, CdSe QDs	15, 20	Mice	i v. 0.1 nmol per mouse	Uterus, placenta	107 ng/g in uterus, 352 ng/g in placenta	Journal of Hazardous Materials 2016 [9]
CdSe/ZnS QDs	20	Lactating rats	i v. 1 nmol and 5 nmol per rat	Milk, blood, liver and spleen	50-200 ng/g in milk, 0-600 ng/g in blood, 2353-11495 ng/g in liver, 931-14566 ng/g in spleen	This study

## References

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3. Hauck TS, Anderson RE, Fischer HC, Newbigging S, Chan WC. In vivo quantum-dot toxicity assessment. *Small.* 2010;6(1):138-144
4. Chu M, Wu Q, Yang H, et al. Transfer of quantum dots from pregnant mice to pups across the placental barrier. *Small.* 2010;6(5):670-678.
5. Ling Ye, Ken-Tye Yong, Liwei Liu, et al. A pilot study in non-human primates shows no adverse response to intravenous injection of quantum dots. *Nat Nanotechnol.* 2012;7:453-458.
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7. Morishita Y, Yoshioka Y, Takimura Y, et al. Distribution of Silver Nanoparticles to Breast Milk and Their Biological Effects on Breast-Fed Offspring Mice. *ACS Nano*. 2016;10(9):8180-91.
8. Liu J, Yang C, Liu J, et al. Effects of Cd-based Quantum Dot Exposure on the Reproduction and Offspring of Kunming Mice over Multiple Generations. *Nanotheranostics*, 2017; 1(1): 23-37.
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**Table S2.** The visceral index of organs of dams following intravenous injection of high and low doses QDs. D1 and D18 refer to collection of dam organ on post-injection in day 1 and day 18. These results show mean and standard deviation, n=3 or 6. \*P < 0.05 and \*\*P < 0.01 versus the control group.

	<b>BW (g)</b>	<b>Liver (mg/g)</b>	<b>Spleen (mg/g)</b>	<b>Kidney (mg/g)</b>	<b>Lung (mg/g)</b>	<b>Heart (mg/g)</b>	<b>Brain (mg/g)</b>
Low (D1)	345.77±7.45	39.99±4.56	2.36±0.15	5.66±1.81	5.73±0.05	5.40±0.99	5.54±0.17
High (D1)	326.71±21.96	51.28±0.61	5.20±2.03**	7.74±0.42	7.16±2.20	4.23±0.61	5.93±0.46
Low (D18)	362.60±18.80	51.80±6.36	2.17±0.23	6.88±0.50	5.42±0.28	4.77±0.75	4.57±0.72
High (D18)	360.23±10.17	49.20±1.82	5.12±1.36**	6.00±1.59	4.91±0.91	4.44±0.20	5.41±0.31
Control	362.17±22.53	49.37±6.91	1.96±0.18	6.48±1.56	5.07±0.14	4.76±0.80	4.75±0.77

**Table S3.** Serum biochemical indicators of maternal rats treated with 5 nmol (high) or 1 nmol (low) QDs and vehicle control. Abbreviations: alanine aminotransferase, ALT; aspartate aminotransferase, AST; total bilirubin, TBIL; direct bilirubin, DBIL; total protein, TP; albumin, ALB; globulin, GLB; the ratio of albumin to globulin, A/G; gamma glutamyl transaminase, GGT; alkaline phosphatase, ALP; creatinine, CRE; blood urea nitrogen, BUN; and urea, UA, n = 3. \*P < 0.05 and \*\*P < 0.01 versus the control group.

Parameters	D1			D5			D10			D18		
	Control	Low	High	Control	Low	High	Control	Low	High	Control	Low	High
ALT (U/L)	62±11.22	62.66±17.30	1613.5±180.5**	74.66±10.35	66.5±14.28	176.5±14.28**	87.5±0.41	103.5±19.18	75.5±11.84	89±8.98	112.33±12.07	84.5±11.02
AST (U/L)	201.67±49.40	408±3*	11435±875**	224±23.36	214.5±11.02	832±67.77**	194.5±11.0	312.67±16.12	214.5±52.66	197±8.98	166±22.72	312.5±120.43
TBIL (µmol/L)	0.46±0.04	0.56±0.32	103.1±67.9**	0.43±0.04	0.4±0.08	5.2±1.38**	0.4	0.5±0.12	0.5±0.08	0.35±0.04	0.5±0.14	0.35±0.04
DBIL (µmol/L)	0.1	0.1	15.85±6.85**	0.1	0.2±0.08	2±0.41**	0.1	0.1	0.15±0.04	0.1	0.13±0.04	0.1
TP (g/L)	75.8±5.50	58.5±12.19*	54.15±8.35**	77.23±3.24	69.15±0.04	52.87±4.73**	72.6±0.33	77.73±5.19	78.5±0.65	75.3±3.51	63.87±1.33	74.25±1.10
ALB (g/L)	25.4±5.15	18.3±3.89*	19.3±1.9	26.03±4.48	22.1±0.08	18.1±1.07*	26±0.73	26.4±2.40	23.1±0.16	23.75±1.68	23.86±0.52	19.45±3.63
GLB (g/L)	50.4±5.55	40.2±8.43	34.85±6.45*	51.2±4.01	47.05±0.12	34.76±3.84*	46.6±0.41	51.33±2.99	55.4±0.81	51.55±5.18	40±1.02	54.8±4.74
A/G	0.52±0.13	0.45±0.03	0.56±0.05	0.52±0.11	0.47±0.09	0.52±0.04	0.56±0.02	0.51±0.02	0.42±0.01*	0.47±0.08	0.59±0.02*	0.37±0.09
GGT (U/L)	1.33±0.47	1	7±1**	1	2	6.66±2.94**	1	1.67±0.41	1.5±0.41	1	1.33±0.41	1
ALP (U/L)	302.33±86.73	170.7±51.18*	478.5±20.5*	375±82.93	332.5±15.93	514.67±52.39*	409±40.82	423.5±28.17	469.5±181.67	616.5±61.23	422.5±117.1	454±209.02
CREA (µmol/L)	44.63±8.74	35.33±12.41	51.8±1.6	38.96±1.69	27.95±2.5**	37.46±3.31	30.35±7.63	33.4±5.49	30.5±3.76	36.1±2.12	36.2±5.3	29.25±5.59
BUN (mmol/L)	8.16±0.98	5.63±1.54*	8.85±2.25	8.9±0.37	6.7±0.89	11.86±4.43	9.45±0.29	10.37±1.13	8.7±0.48	8.5±0.57	9.03±0.93	9.1±1.39
UA (µmol/L)	214±50.64	221.33±73.28	150±29	186.6±54.42	270.5±24.9*	158±40.72	219±69.40	203.33±24.96	211.5±7.76	163±18.78	249±44.45*	199±8.16

**Table S4** Cadmium concentrations in dams consecutive blood and feces samples from day 1 (D1) to day 18 (D18) after injection. ( $\mu\text{g/g}$ )

	<b>Control</b>	<b>Low (D1)</b>	<b>High (D1)</b>	<b>Low (D5)</b>	<b>High (D5)</b>	<b>Low (D10)</b>	<b>High (D10)</b>	<b>Low (D18)</b>	<b>High (D18)</b>
<b>Blood</b>	-0.024 $\pm$ 0.004	-0.044 $\pm$ 0.040	0.017 $\pm$ 0.008	-0.035 $\pm$ 0.023	0.028 $\pm$ 0.006	-0.070 $\pm$ 0.019	0.057 $\pm$ 0.017	-0.034 $\pm$ 0.027	0.064 $\pm$ 0.019
<b>feces</b>	0.071 $\pm$ 0.011	0.140 $\pm$ 0.027	2.057 $\pm$ 0.964	0.111 $\pm$ 0.009	0.082 $\pm$ 0.026	0.037 $\pm$ 0.031	0.015 $\pm$ 0.009	0.07 $\pm$ 0.013	0.016 $\pm$ 0.136

**Table S5** Cadmium concentrations in maternal tissues at day 1 (D1) and day 18 (D18) after injection.

<b>QDs</b>	<b>Heart (<math>\mu\text{g/g}</math>)</b>	<b>Liver (<math>\mu\text{g/g}</math>)</b>	<b>Spleen (<math>\mu\text{g/g}</math>)</b>	<b>Lung (<math>\mu\text{g/g}</math>)</b>	<b>Kidney (<math>\mu\text{g/g}</math>)</b>	<b>Brain (<math>\mu\text{g/g}</math>)</b>	<b>Stomach (<math>\mu\text{g/g}</math>)</b>	<b>Intestine (<math>\mu\text{g/g}</math>)</b>	<b>Breast(<math>\mu\text{g/g}</math>)</b>	<b>Uterus (<math>\mu\text{g/g}</math>)</b>
<b>Low (D1)</b>	0.045 $\pm$ 0.028	2.353 $\pm$ 1.737	0.931 $\pm$ 0.583	0.545 $\pm$ 0.417	0.707 $\pm$ 0.311	0.020 $\pm$ 0.015	0.082 $\pm$ 0.075	0.191 $\pm$ 0.087	0.053 $\pm$ 0.018	0.087 $\pm$ 0.079
<b>High (D1)</b>	0.398 $\pm$ 0.114	11.495 $\pm$ 6.885	14.566 $\pm$ 5.988	11.614 $\pm$ 5.503	5.406 $\pm$ 3.640	0.048 $\pm$ 0.007	0.251 $\pm$ 0.097	0.969 $\pm$ 0.554	0.474 $\pm$ 0.042	0.600 $\pm$ 0.359
<b>Low (D18)</b>	0.165 $\pm$ 0.019	4.493 $\pm$ 0.599	11.825 $\pm$ 1.401	0.966 $\pm$ 0.344	12.509 $\pm$ 0.437	0.019 $\pm$ 0.006	0.109 $\pm$ 0.010	0.447 $\pm$ 0.056	0.163 $\pm$ 0.043	0.532 $\pm$ 0.042
<b>High (D18)</b>	0.423 $\pm$ 0.047	10.374 $\pm$ 1.364	14.224 $\pm$ 1.885	2.505 $\pm$ 0.383	42.313 $\pm$ 1.684	0.044 $\pm$ 0.005	0.287 $\pm$ 0.050	0.780 $\pm$ 0.117	0.332 $\pm$ 0.106	1.118 $\pm$ 0.058
<b>Control</b>	-0.024 $\pm$ 0.001	-0.009 $\pm$ 0.001	-0.074 $\pm$ 0.008	-0.017 $\pm$ 0.002	0.047 $\pm$ 0.015	-0.023 $\pm$ 0.001	-0.008 $\pm$ 0.007	0.174 $\pm$ 0.009	-0.043 $\pm$ 0.001	-0.029 $\pm$ 0.006



**Table S6** Cadmium concentrations in breast milk samples at day 2 (D2), day 9 (D9) and day 18 (D18) after injection. n=3.

Milk (ng/g)	D2	D9	D16
Control	5.64±0.55	8.99±2.52	19.55±5.55
Low	29.55±17.72*	11.82±1.02	39.28±8.03*

D2: P=0.023, D9: P=0.215, D16: P=0.015

**Table S7** Cadmium concentrations in offspring tissues from day 1 (D1) and day 180 (D180) following the maternal exposure to high and low dose QDs. n=4. \*P < 0.05 and \*\*P < 0.01 versus the control group. ND refers to not detected.

QDs	Breast(ng/g)	Stomach (ng/g)	Intestine (ng/g)	Liver (ng/g)	Kidney (ng/g)	Spleen (ng/g)
Low (D1)	52.79±18.47	6.15±1.94	6.53±1.18	2.46±0.23	5.12±2.2	4.01±2.1
High (D1)	473.78±42.08	8.64±2.67	7.78±2.61	6.83 ± 2.99	6.33±0.54	3.28±0.12
Control (D1)	< 0	6.05±3.02	6.93±3.90	3.76±0.36	4.86±0.45	4.10±0.70
Low (D5)	ND	7.38±1.84	94.74±0.57*	2.82±0.50	3.62±1.04	1.72±0.5
High (D5)	ND	22.72±13.94*	130.25±23.17**	8.36±2.00	7.87±0.88	2.26±0.78
Control (D5)	ND	9.25±0.36	60.15±13.56	6.34±1.20	5.78±0.72	1.98±0.28
Low (D10)	ND	13.19±3.65	168.23±56.23*	4.28±0.71	4.48±1.00	6.52±1.3
High (D10)	ND	19.99±6.56*	198.27±43.76**	4.22±1.43	8.65±0.11	4.82±0.25
Control (D10)	ND	10.23±1.89	103.24±33.25	3.68±0.35	7.92±1.62	3.89±0.63
Low (D18)	162.55±42.79	9.17±0.02	234.72±78.03*	5.12±0.91	6.66±0.69	4.52±0.44
High (D18)	332.33±105.96	10.40±0.60	267.32±56.92**	5.82±0.96	9.12±0.58	2.67±0.98
Control (D18)	< 0	9.83±0.52	140.23±25.68	4.34±0.83	8.98±1.35	3.46±0.55
Low (D60)	ND	ND	131.39±39.45	3.99±0.24	13.12±2.82	2.77±0.21
High (D60)	ND	ND	ND	ND	ND	ND
Control (D60)	ND	ND	126.34±31.25	4.68±0.58	11.63±3.21	2.89±0.38
Low (D120)	ND	ND	29.17±6.79	6.46±0.31	15.16±0.79	1.37±0.01
High (D120)	ND	ND	13.30±7.75	5.63±0.14	16.23±0.70	1.63±0.26
Low (D180)	ND	ND	83.12±25.66	10.41±0.12	31.55±2.51	2.25±0.01
High (D180)	ND	ND	77.78±15.80	14.34±1.03	35.50±7.37	4.47±1.86
Control (D180)	ND	ND	50.34±3.97	11.71±3.34	37.51±1.26	2.99±0.78

**Table S8.** The visceral index of organs of offspring following the maternal exposure to high and low dose QDs. D60, D120 and D180 refer to collection of offspring organ on post-injection in day 60, 120 and day 180. These results show mean and standard deviation, n=4. \*P < 0.05 and \*\*P < 0.01 versus the control group.

		<b>BW (g)</b>	<b>Liver (mg/g)</b>	<b>Spleen (mg/g)</b>	<b>Kidney (mg/g)</b>	<b>Lung (mg/g)</b>	<b>Heart (mg/g)</b>	<b>Brain (mg/g)</b>	<b>Testis/Uterus (mg/g)</b>
Male	Control (D60)	295.86±27.89	44.05±1.14	2.21±0.32	8.30±0.24	4.69±0.48	4.11±0.49	4.84±0.21	9.74±0.94
	Low (D60)	266.62±9.66*	51.58±1.08	2.82±0.09	7.95±0.20	5.95±0.64	5.01±0.62	5.64±0.27	9.21±0.36
Female	Control (120)	275.85±18.22	37.39±2.30	2.24±0.09	7.14±0.24	9.36±0.04	4.62±0.68	6.17±0.29	2.81±0.64
	Low (D120)	280.64±20.62	39.75±1.53	2.08±0.28	7.08±0.23	5.48±0.65**	3.97±0.35	4.95±0.86	1.92±0.25
	High (D120)	265.22±29.58	42.80±2.21	2.18±0.20	7.16±0.31	5.47±0.14**	4.52±0.12	6.67±0.87	4.85±0.63**
Female	Control (180)	308.15±28.74	31.07±2.65	1.83±0.33	5.80±0.38	9.26±2.96	4.12±0.46	5.55±0.88	2.90±1.11
	Low (D180)	332.62±18.50	32.70±1.37	1.86±0.33	5.60±0.30	7.68±1.41	3.37±0.30	4.73±0.26	1.84±0.38
	High (D180)	303.01±31.55	29.01±2.20	2.59±0.69	5.88±0.80	10.93±2.30	4.00±0.25	5.77±0.32	2.83±0.93

**Table S9.** Serum biochemical indicators of offspring following maternal exposure to 5 nmol (high) or 1 nmol (low) QDs and vehicle control. Abbreviations: total bilirubin, TBIL; total protein, TP; albumin, ALB; globulin, GLB; the ratio of albumin to globulin, A/G; alkaline phosphatase, ALP; creatinine, CREA and urea, UA, n = 3. \*P < 0.05 and \*\*P < 0.01 versus the control group.

		TBIL (μmol/L)	TP (g/L)	ALB (g/L)	GLB (g/L)	A/G	ALP (U/L)	CREA (μmol/L)	UA (μmol/L)
D18	Control	0.77±0.04	51.96±1.15	24.27±0.20	27.7±0.95	0.87±0.25	800±425.74	12.3±0.21	230±16.46
	Low	1.08±0.25	54.16±2.86	24.74±1.30	29.42±1.62	0.84±0.02	655.2±38.11	11.92±4.58	170±33.29
	High	1.30±0.07*	53.93±1.43	23.96±0.29	29.96±1.35	0.8±0.04	2102±1058.18**	10.16±2.44	221.34±25.42
D60	Control	0.45±0.04	67.8±4.65	29.7±1.14	40.1±1.87	0.74±0.01	508±22.86	21.2±0.90	232±24.50
	Low	0.20±0	58.05±3.31	25.6±1.39	32.45±1.92	0.79±0.01	414±6.53	17.3±0.25	272.5±42.87
	High	1.33±0.77**	79.45±4.63	29.77±4.59	49.7±2.18	0.60±0.10	227.67±133.56**	35.46±5.01*	110±3.94**
D120	Control	0.63±0.15	81.43±2.16	25.43±2.44	56±2.96	0.46±0.07	177±26.69	34.27±3.92	190±7.97
	Low	1.1±0.19*	73.53±2.40	27.7±0.92	45.83±2.53	0.60±0.04	169±60.02	29.23±4.15	287.33±55.41
	High	0.58±0.12	83.25±2.25	33±0.75	50.25±2.31	0.66±0.04	364±98.06**	32.73±2.13	141.25±53.63
D150	Control	1.25±0.34	74.3±1.86	25.83±0.66	48.35±2.12	0.54±0.03	125.25±23.15	36.3±3.70	94.5±21.91
	Low	1.15±0.26	74.35±3.01	24.83±3.95	49.53±6.21	0.52±0.13	119±39.81	33.63±1.44	118.75±12.45
	High	1.98±0.53	69.65±1.72	25.55±2.75	44.1±3.86	0.59±0.11	110.25±31.30	30.83±6.60	110±5.18
D180	Control	0.83±0.12	80.48±1.68	26.93±2.11	53.58±1.67	0.51±0.05	95.25±3.06	38.65±3.18	127.25±18.29
	Low	0.77±0.18	81.73±3.02	28.97±1.24	52.77±2.97	0.55±0.04	104.33±15.90	34.53±4.29	158.33±39.07
	High	0.60±0.17	81.38±2.27	23.63±4.06	57.75±4.75	0.42±0.10	120.75±34.17	41.83±3.38	145±35.13