Pulmonary clearance kinetics and extrapulmonary translocation of seven titanium dioxide nano and submicron materials following intratracheal administration in rats

Supplemental Information

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Table S1. Conditions for the preparation of TiO₂ suspension.

	Ultrasonication [h]	Centrifugal acceleration [× g]	Centrifugal time [min]
P25	3	1000	20
MT-150AW	3	1000	25
AMT-100	1	350	5
MP-100	1	20	15
FTL-100	3	100	12
TTOS-3 without coating	3	1000	30
TTOS-3 with coating	3	100	40

Table S2. Body weights of administered rats in the present study.

	Body weight [g]	
	Ave	SD
P25	246	10
MT-150A	247	11
AMT-100	258	11
MP-100	252	8.8
FTL-100	253	12
TTO-S-3 without coating	253	15
TTO-S-3 with coating	256	9.1

Table S3. Sample amount and acid volume for the acid treatment.

		Sample amount	HNO ₃	H ₂ SO ₄	HF	Final deluted volume
P25, MT-150AW, AMT-100, TTOS-3 without coating, TTOS-3 with Al(OH) ₃ coating	Homogenized organ tissues	1 g/0.1g [*]	1 mL	0.2 mL	-	10 mL
	BALF	0.1 mL	0.5 mL	0.1 mL	-	5 mL
	Trachea	Whole	1 mL	0.2 mL	-	5 mL
	Lymph nodes	Whole	0.5 mL	0.1 mL	-	5 mL
	Suspension	50 µL	-	1 mL	1 mL	50 mL
MP-100, FTL-100	Homogenized organ tissues	1 g/0.1g [*]	1 mL	0.2 mL	0.2 mL	10 mL
	BALF	0.1 mL	1 mL	0.2 mL	0.2 mL	5 mL
	Trachea	Whole	1 mL	0.2 mL	0.2 mL	10 mL
	Lymph nodes	Whole	0.5 mL	0.1 mL	0.1 mL	5 mL
	Suspension	50 µL	-	1 mL	1 mL	50 mL

^{*} 0.1 g for lung and 1 g for the other organs.

Table S4 Ti/Al ratio in the suspension, lung, BALF, and the thoracic lymph nodes

		Ti/Al ratio								
		0.67 mg/kg			2.0 mg/kg			6.0 mg/kg		
		Mean	SD	Number	Mean	SD	Number	Mean	SD	Number
Suspension		93%/7.5%	0.55%	3	92%/8.1%	0.16%	3	92%/8.2%	0.030%	3
Lung	3 days	93%/6.5%	0.27%	5	93%/7.2%	0.32%	5	92%/7.6%	0.57%	5
	28 days	93%/7.3%	0.16%	5	93%/7.3%	0.37%	5	93%/7.3%	0.10%	5
	91 days	93%/6.7%	0.39%	5	94%/6.0%	0.33%	5	95%/5.4%	1.2%	5
BALF	3 days	92%/8.1%	1.9%	5	91%/9.0%	0.63%	5	85%/15%	11%	5
	28 days	89%/11%	5.0%	5	90%/10%	3.8%	5	87%/13%	6.2%	5
	91 days	91%/9.3%	5.6%	5	93%/7.0%	3.1%	5	94%/6.0%	2.1%	5
Thoracic lymph nodes	3 days	89%/11%	3.7%	5	75%/25%	37%	5	87%/13%	3.3%	5
	28 days	91%/8.8%	3.4%	5	91%/8.5%	2.5%	5	93%/7.2%	0.094%	5
	91 days	93%/7.2%	1.0%	5	94%/6.0%	0.084%	5	95%/5.3%	0.084%	5

Table S5. TiO₂ burdens per initial body weight at the time of administration in (A) lung, (B) BALF, (C) trachea, (D) lymph nodes, and (E) liver.

(A) Lung

		Lung TiO ₂ burden per initial body weight [mg/kg bw]		
		3 days after i.t.	28 days after i.t.	91 days after i.t.
Solvent		$<1.9 \times 10^{-4}$	$<2.0 \times 10^{-4}$	$<2.2 \times 10^{-4}$
P25	0.375 mg/kg	$0.27 \pm 4.0 \times 10^{-2}$	$0.12 \pm 3.4 \times 10^{-2}$	$5.5 \times 10^{-2} \pm 6.5 \times 10^{-3}$
	0.75 mg/kg	$0.55 \pm 7.0 \times 10^{-2}$	$0.28 \pm 7.8 \times 10^{-2}$	$0.12 \pm 1.7 \times 10^{-2}$
	1.5 mg/kg	0.97 ± 0.15	0.65 ± 0.18	$0.22 \pm 2.3 \times 10^{-2}$
	3.0 mg/kg	1.9 ± 0.27	1.4 ± 0.44	0.70 ± 0.19
	6.0 mg/kg	4.5 ± 0.39	3.5 ± 0.73	1.9 ± 0.34
MT-150A	0.67 mg/kg	$0.42 \pm 4.0 \times 10^{-2}$	$0.23 \pm 3.6 \times 10^{-2}$	$8.8 \times 10^{-2} \pm 1.9 \times 10^{-2}$
	2.0 mg/kg	1.4 ± 0.12	$0.81 \pm 8.5 \times 10^{-2}$	$0.31 \pm 3.4 \times 10^{-2}$
	6.0 mg/kg	5.1 ± 0.36	3.4 ± 0.33	1.8 ± 0.27
AMT-100	0.67 mg/kg	$0.39 \pm 1.8 \times 10^{-2}$	$0.22 \pm 7.2 \times 10^{-3}$	$8.9 \times 10^{-2} \pm 7.4 \times 10^{-3}$
	2.0 mg/kg	1.4 ± 0.12	$0.66 \pm 9.6 \times 10^{-2}$	$0.26 \pm 2.0 \times 10^{-2}$
	6.0 mg/kg	4.3 ± 0.15	1.9 ± 0.56	1.2 ± 0.17
MP-100	0.67 mg/kg	$0.36 \pm 2.9 \times 10^{-2}$	$0.20 \pm 1.1 \times 10^{-2}$	$8.4 \times 10^{-2} \pm 4.2 \times 10^{-3}$
	2.0 mg/kg	$1.2 \pm 9.7 \times 10^{-2}$	$0.73 \pm 3.9 \times 10^{-2}$	$0.28 \pm 5.0 \times 10^{-2}$
	6.0 mg/kg	4.0 ± 0.20	2.9 ± 0.23	1.7 ± 0.33
FTL-100	0.67 mg/kg	$0.47 \pm 8.0 \times 10^{-2}$	$0.25 \pm 1.3 \times 10^{-2}$	$8.9 \times 10^{-2} \pm 9.3 \times 10^{-3}$
	2.0 mg/kg	$1.3 \pm 9.3 \times 10^{-2}$	$0.54 \pm 7.0 \times 10^{-2}$	$0.31 \pm 2.0 \times 10^{-2}$
	6.0 mg/kg	4.5 ± 0.31	2.6 ± 0.25	2.2 ± 0.16
TTO-S-3 without coating	0.67 mg/kg	$0.35 \pm 5.1 \times 10^{-2}$	$0.18 \pm 4.3 \times 10^{-2}$	$5.5 \times 10^{-2} \pm 6.3 \times 10^{-3}$
	2.0 mg/kg	1.5 ± 0.14	$0.68 \pm 6.7 \times 10^{-2}$	$0.26 \pm 2.6 \times 10^{-2}$
	6.0 mg/kg	4.4 ± 0.23	3.3 ± 0.38	1.7 ± 0.27
TTO-S-3 with coating	0.67 mg/kg	$0.45 \pm 1.9 \times 10^{-2}$	$0.30 \pm 7.5 \times 10^{-2}$	$0.16 \pm 6.5 \times 10^{-2}$
	2.0 mg/kg	1.2 ± 0.20	$1.1 \pm 3.3 \times 10^{-2}$	0.81 ± 0.25
	6.0 mg/kg	3.2 ± 0.38	3.3 ± 0.30	3.2 ± 0.21

(B) BALF

		BALF TiO ₂ per initial body weight [mg/kg bw]		
Solvent		3 days after i.t.	28 days after i.t.	91 days after i.t.
		$<8.6 \times 10^{-5}$	$1.1 \times 10^{-4} \pm 1.6 \times 10^{-4}$	$<9.0 \times 10^{-5}$
P25	0.375 mg/kg	$1.6 \times 10^{-2} \pm 4.6 \times 10^{-3}$	$6.8 \times 10^{-3} \pm 1.4 \times 10^{-3}$	$2.8 \times 10^{-3} \pm 3.4 \times 10^{-4}$
	0.75 mg/kg	$3.4 \times 10^{-2} \pm 9.2 \times 10^{-3}$	$1.6 \times 10^{-2} \pm 6.1 \times 10^{-3}$	$5.8 \times 10^{-3} \pm 9.6 \times 10^{-4}$
	1.5 mg/kg	$5.2 \times 10^{-2} \pm 8.1 \times 10^{-3}$	$3.0 \times 10^{-2} \pm 9.0 \times 10^{-3}$	$1.2 \times 10^{-2} \pm 1.2 \times 10^{-3}$
	3.0 mg/kg	$0.10 \pm 3.5 \times 10^{-2}$	$5.0 \times 10^{-2} \pm 2.2 \times 10^{-2}$	$2.1 \times 10^{-2} \pm 2.6 \times 10^{-3}$
	6.0 mg/kg	$0.20 \pm 4.6 \times 10^{-2}$	$5.8 \times 10^{-2} \pm 4.0 \times 10^{-2}$	$6.6 \times 10^{-2} \pm 3.1 \times 10^{-2}$
MT-150A	0.67 mg/kg	$5.5 \times 10^{-2} \pm 1.5 \times 10^{-2}$	$2.4 \times 10^{-2} \pm 4.2 \times 10^{-3}$	$6.1 \times 10^{-3} \pm 3.0 \times 10^{-3}$
	2.0 mg/kg	0.16 ± 0.15	$7.6 \times 10^{-2} \pm 2.7 \times 10^{-2}$	$4.2 \times 10^{-2} \pm 3.3 \times 10^{-2}$
	6.0 mg/kg	$0.24 \pm 7.0 \times 10^{-2}$	$0.16 \pm 2.5 \times 10^{-2}$	$6.0 \times 10^{-2} \pm 4.3 \times 10^{-3}$
AMT-100	0.67 mg/kg	$3.9 \times 10^{-2} \pm 2.5 \times 10^{-3}$	$1.3 \times 10^{-2} \pm 1.8 \times 10^{-3}$	$4.4 \times 10^{-3} \pm 6.3 \times 10^{-4}$
	2.0 mg/kg	$9.6 \times 10^{-2} \pm 1.8 \times 10^{-2}$	$4.1 \times 10^{-2} \pm 1.0 \times 10^{-2}$	$1.2 \times 10^{-2} \pm 1.4 \times 10^{-3}$
	6.0 mg/kg	$0.24 \pm 3.5 \times 10^{-2}$	$0.11 \pm 2.9 \times 10^{-2}$	$4.0 \times 10^{-2} \pm 5.4 \times 10^{-3}$
MP-100	0.67 mg/kg	$4.0 \times 10^{-2} \pm 5.2 \times 10^{-3}$	$1.3 \times 10^{-2} \pm 1.8 \times 10^{-3}$	$4.7 \times 10^{-3} \pm 1.1 \times 10^{-3}$
	2.0 mg/kg	$9.7 \times 10^{-2} \pm 2.9 \times 10^{-2}$	$3.1 \times 10^{-2} \pm 1.5 \times 10^{-2}$	$1.4 \times 10^{-2} \pm 5.1 \times 10^{-3}$
	6.0 mg/kg	$0.22 \pm 9.8 \times 10^{-2}$	$9.3 \times 10^{-2} \pm 3.1 \times 10^{-3}$	$3.5 \times 10^{-2} \pm 7.9 \times 10^{-3}$
FTL-100	0.67 mg/kg	$5.0 \times 10^{-2} \pm 7.2 \times 10^{-3}$	$2.6 \times 10^{-2} \pm 2.7 \times 10^{-3}$	$5.1 \times 10^{-3} \pm 8.7 \times 10^{-4}$
	2.0 mg/kg	$0.10 \pm 2.8 \times 10^{-2}$	$5.0 \times 10^{-2} \pm 1.3 \times 10^{-2}$	$1.1 \times 10^{-2} \pm 2.0 \times 10^{-3}$
	6.0 mg/kg	$0.19 \pm 3.4 \times 10^{-2}$	$0.10 \pm 2.3 \times 10^{-2}$	$1.9 \times 10^{-2} \pm 4.1 \times 10^{-3}$
TTO-S-3 without coating	0.67 mg/kg	$2.3 \times 10^{-2} \pm 7.9 \times 10^{-3}$	$9.0 \times 10^{-3} \pm 5.9 \times 10^{-3}$	$5.2 \times 10^{-3} \pm 9.4 \times 10^{-4}$
	2.0 mg/kg	$6.1 \times 10^{-2} \pm 7.3 \times 10^{-3}$	$3.4 \times 10^{-2} \pm 7.7 \times 10^{-3}$	$1.6 \times 10^{-2} \pm 4.0 \times 10^{-3}$
	6.0 mg/kg	$0.12 \pm 4.0 \times 10^{-2}$	$9.4 \times 10^{-2} \pm 3.7 \times 10^{-2}$	$5.6 \times 10^{-2} \pm 9.7 \times 10^{-3}$
TTO-S-3 with coating	0.67 mg/kg	$1.0 \times 10^{-2} \pm 2.3 \times 10^{-3}$	$8.9 \times 10^{-3} \pm 2.8 \times 10^{-3}$	$4.0 \times 10^{-3} \pm 2.4 \times 10^{-3}$
	2.0 mg/kg	$4.6 \times 10^{-2} \pm 1.8 \times 10^{-2}$	$1.9 \times 10^{-2} \pm 1.2 \times 10^{-2}$	$1.7 \times 10^{-2} \pm 7.3 \times 10^{-3}$
	6.0 mg/kg	$9.6 \times 10^{-2} \pm 3.1 \times 10^{-2}$	$2.5 \times 10^{-2} \pm 1.2 \times 10^{-2}$	$6.4 \times 10^{-2} \pm 4.6 \times 10^{-2}$

(C) Trachea

		Trachea TiO ₂ burden per initial body weight [mg/kg bw]		
		3 days after i.t.	28 days after i.t.	91 days after i.t.
Solvent		$4.3 \times 10^{-5} \pm 2.4 \times 10^{-5}$	$2.7 \times 10^{-5} \pm 2.9 \times 10^{-5}$	$2.5 \times 10^{-5} \pm 1.4 \times 10^{-5}$
P25	0.375 mg/kg	$4.1 \times 10^{-3} \pm 8.6 \times 10^{-4}$	$1.2 \times 10^{-3} \pm 3.3 \times 10^{-4}$	$6.8 \times 10^{-3} \pm 3.1 \times 10^{-3}$
	0.75 mg/kg	$7.2 \times 10^{-3} \pm 3.9 \times 10^{-3}$	$1.8 \times 10^{-3} \pm 1.1 \times 10^{-3}$	$6.1 \times 10^{-3} \pm 4.3 \times 10^{-3}$
	1.5 mg/kg	$1.4 \times 10^{-2} \pm 6.5 \times 10^{-3}$	$4.9 \times 10^{-3} \pm 9.9 \times 10^{-4}$	$8.8 \times 10^{-3} \pm 5.4 \times 10^{-3}$
	3.0 mg/kg	$1.1 \times 10^{-2} \pm 3.7 \times 10^{-3}$	$5.9 \times 10^{-3} \pm 1.3 \times 10^{-3}$	$1.7 \times 10^{-2} \pm 2.0 \times 10^{-2}$
	6.0 mg/kg	$2.2 \times 10^{-2} \pm 6.9 \times 10^{-3}$	$1.5 \times 10^{-2} \pm 6.5 \times 10^{-3}$	$2.8 \times 10^{-2} \pm 1.7 \times 10^{-2}$
MT-150A	0.67 mg/kg	$8.4 \times 10^{-3} \pm 6.3 \times 10^{-3}$	$5.6 \times 10^{-3} \pm 1.4 \times 10^{-3}$	$8.5 \times 10^{-3} \pm 6.3 \times 10^{-3}$
	2.0 mg/kg	$3.1 \times 10^{-2} \pm 1.1 \times 10^{-2}$	$2.0 \times 10^{-2} \pm 7.9 \times 10^{-3}$	$1.8 \times 10^{-2} \pm 1.3 \times 10^{-2}$
	6.0 mg/kg	$5.8 \times 10^{-2} \pm 3.2 \times 10^{-2}$	$3.5 \times 10^{-2} \pm 9.5 \times 10^{-3}$	$7.0 \times 10^{-2} \pm 2.9 \times 10^{-2}$
AMT-100	0.67 mg/kg	$2.0 \times 10^{-3} \pm 6.8 \times 10^{-4}$	$2.0 \times 10^{-3} \pm 3.6 \times 10^{-4}$	$9.3 \times 10^{-4} \pm 1.6 \times 10^{-4}$
	2.0 mg/kg	$7.9 \times 10^{-3} \pm 2.0 \times 10^{-3}$	$4.7 \times 10^{-3} \pm 6.1 \times 10^{-4}$	$2.4 \times 10^{-3} \pm 3.9 \times 10^{-4}$
	6.0 mg/kg	$2.5 \times 10^{-2} \pm 1.0 \times 10^{-2}$	$1.6 \times 10^{-2} \pm 4.0 \times 10^{-3}$	$8.9 \times 10^{-3} \pm 3.2 \times 10^{-3}$
MP-100	0.67 mg/kg	$1.6 \times 10^{-2} \pm 1.9 \times 10^{-2}$	$1.3 \times 10^{-2} \pm 1.0 \times 10^{-2}$	$7.1 \times 10^{-3} \pm 5.7 \times 10^{-3}$
	2.0 mg/kg	$3.8 \times 10^{-2} \pm 9.2 \times 10^{-3}$	$4.6 \times 10^{-2} \pm 2.3 \times 10^{-2}$	$3.8 \times 10^{-2} \pm 5.2 \times 10^{-2}$
	6.0 mg/kg	$7.7 \times 10^{-2} \pm 2.8 \times 10^{-2}$	$7.8 \times 10^{-2} \pm 4.4 \times 10^{-2}$	$5.9 \times 10^{-2} \pm 2.2 \times 10^{-2}$
FTL-100	0.67 mg/kg	$3.4 \times 10^{-3} \pm 7.6 \times 10^{-4}$	$1.0 \times 10^{-3} \pm 5.1 \times 10^{-4}$	$1.1 \times 10^{-3} \pm 2.9 \times 10^{-4}$
	2.0 mg/kg	$7.2 \times 10^{-3} \pm 3.6 \times 10^{-3}$	$3.1 \times 10^{-3} \pm 8.5 \times 10^{-4}$	$2.4 \times 10^{-3} \pm 5.1 \times 10^{-4}$
	6.0 mg/kg	$1.3 \times 10^{-2} \pm 1.9 \times 10^{-3}$	$8.2 \times 10^{-3} \pm 2.4 \times 10^{-3}$	$7.8 \times 10^{-3} \pm 2.3 \times 10^{-3}$
TTO-S-3 without coating	0.67 mg/kg	$2.8 \times 10^{-3} \pm 1.2 \times 10^{-3}$	$1.8 \times 10^{-3} \pm 8.5 \times 10^{-4}$	$6.6 \times 10^{-4} \pm 2.2 \times 10^{-4}$
	2.0 mg/kg	$1.1 \times 10^{-2} \pm 3.3 \times 10^{-3}$	$3.8 \times 10^{-3} \pm 1.2 \times 10^{-3}$	$2.4 \times 10^{-3} \pm 1.2 \times 10^{-3}$
	6.0 mg/kg	$2.1 \times 10^{-2} \pm 1.3 \times 10^{-2}$	$1.5 \times 10^{-2} \pm 5.3 \times 10^{-3}$	$6.5 \times 10^{-3} \pm 2.5 \times 10^{-3}$
TTO-S-3 with coating	0.67 mg/kg	$3.9 \times 10^{-3} \pm 1.1 \times 10^{-3}$	$1.9 \times 10^{-3} \pm 1.8 \times 10^{-3}$	$2.5 \times 10^{-3} \pm 1.9 \times 10^{-3}$
	2.0 mg/kg	$5.8 \times 10^{-3} \pm 1.4 \times 10^{-3}$	$6.5 \times 10^{-3} \pm 1.3 \times 10^{-3}$	$6.2 \times 10^{-3} \pm 1.9 \times 10^{-3}$
	6.0 mg/kg	$1.6 \times 10^{-2} \pm 6.5 \times 10^{-3}$	$1.4 \times 10^{-2} \pm 6.9 \times 10^{-3}$	$1.6 \times 10^{-2} \pm 5.1 \times 10^{-3}$

(D) Lymph nodes

		Lymph nodes TiO ₂ burden per initial body weight [mg/kg bw]		
		3 days after i.t.	28 days after i.t.	91 days after i.t.
Solvent		$2.8 \times 10^{-5} \pm 4.3 \times 10^{-5}$	$1.1 \times 10^{-4} \pm 5.8 \times 10^{-5}$	$3.4 \times 10^{-5} \pm 3.2 \times 10^{-5}$
P25	0.375 mg/kg	$1.9 \times 10^{-4} \pm 9.9 \times 10^{-5}$	$3.4 \times 10^{-4} \pm 1.6 \times 10^{-4}$	$5.5 \times 10^{-4} \pm 1.6 \times 10^{-4}$
	0.75 mg/kg	$1.5 \times 10^{-4} \pm 1.2 \times 10^{-4}$	$1.8 \times 10^{-4} \pm 1.2 \times 10^{-4}$	$6.1 \times 10^{-4} \pm 2.1 \times 10^{-4}$
	1.5 mg/kg	$8.0 \times 10^{-4} \pm 2.5 \times 10^{-4}$	$1.7 \times 10^{-3} \pm 8.8 \times 10^{-4}$	$3.7 \times 10^{-3} \pm 1.0 \times 10^{-3}$
	3.0 mg/kg	$2.0 \times 10^{-3} \pm 1.4 \times 10^{-3}$	$1.4 \times 10^{-2} \pm 6.6 \times 10^{-3}$	$2.5 \times 10^{-2} \pm 7.4 \times 10^{-3}$
	6.0 mg/kg	$1.3 \times 10^{-2} \pm 2.5 \times 10^{-3}$	$0.11 \pm 1.1 \times 10^{-2}$	$0.11 \pm 3.7 \times 10^{-2}$
MT-150A	0.67 mg/kg	$4.5 \times 10^{-4} \pm 3.3 \times 10^{-4}$	$4.6 \times 10^{-4} \pm 9.5 \times 10^{-5}$	$7.2 \times 10^{-4} \pm 2.0 \times 10^{-4}$
	2.0 mg/kg	$2.6 \times 10^{-3} \pm 2.5 \times 10^{-3}$	$7.0 \times 10^{-3} \pm 1.5 \times 10^{-3}$	$5.9 \times 10^{-3} \pm 3.6 \times 10^{-3}$
	6.0 mg/kg	$1.8 \times 10^{-2} \pm 2.2 \times 10^{-3}$	$5.2 \times 10^{-2} \pm 6.7 \times 10^{-3}$	$7.9 \times 10^{-2} \pm 8.0 \times 10^{-3}$
AMT-100	0.67 mg/kg	$8.2 \times 10^{-5} \pm 2.2 \times 10^{-5}$	$1.6 \times 10^{-4} \pm 4.3 \times 10^{-5}$	$2.0 \times 10^{-4} \pm 5.6 \times 10^{-5}$
	2.0 mg/kg	$4.4 \times 10^{-4} \pm 1.2 \times 10^{-4}$	$1.4 \times 10^{-3} \pm 3.7 \times 10^{-4}$	$1.4 \times 10^{-3} \pm 3.2 \times 10^{-4}$
	6.0 mg/kg	$7.1 \times 10^{-3} \pm 9.2 \times 10^{-4}$	$2.0 \times 10^{-2} \pm 7.9 \times 10^{-3}$	$3.2 \times 10^{-2} \pm 6.2 \times 10^{-3}$
MP-100	0.67 mg/kg	$2.0 \times 10^{-4} \pm 1.3 \times 10^{-4}$	$1.9 \times 10^{-3} \pm 7.7 \times 10^{-4}$	$3.2 \times 10^{-3} \pm 2.7 \times 10^{-3}$
	2.0 mg/kg	$1.2 \times 10^{-3} \pm 3.1 \times 10^{-4}$	$8.9 \times 10^{-3} \pm 4.0 \times 10^{-3}$	$1.7 \times 10^{-2} \pm 9.2 \times 10^{-3}$
	6.0 mg/kg	$5.5 \times 10^{-3} \pm 1.3 \times 10^{-3}$	$1.7 \times 10^{-2} \pm 7.4 \times 10^{-3}$	$7.4 \times 10^{-2} \pm 2.4 \times 10^{-2}$
FTL-100	0.67 mg/kg	$1.2 \times 10^{-4} \pm 1.8 \times 10^{-5}$	$1.5 \times 10^{-4} \pm 2.9 \times 10^{-5}$	$2.7 \times 10^{-4} \pm 7.7 \times 10^{-5}$
	2.0 mg/kg	$1.1 \times 10^{-3} \pm 2.1 \times 10^{-4}$	$8.5 \times 10^{-4} \pm 1.6 \times 10^{-4}$	$4.1 \times 10^{-3} \pm 1.0 \times 10^{-3}$
	6.0 mg/kg	$7.3 \times 10^{-3} \pm 2.2 \times 10^{-3}$	$1.9 \times 10^{-2} \pm 8.9 \times 10^{-4}$	$9.1 \times 10^{-2} \pm 1.3 \times 10^{-2}$
TTO-S-3 without coating	0.67 mg/kg	$1.1 \times 10^{-4} \pm 6.5 \times 10^{-5}$	$2.1 \times 10^{-4} \pm 9.1 \times 10^{-5}$	$1.0 \times 10^{-4} \pm 5.8 \times 10^{-5}$
	2.0 mg/kg	$1.8 \times 10^{-3} \pm 6.1 \times 10^{-4}$	$2.9 \times 10^{-3} \pm 1.1 \times 10^{-3}$	$2.8 \times 10^{-3} \pm 1.1 \times 10^{-3}$
	6.0 mg/kg	$1.5 \times 10^{-2} \pm 1.7 \times 10^{-3}$	$5.5 \times 10^{-2} \pm 1.1 \times 10^{-2}$	$6.5 \times 10^{-2} \pm 1.5 \times 10^{-2}$
TTO-S-3 with coating	0.67 mg/kg	$1.8 \times 10^{-4} \pm 2.9 \times 10^{-5}$	$1.2 \times 10^{-3} \pm 5.2 \times 10^{-4}$	$4.8 \times 10^{-3} \pm 4.1 \times 10^{-3}$
	2.0 mg/kg	$9.1 \times 10^{-4} \pm 2.3 \times 10^{-4}$	$1.9 \times 10^{-2} \pm 2.2 \times 10^{-3}$	$5.2 \times 10^{-2} \pm 1.9 \times 10^{-2}$
	6.0 mg/kg	$4.5 \times 10^{-3} \pm 7.9 \times 10^{-4}$	$7.7 \times 10^{-2} \pm 3.7 \times 10^{-3}$	$0.31 \pm 5.7 \times 10^{-2}$

(E) Liver.

		Liver TiO ₂ burden per initial body weight [mg/kg bw]		
Solvent		3 days after i.t.	28 days after i.t.	91 days after i.t.
		$<8.1 \times 10^{-5}$	$<9.5 \times 10^{-5}$	$<1.1 \times 10^{-4}$
P25	0.375 mg/kg	$1.1 \times 10^{-4} \pm 5.1 \times 10^{-5}$	$1.6 \times 10^{-4} \pm 5.1 \times 10^{-5}$	$1.1 \times 10^{-4} \pm 5.5 \times 10^{-5}$
	0.75 mg/kg	$<8.0 \times 10^{-5}$	$9.5 \times 10^{-5} \pm 6.5 \times 10^{-5}$	$1.8 \times 10^{-3} \pm 3.0 \times 10^{-3}$
	1.5 mg/kg	$2.1 \times 10^{-4} \pm 3.7 \times 10^{-4}$	$2.6 \times 10^{-4} \pm 3.2 \times 10^{-4}$	$2.1 \times 10^{-4} \pm 2.1 \times 10^{-4}$
	3.0 mg/kg	$<7.9 \times 10^{-5}$	$1.8 \times 10^{-3} \pm 3.0 \times 10^{-3}$	$5.9 \times 10^{-4} \pm 8.9 \times 10^{-4}$
	6.0 mg/kg	$1.4 \times 10^{-4} \pm 7.8 \times 10^{-5}$	$1.7 \times 10^{-4} \pm 3.4 \times 10^{-5}$	$7.4 \times 10^{-4} \pm 3.2 \times 10^{-4}$
MT-150A	0.67 mg/kg	$1.3 \times 10^{-4} \pm 8.9 \times 10^{-5}$	$2.9 \times 10^{-4} \pm 4.4 \times 10^{-4}$	$1.4 \times 10^{-4} \pm 1.8 \times 10^{-4}$
	2.0 mg/kg	$7.5 \times 10^{-4} \pm 5.9 \times 10^{-4}$	$1.4 \times 10^{-4} \pm 1.2 \times 10^{-4}$	$2.4 \times 10^{-4} \pm 1.6 \times 10^{-4}$
	6.0 mg/kg	$7.6 \times 10^{-4} \pm 2.0 \times 10^{-4}$	$4.9 \times 10^{-4} \pm 2.5 \times 10^{-4}$	$1.1 \times 10^{-3} \pm 4.5 \times 10^{-4}$
AMT-100	0.67 mg/kg	$1.6 \times 10^{-4} \pm 7.1 \times 10^{-5}$	$1.5 \times 10^{-4} \pm 5.9 \times 10^{-5}$	$1.2 \times 10^{-4} \pm 1.0 \times 10^{-4}$
	2.0 mg/kg	$1.9 \times 10^{-4} \pm 1.0 \times 10^{-4}$	$3.9 \times 10^{-4} \pm 6.1 \times 10^{-4}$	$9.6 \times 10^{-5} \pm 4.3 \times 10^{-5}$
	6.0 mg/kg	$3.2 \times 10^{-4} \pm 1.8 \times 10^{-4}$	$7.4 \times 10^{-4} \pm 5.3 \times 10^{-4}$	$6.1 \times 10^{-4} \pm 3.9 \times 10^{-4}$
MP-100	0.67 mg/kg	$1.5 \times 10^{-4} \pm 7.7 \times 10^{-5}$	$1.8 \times 10^{-4} \pm 1.4 \times 10^{-4}$	$1.5 \times 10^{-4} \pm 1.0 \times 10^{-4}$
	2.0 mg/kg	$1.8 \times 10^{-4} \pm 4.7 \times 10^{-5}$	$9.6 \times 10^{-4} \pm 1.3 \times 10^{-3}$	$2.9 \times 10^{-4} \pm 1.1 \times 10^{-4}$
	6.0 mg/kg	$1.6 \times 10^{-3} \pm 1.7 \times 10^{-3}$	$8.2 \times 10^{-4} \pm 4.1 \times 10^{-4}$	$1.5 \times 10^{-3} \pm 1.9 \times 10^{-3}$
FTL-100	0.67 mg/kg	$1.7 \times 10^{-4} \pm 1.2 \times 10^{-4}$	$2.3 \times 10^{-4} \pm 2.5 \times 10^{-5}$	$4.0 \times 10^{-4} \pm 3.4 \times 10^{-5}$
	2.0 mg/kg	$1.6 \times 10^{-4} \pm 7.5 \times 10^{-5}$	$3.7 \times 10^{-4} \pm 1.4 \times 10^{-5}$	$1.3 \times 10^{-3} \pm 3.0 \times 10^{-4}$
	6.0 mg/kg	$2.8 \times 10^{-4} \pm 1.6 \times 10^{-4}$	$7.8 \times 10^{-4} \pm 9.2 \times 10^{-5}$	$6.4 \times 10^{-3} \pm 5.2 \times 10^{-3}$
TTO-S-3 without coating	0.67 mg/kg	$1.7 \times 10^{-4} \pm 6.6 \times 10^{-5}$	$1.2 \times 10^{-4} \pm 1.8 \times 10^{-5}$	$1.2 \times 10^{-4} \pm 1.4 \times 10^{-4}$
	2.0 mg/kg	$3.3 \times 10^{-4} \pm 1.3 \times 10^{-4}$	$6.2 \times 10^{-4} \pm 6.3 \times 10^{-4}$	$<1.0 \times 10^{-4}$
	6.0 mg/kg	$3.8 \times 10^{-4} \pm 2.3 \times 10^{-4}$	$5.3 \times 10^{-4} \pm 2.1 \times 10^{-4}$	$6.5 \times 10^{-4} \pm 7.3 \times 10^{-4}$
TTO-S-3 with coating	0.67 mg/kg	$1.6 \times 10^{-4} \pm 8.9 \times 10^{-5}$	$<8.6 \times 10^{-5}$	$2.1 \times 10^{-4} \pm 2.8 \times 10^{-4}$
	2.0 mg/kg	$<9.1 \times 10^{-5}$	$1.2 \times 10^{-4} \pm 1.6 \times 10^{-4}$	$2.7 \times 10^{-4} \pm 3.4 \times 10^{-4}$
	6.0 mg/kg	$5.3 \times 10^{-4} \pm 2.6 \times 10^{-4}$	$2.9 \times 10^{-4} \pm 2.1 \times 10^{-4}$	$8.0 \times 10^{-4} \pm 7.5 \times 10^{-4}$

Table S6. TiO₂ burdens per organ tissue weight in (A) lung, (B) BALF, (C) trachea, (D) lymph nodes, and (E) liver.

(A) Lung

		Lung TiO ₂ burden per organ weight [mg/g tissue]		
		3 days after i.t.	28 days after i.t.	91 days after i.t.
Solvent		$<3.3 \times 10^{-5}$	$<3.3 \times 10^{-5}$	$<3.3 \times 10^{-5}$
P25	0.375 mg/kg	$4.8 \times 10^{-2} \pm 7.3 \times 10^{-3}$	$2.0 \times 10^{-2} \pm 5.0 \times 10^{-3}$	$8.5 \times 10^{-3} \pm 1.1 \times 10^{-3}$
	0.75 mg/kg	$9.7 \times 10^{-2} \pm 1.8 \times 10^{-2}$	$4.6 \times 10^{-2} \pm 1.3 \times 10^{-2}$	$1.7 \times 10^{-2} \pm 2.5 \times 10^{-3}$
	1.5 mg/kg	$0.17 \pm 2.8 \times 10^{-2}$	$0.11 \pm 3.2 \times 10^{-2}$	$3.3 \times 10^{-2} \pm 3.2 \times 10^{-3}$
	3.0 mg/kg	$0.33 \pm 4.8 \times 10^{-2}$	$0.23 \pm 6.3 \times 10^{-2}$	$0.11 \pm 3.1 \times 10^{-2}$
	6.0 mg/kg	$0.71 \pm 7.6 \times 10^{-2}$	0.58 ± 0.13	$0.28 \pm 3.9 \times 10^{-2}$
MT-150A	0.67 mg/kg	$7.4 \times 10^{-2} \pm 6.8 \times 10^{-3}$	$4.0 \times 10^{-2} \pm 9.0 \times 10^{-3}$	$1.3 \times 10^{-2} \pm 2.8 \times 10^{-3}$
	2.0 mg/kg	$0.23 \pm 1.2 \times 10^{-2}$	$0.14 \pm 1.9 \times 10^{-2}$	$4.4 \times 10^{-2} \pm 7.7 \times 10^{-3}$
	6.0 mg/kg	$0.74 \pm 4.8 \times 10^{-2}$	$0.55 \pm 4.3 \times 10^{-2}$	$0.25 \pm 4.2 \times 10^{-2}$
AMT-100	0.67 mg/kg	$6.8 \times 10^{-2} \pm 6.2 \times 10^{-3}$	$3.8 \times 10^{-2} \pm 2.2 \times 10^{-3}$	$1.4 \times 10^{-2} \pm 1.5 \times 10^{-3}$
	2.0 mg/kg	$0.25 \pm 3.1 \times 10^{-2}$	$0.11 \pm 1.7 \times 10^{-2}$	$4.0 \times 10^{-2} \pm 5.7 \times 10^{-3}$
	6.0 mg/kg	$0.72 \pm 3.5 \times 10^{-2}$	$0.33 \pm 9.3 \times 10^{-2}$	$0.18 \pm 3.2 \times 10^{-2}$
MP-100	0.67 mg/kg	$6.5 \times 10^{-2} \pm 7.0 \times 10^{-3}$	$3.3 \times 10^{-2} \pm 1.5 \times 10^{-3}$	$1.3 \times 10^{-2} \pm 1.0 \times 10^{-3}$
	2.0 mg/kg	$0.21 \pm 2.7 \times 10^{-2}$	$0.13 \pm 8.1 \times 10^{-3}$	$4.6 \times 10^{-2} \pm 6.9 \times 10^{-3}$
	6.0 mg/kg	$0.74 \pm 6.7 \times 10^{-2}$	$0.50 \pm 5.1 \times 10^{-2}$	$0.29 \pm 6.2 \times 10^{-2}$
FTL-100	0.67 mg/kg	$8.3 \times 10^{-2} \pm 1.5 \times 10^{-2}$	$4.3 \times 10^{-2} \pm 3.6 \times 10^{-3}$	$1.4 \times 10^{-2} \pm 1.5 \times 10^{-3}$
	2.0 mg/kg	$0.22 \pm 2.2 \times 10^{-2}$	$9.0 \times 10^{-2} \pm 1.8 \times 10^{-2}$	$4.8 \times 10^{-2} \pm 4.2 \times 10^{-3}$
	6.0 mg/kg	$0.73 \pm 4.7 \times 10^{-2}$	$0.45 \pm 5.7 \times 10^{-2}$	$0.34 \pm 2.5 \times 10^{-2}$
TTO-S-3 without coating	0.67 mg/kg	$5.6 \times 10^{-2} \pm 1.0 \times 10^{-2}$	$2.9 \times 10^{-2} \pm 6.6 \times 10^{-3}$	$8.1 \times 10^{-3} \pm 1.0 \times 10^{-3}$
	2.0 mg/kg	$0.23 \pm 3.1 \times 10^{-2}$	$0.11 \pm 1.5 \times 10^{-2}$	$4.0 \times 10^{-2} \pm 6.0 \times 10^{-3}$
	6.0 mg/kg	$0.65 \pm 8.0 \times 10^{-2}$	$0.55 \pm 6.9 \times 10^{-2}$	$0.26 \pm 4.6 \times 10^{-2}$
TTO-S-3 with coating	0.67 mg/kg	$7.7 \times 10^{-2} \pm 3.0 \times 10^{-3}$	$5.0 \times 10^{-2} \pm 1.4 \times 10^{-2}$	$2.5 \times 10^{-2} \pm 9.9 \times 10^{-3}$
	2.0 mg/kg	$0.20 \pm 3.5 \times 10^{-2}$	$0.18 \pm 1.4 \times 10^{-2}$	$0.13 \pm 4.0 \times 10^{-2}$
	6.0 mg/kg	$0.51 \pm 4.2 \times 10^{-2}$	$0.51 \pm 6.2 \times 10^{-2}$	$0.47 \pm 3.2 \times 10^{-2}$

(B) BALF

		BALF TiO ₂ burden per volume [mg/mL BALF]		
		3 days after i.t.	28 days after i.t.	91 days after i.t.
Solvent		$<1.7 \times 10^{-6}$	$2.2 \times 10^{-6} \pm 3.1 \times 10^{-6}$	$<1.7 \times 10^{-6}$
P25	0.375 mg/kg	$3.1 \times 10^{-4} \pm 9.3 \times 10^{-5}$	$1.4 \times 10^{-4} \pm 2.8 \times 10^{-5}$	$5.3 \times 10^{-5} \pm 9.4 \times 10^{-6}$
	0.75 mg/kg	$6.6 \times 10^{-4} \pm 1.8 \times 10^{-4}$	$3.2 \times 10^{-4} \pm 1.3 \times 10^{-4}$	$1.1 \times 10^{-4} \pm 2.1 \times 10^{-5}$
	1.5 mg/kg	$1.0 \times 10^{-3} \pm 2.0 \times 10^{-4}$	$6.1 \times 10^{-4} \pm 1.9 \times 10^{-4}$	$2.3 \times 10^{-4} \pm 2.5 \times 10^{-5}$
	3.0 mg/kg	$1.9 \times 10^{-3} \pm 6.9 \times 10^{-4}$	$1.0 \times 10^{-3} \pm 4.2 \times 10^{-4}$	$4.2 \times 10^{-4} \pm 8.3 \times 10^{-5}$
	6.0 mg/kg	$3.9 \times 10^{-3} \pm 8.4 \times 10^{-4}$	$1.1 \times 10^{-3} \pm 7.1 \times 10^{-4}$	$1.2 \times 10^{-3} \pm 5.2 \times 10^{-4}$
MT-150A	0.67 mg/kg	$1.1 \times 10^{-3} \pm 3.4 \times 10^{-4}$	$4.5 \times 10^{-4} \pm 9.5 \times 10^{-5}$	$1.2 \times 10^{-4} \pm 6.1 \times 10^{-5}$
	2.0 mg/kg	$2.9 \times 10^{-3} \pm 2.6 \times 10^{-3}$	$1.4 \times 10^{-3} \pm 5.2 \times 10^{-4}$	$8.5 \times 10^{-4} \pm 6.7 \times 10^{-4}$
	6.0 mg/kg	$4.6 \times 10^{-3} \pm 1.5 \times 10^{-3}$	$3.0 \times 10^{-3} \pm 5.1 \times 10^{-4}$	$1.2 \times 10^{-3} \pm 1.3 \times 10^{-4}$
AMT-100	0.67 mg/kg	$8.1 \times 10^{-4} \pm 9.7 \times 10^{-5}$	$2.8 \times 10^{-4} \pm 4.0 \times 10^{-5}$	$8.7 \times 10^{-5} \pm 1.1 \times 10^{-5}$
	2.0 mg/kg	$2.0 \times 10^{-3} \pm 4.3 \times 10^{-4}$	$8.1 \times 10^{-4} \pm 2.0 \times 10^{-4}$	$2.5 \times 10^{-4} \pm 3.1 \times 10^{-5}$
	6.0 mg/kg	$5.1 \times 10^{-3} \pm 7.7 \times 10^{-4}$	$2.2 \times 10^{-3} \pm 5.5 \times 10^{-4}$	$8.0 \times 10^{-4} \pm 1.2 \times 10^{-4}$
MP-100	0.67 mg/kg	$7.7 \times 10^{-4} \pm 1.0 \times 10^{-4}$	$2.6 \times 10^{-4} \pm 3.0 \times 10^{-5}$	$9.0 \times 10^{-5} \pm 2.2 \times 10^{-5}$
	2.0 mg/kg	$1.9 \times 10^{-3} \pm 5.8 \times 10^{-4}$	$6.1 \times 10^{-4} \pm 3.0 \times 10^{-4}$	$2.8 \times 10^{-4} \pm 9.8 \times 10^{-5}$
	6.0 mg/kg	$4.4 \times 10^{-3} \pm 2.0 \times 10^{-3}$	$1.9 \times 10^{-3} \pm 1.5 \times 10^{-4}$	$6.8 \times 10^{-4} \pm 1.6 \times 10^{-4}$
FTL-100	0.67 mg/kg	$9.4 \times 10^{-4} \pm 1.7 \times 10^{-4}$	$5.0 \times 10^{-4} \pm 7.7 \times 10^{-5}$	$1.1 \times 10^{-4} \pm 2.3 \times 10^{-5}$
	2.0 mg/kg	$1.9 \times 10^{-3} \pm 5.3 \times 10^{-4}$	$9.6 \times 10^{-4} \pm 2.8 \times 10^{-4}$	$2.2 \times 10^{-4} \pm 4.4 \times 10^{-5}$
	6.0 mg/kg	$3.6 \times 10^{-3} \pm 7.1 \times 10^{-4}$	$1.9 \times 10^{-3} \pm 4.5 \times 10^{-4}$	$3.9 \times 10^{-4} \pm 8.5 \times 10^{-5}$
TTO-S-3 without coating	0.67 mg/kg	$4.5 \times 10^{-4} \pm 1.6 \times 10^{-4}$	$1.8 \times 10^{-4} \pm 1.2 \times 10^{-4}$	$1.1 \times 10^{-4} \pm 2.8 \times 10^{-5}$
	2.0 mg/kg	$1.2 \times 10^{-3} \pm 1.2 \times 10^{-4}$	$6.8 \times 10^{-4} \pm 8.7 \times 10^{-5}$	$3.1 \times 10^{-4} \pm 8.3 \times 10^{-5}$
	6.0 mg/kg	$2.5 \times 10^{-3} \pm 8.5 \times 10^{-4}$	$1.9 \times 10^{-3} \pm 8.3 \times 10^{-4}$	$1.1 \times 10^{-3} \pm 1.9 \times 10^{-4}$
TTO-S-3 with coating	0.67 mg/kg	$2.3 \times 10^{-4} \pm 3.5 \times 10^{-5}$	$2.0 \times 10^{-4} \pm 6.2 \times 10^{-5}$	$9.2 \times 10^{-5} \pm 5.2 \times 10^{-5}$
	2.0 mg/kg	$1.1 \times 10^{-3} \pm 3.1 \times 10^{-4}$	$4.2 \times 10^{-4} \pm 2.2 \times 10^{-4}$	$4.0 \times 10^{-4} \pm 1.7 \times 10^{-4}$
	6.0 mg/kg	$2.4 \times 10^{-3} \pm 6.8 \times 10^{-4}$	$5.6 \times 10^{-4} \pm 2.5 \times 10^{-4}$	$1.6 \times 10^{-3} \pm 1.1 \times 10^{-3}$

(C) Trachea

		Trachea TiO ₂ burden per organ weight [mg/g tissue]		
		3 days after i.t.	28 days after i.t.	91 days after i.t.
Solvent		$1.4 \times 10^{-4} \pm 6.0 \times 10^{-5}$	$7.8 \times 10^{-5} \pm 6.5 \times 10^{-5}$	$8.3 \times 10^{-5} \pm 4.3 \times 10^{-5}$
P25	0.375 mg/kg	$1.6 \times 10^{-2} \pm 5.0 \times 10^{-3}$	$4.2 \times 10^{-3} \pm 1.4 \times 10^{-3}$	$2.1 \times 10^{-2} \pm 1.0 \times 10^{-2}$
	0.75 mg/kg	$3.4 \times 10^{-2} \pm 1.4 \times 10^{-2}$	$6.9 \times 10^{-3} \pm 3.1 \times 10^{-3}$	$3.8 \times 10^{-2} \pm 2.9 \times 10^{-2}$
	1.5 mg/kg	$5.4 \times 10^{-2} \pm 2.6 \times 10^{-2}$	$2.0 \times 10^{-2} \pm 8.2 \times 10^{-3}$	$4.5 \times 10^{-2} \pm 1.8 \times 10^{-2}$
	3.0 mg/kg	$4.5 \times 10^{-2} \pm 1.9 \times 10^{-2}$	$2.5 \times 10^{-2} \pm 5.1 \times 10^{-3}$	$5.9 \times 10^{-2} \pm 4.3 \times 10^{-2}$
	6.0 mg/kg	$8.6 \times 10^{-2} \pm 4.0 \times 10^{-2}$	$5.3 \times 10^{-2} \pm 2.0 \times 10^{-2}$	$0.10 \pm 2.1 \times 10^{-2}$
MT-150A	0.67 mg/kg	$4.0 \times 10^{-2} \pm 2.5 \times 10^{-2}$	$1.9 \times 10^{-2} \pm 6.3 \times 10^{-3}$	$2.3 \times 10^{-2} \pm 6.2 \times 10^{-3}$
	2.0 mg/kg	$0.12 \pm 5.8 \times 10^{-2}$	$6.3 \times 10^{-2} \pm 1.5 \times 10^{-2}$	$4.7 \times 10^{-2} \pm 4.0 \times 10^{-2}$
	6.0 mg/kg	0.22 ± 0.10	$0.11 \pm 3.6 \times 10^{-2}$	$0.18 \pm 8.7 \times 10^{-2}$
AMT-100	0.67 mg/kg	$7.3 \times 10^{-3} \pm 1.8 \times 10^{-3}$	$6.4 \times 10^{-3} \pm 1.1 \times 10^{-3}$	$2.6 \times 10^{-3} \pm 5.6 \times 10^{-4}$
	2.0 mg/kg	$2.6 \times 10^{-2} \pm 7.4 \times 10^{-3}$	$1.6 \times 10^{-2} \pm 3.6 \times 10^{-3}$	$6.8 \times 10^{-3} \pm 1.1 \times 10^{-3}$
	6.0 mg/kg	$9.2 \times 10^{-2} \pm 3.8 \times 10^{-2}$	$5.3 \times 10^{-2} \pm 9.3 \times 10^{-3}$	$2.6 \times 10^{-2} \pm 1.3 \times 10^{-2}$
MP-100	0.67 mg/kg	$6.8 \times 10^{-2} \pm 9.2 \times 10^{-2}$	$3.7 \times 10^{-2} \pm 2.9 \times 10^{-2}$	$1.9 \times 10^{-2} \pm 1.2 \times 10^{-2}$
	2.0 mg/kg	$0.12 \pm 2.6 \times 10^{-2}$	$0.15 \pm 8.3 \times 10^{-2}$	0.11 ± 0.16
	6.0 mg/kg	$0.27 \pm 7.7 \times 10^{-2}$	0.25 ± 0.15	$0.18 \pm 5.3 \times 10^{-2}$
FTL-100	0.67 mg/kg	$1.2 \times 10^{-2} \pm 3.3 \times 10^{-3}$	$3.7 \times 10^{-3} \pm 1.5 \times 10^{-3}$	$2.8 \times 10^{-3} \pm 7.8 \times 10^{-4}$
	2.0 mg/kg	$2.8 \times 10^{-2} \pm 1.4 \times 10^{-2}$	$9.8 \times 10^{-3} \pm 3.2 \times 10^{-3}$	$6.5 \times 10^{-3} \pm 1.1 \times 10^{-3}$
	6.0 mg/kg	$5.0 \times 10^{-2} \pm 4.9 \times 10^{-3}$	$3.3 \times 10^{-2} \pm 8.6 \times 10^{-3}$	$2.2 \times 10^{-2} \pm 6.5 \times 10^{-3}$
TTO-S-3 without coating	0.67 mg/kg	$9.9 \times 10^{-3} \pm 4.3 \times 10^{-3}$	$6.8 \times 10^{-3} \pm 2.6 \times 10^{-3}$	$2.3 \times 10^{-3} \pm 6.0 \times 10^{-4}$
	2.0 mg/kg	$3.8 \times 10^{-2} \pm 1.3 \times 10^{-2}$	$1.3 \times 10^{-2} \pm 4.4 \times 10^{-3}$	$6.8 \times 10^{-3} \pm 3.5 \times 10^{-3}$
	6.0 mg/kg	$7.0 \times 10^{-2} \pm 3.9 \times 10^{-2}$	$4.6 \times 10^{-2} \pm 1.8 \times 10^{-2}$	$2.0 \times 10^{-2} \pm 7.3 \times 10^{-3}$
TTO-S-3 with coating	0.67 mg/kg	$1.4 \times 10^{-2} \pm 4.2 \times 10^{-3}$	$6.5 \times 10^{-3} \pm 3.0 \times 10^{-3}$	$6.4 \times 10^{-3} \pm 3.6 \times 10^{-3}$
	2.0 mg/kg	$2.4 \times 10^{-2} \pm 4.9 \times 10^{-3}$	$2.2 \times 10^{-2} \pm 8.0 \times 10^{-3}$	$1.6 \times 10^{-2} \pm 3.8 \times 10^{-3}$
	6.0 mg/kg	$5.8 \times 10^{-2} \pm 1.7 \times 10^{-2}$	$4.0 \times 10^{-2} \pm 8.4 \times 10^{-3}$	$4.4 \times 10^{-2} \pm 2.9 \times 10^{-2}$

(D) Lymph nodes

		Lymph nodes TiO ₂ burden per organ weight [mg/g tissue]		
		3 days after i.t.	28 days after i.t.	91 days after i.t.
Solvent		$2.4 \times 10^{-4} \pm 3.9 \times 10^{-4}$	$6.6 \times 10^{-4} \pm 3.9 \times 10^{-4}$	$3.2 \times 10^{-4} \pm 3.2 \times 10^{-4}$
P25	0.375 mg/kg	$8.8 \times 10^{-4} \pm 4.7 \times 10^{-4}$	$1.9 \times 10^{-3} \pm 1.0 \times 10^{-3}$	$4.5 \times 10^{-3} \pm 2.2 \times 10^{-3}$
	0.75 mg/kg	$9.1 \times 10^{-4} \pm 6.1 \times 10^{-4}$	$1.1 \times 10^{-3} \pm 8.8 \times 10^{-4}$	$4.4 \times 10^{-3} \pm 1.8 \times 10^{-3}$
	1.5 mg/kg	$8.4 \times 10^{-3} \pm 4.5 \times 10^{-3}$	$1.0 \times 10^{-2} \pm 5.3 \times 10^{-3}$	$2.4 \times 10^{-2} \pm 9.1 \times 10^{-3}$
	3.0 mg/kg	$1.6 \times 10^{-2} \pm 1.2 \times 10^{-2}$	$0.11 \pm 5.7 \times 10^{-2}$	$0.15 \pm 2.9 \times 10^{-2}$
	6.0 mg/kg	$9.1 \times 10^{-2} \pm 2.6 \times 10^{-2}$	0.74 ± 0.12	0.60 ± 0.23
MT-150A	0.67 mg/kg	$5.0 \times 10^{-3} \pm 5.2 \times 10^{-3}$	$1.1 \times 10^{-2} \pm 5.3 \times 10^{-3}$	$2.0 \times 10^{-3} \pm 6.4 \times 10^{-4}$
	2.0 mg/kg	$1.8 \times 10^{-2} \pm 2.0 \times 10^{-2}$	$5.9 \times 10^{-2} \pm 3.7 \times 10^{-2}$	$2.6 \times 10^{-2} \pm 4.1 \times 10^{-3}$
	6.0 mg/kg	$9.2 \times 10^{-2} \pm 2.0 \times 10^{-2}$	0.30 ± 0.13	$0.19 \pm 5.1 \times 10^{-2}$
AMT-100	0.67 mg/kg	$4.3 \times 10^{-4} \pm 1.8 \times 10^{-4}$	$6.8 \times 10^{-4} \pm 1.3 \times 10^{-4}$	$6.2 \times 10^{-4} \pm 2.0 \times 10^{-4}$
	2.0 mg/kg	$2.3 \times 10^{-3} \pm 6.3 \times 10^{-4}$	$5.7 \times 10^{-3} \pm 2.7 \times 10^{-3}$	$4.8 \times 10^{-3} \pm 1.6 \times 10^{-3}$
	6.0 mg/kg	$3.6 \times 10^{-2} \pm 8.9 \times 10^{-3}$	$7.5 \times 10^{-2} \pm 1.4 \times 10^{-2}$	$0.13 \pm 4.3 \times 10^{-2}$
MP-100	0.67 mg/kg	$9.1 \times 10^{-4} \pm 5.7 \times 10^{-4}$	$7.2 \times 10^{-3} \pm 3.9 \times 10^{-3}$	$1.1 \times 10^{-2} \pm 9.1 \times 10^{-3}$
	2.0 mg/kg	$4.4 \times 10^{-3} \pm 1.2 \times 10^{-3}$	$2.9 \times 10^{-2} \pm 1.3 \times 10^{-2}$	$8.7 \times 10^{-2} \pm 6.4 \times 10^{-2}$
	6.0 mg/kg	$2.6 \times 10^{-2} \pm 1.0 \times 10^{-2}$	$7.0 \times 10^{-2} \pm 2.6 \times 10^{-2}$	0.33 ± 0.13
FTL-100	0.67 mg/kg	$6.5 \times 10^{-4} \pm 9.4 \times 10^{-5}$	$8.1 \times 10^{-4} \pm 2.5 \times 10^{-4}$	$8.0 \times 10^{-4} \pm 2.4 \times 10^{-4}$
	2.0 mg/kg	$6.2 \times 10^{-3} \pm 2.3 \times 10^{-3}$	$5.4 \times 10^{-3} \pm 8.7 \times 10^{-4}$	$1.5 \times 10^{-2} \pm 3.3 \times 10^{-3}$
	6.0 mg/kg	$4.7 \times 10^{-2} \pm 1.3 \times 10^{-2}$	$0.12 \pm 3.7 \times 10^{-2}$	$0.33 \pm 4.8 \times 10^{-2}$
TTO-S-3 without coating	0.67 mg/kg	$4.4 \times 10^{-4} \pm 2.2 \times 10^{-4}$	$1.0 \times 10^{-3} \pm 4.4 \times 10^{-4}$	$8.2 \times 10^{-4} \pm 6.2 \times 10^{-4}$
	2.0 mg/kg	$7.5 \times 10^{-3} \pm 1.9 \times 10^{-3}$	$1.4 \times 10^{-2} \pm 7.4 \times 10^{-3}$	$1.5 \times 10^{-2} \pm 8.2 \times 10^{-3}$
	6.0 mg/kg	$5.9 \times 10^{-2} \pm 8.9 \times 10^{-3}$	$0.25 \pm 7.7 \times 10^{-2}$	$0.26 \pm 6.0 \times 10^{-2}$
TTO-S-3 with coating	0.67 mg/kg	$1.0 \times 10^{-3} \pm 3.0 \times 10^{-4}$	$1.5 \times 10^{-2} \pm 5.0 \times 10^{-3}$	$2.3 \times 10^{-2} \pm 1.5 \times 10^{-2}$
	2.0 mg/kg	$4.9 \times 10^{-3} \pm 1.2 \times 10^{-3}$	$0.16 \pm 2.2 \times 10^{-2}$	$0.16 \pm 5.7 \times 10^{-2}$
	6.0 mg/kg	$2.1 \times 10^{-2} \pm 3.8 \times 10^{-3}$	$0.44 \pm 6.4 \times 10^{-2}$	1.2 ± 0.13

(E) Liver.

		Liver TiO ₂ burden per organ weight [mg/g tissue]		
		3 days after i.t.	28 days after i.t.	91 days after i.t.
Solvent		$<3.3 \times 10^{-6}$	$<3.3 \times 10^{-6}$	$<3.3 \times 10^{-6}$
P25	0.375 mg/kg	$4.4 \times 10^{-6} \pm 2.2 \times 10^{-6}$	$5.7 \times 10^{-6} \pm 9.0 \times 10^{-6}$	$3.5 \times 10^{-6} \pm 1.7 \times 10^{-6}$
	0.75 mg/kg	$<3.3 \times 10^{-6}$	$<3.3 \times 10^{-6}$	$6.0 \times 10^{-6} \pm 9.7 \times 10^{-6}$
	1.5 mg/kg	$8.7 \times 10^{-6} \pm 1.5 \times 10^{-5}$	$9.1 \times 10^{-6} \pm 1.1 \times 10^{-5}$	$6.2 \times 10^{-6} \pm 6.0 \times 10^{-6}$
	3.0 mg/kg	$<3.3 \times 10^{-6}$	$6.0 \times 10^{-5} \pm 9.9 \times 10^{-5}$	$2.0 \times 10^{-5} \pm 3.0 \times 10^{-5}$
	6.0 mg/kg	$5.5 \times 10^{-6} \pm 3.1 \times 10^{-6}$	$6.0 \times 10^{-6} \pm 1.6 \times 10^{-6}$	$2.2 \times 10^{-5} \pm 9.5 \times 10^{-6}$
MT-150A	0.67 mg/kg	$5.3 \times 10^{-6} \pm 3.6 \times 10^{-6}$	$9.4 \times 10^{-6} \pm 1.5 \times 10^{-5}$	$4.9 \times 10^{-6} \pm 6.1 \times 10^{-6}$
	2.0 mg/kg	$3.1 \times 10^{-5} \pm 2.4 \times 10^{-5}$	$4.5 \times 10^{-6} \pm 3.7 \times 10^{-6}$	$7.3 \times 10^{-6} \pm 4.7 \times 10^{-6}$
	6.0 mg/kg	$3.1 \times 10^{-5} \pm 8.0 \times 10^{-6}$	$1.6 \times 10^{-5} \pm 9.0 \times 10^{-6}$	$3.7 \times 10^{-5} \pm 1.3 \times 10^{-5}$
AMT-100	0.67 mg/kg	$6.4 \times 10^{-6} \pm 2.9 \times 10^{-6}$	$5.2 \times 10^{-6} \pm 2.1 \times 10^{-6}$	$4.0 \times 10^{-6} \pm 3.3 \times 10^{-6}$
	2.0 mg/kg	$7.6 \times 10^{-6} \pm 3.9 \times 10^{-6}$	$1.4 \times 10^{-5} \pm 2.2 \times 10^{-5}$	$3.2 \times 10^{-6} \pm 1.4 \times 10^{-6}$
	6.0 mg/kg	$1.2 \times 10^{-5} \pm 7.0 \times 10^{-6}$	$2.8 \times 10^{-5} \pm 2.1 \times 10^{-5}$	$2.0 \times 10^{-5} \pm 1.3 \times 10^{-5}$
MP-100	0.67 mg/kg	$5.9 \times 10^{-6} \pm 3.0 \times 10^{-6}$	$6.5 \times 10^{-6} \pm 4.7 \times 10^{-6}$	$4.8 \times 10^{-6} \pm 3.4 \times 10^{-6}$
	2.0 mg/kg	$7.1 \times 10^{-6} \pm 1.8 \times 10^{-6}$	$3.5 \times 10^{-5} \pm 4.8 \times 10^{-5}$	$9.2 \times 10^{-6} \pm 3.8 \times 10^{-6}$
	6.0 mg/kg	$5.9 \times 10^{-5} \pm 6.3 \times 10^{-5}$	$3.0 \times 10^{-5} \pm 1.5 \times 10^{-5}$	$5.1 \times 10^{-5} \pm 6.8 \times 10^{-5}$
FTL-100	0.67 mg/kg	$6.8 \times 10^{-6} \pm 4.8 \times 10^{-6}$	$7.7 \times 10^{-6} \pm 6.0 \times 10^{-7}$	$1.3 \times 10^{-5} \pm 1.7 \times 10^{-6}$
	2.0 mg/kg	$6.0 \times 10^{-6} \pm 2.6 \times 10^{-6}$	$1.2 \times 10^{-5} \pm 5.9 \times 10^{-7}$	$4.3 \times 10^{-5} \pm 9.7 \times 10^{-6}$
	6.0 mg/kg	$1.1 \times 10^{-5} \pm 5.7 \times 10^{-6}$	$2.6 \times 10^{-5} \pm 3.7 \times 10^{-6}$	$2.1 \times 10^{-4} \pm 1.7 \times 10^{-4}$
TTO-S-3 without coating	0.67 mg/kg	$6.6 \times 10^{-6} \pm 2.7 \times 10^{-6}$	$4.2 \times 10^{-6} \pm 6.1 \times 10^{-7}$	$4.2 \times 10^{-6} \pm 5.7 \times 10^{-6}$
	2.0 mg/kg	$1.3 \times 10^{-5} \pm 4.8 \times 10^{-6}$	$1.9 \times 10^{-5} \pm 2.0 \times 10^{-5}$	$<3.3 \times 10^{-6}$
	6.0 mg/kg	$1.5 \times 10^{-5} \pm 8.8 \times 10^{-6}$	$1.9 \times 10^{-5} \pm 7.4 \times 10^{-6}$	$2.1 \times 10^{-5} \pm 2.4 \times 10^{-5}$
TTO-S-3 with coating	0.67 mg/kg	$6.2 \times 10^{-6} \pm 3.4 \times 10^{-6}$	$<3.3 \times 10^{-6}$	$5.9 \times 10^{-6} \pm 7.2 \times 10^{-6}$
	2.0 mg/kg	$<3.3 \times 10^{-6}$	$4.0 \times 10^{-6} \pm 5.3 \times 10^{-6}$	$8.5 \times 10^{-6} \pm 1.0 \times 10^{-5}$
	6.0 mg/kg	$2.0 \times 10^{-5} \pm 9.2 \times 10^{-6}$	$1.0 \times 10^{-5} \pm 7.3 \times 10^{-6}$	$2.7 \times 10^{-5} \pm 2.6 \times 10^{-5}$

Table S7. Burden ratio in parathymic lymph nodes and right and left mediastinal lymph nodes in total lymph nodes.

	Dose	Parathymic lymph nodes / Total thoracic lymph nodes			Left mediastinal lymph nodes / Total thoracic lymph nodes			Right mediastinal lymph nodes / Total thoracic lymph nodes		
		3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.
P25	0.375 mg/kg	2.9% ± 3.3%	0.63% ± 0.37%	9.8% ± 20%	57% ± 34%	65% ± 15%	53% ± 28%	40% ± 34%	34% ± 15%	37% ± 28%
	0.75 mg/kg	9.5% ± 13%	4.5% ± 7.3%	6.0% ± 12%	30% ± 37%	37% ± 34%	48% ± 31%	60% ± 34%	59% ± 31%	46% ± 21%
	1.5 mg/kg	8.0% ± 15%	9.2% ± 3.4%	3.7% ± 4.8%	51% ± 23%	45% ± 30%	43% ± 11%	41% ± 26%	46% ± 25%	53% ± 14%
	3.0 mg/kg	4.2% ± 5.2%	4.0% ± 6.7%	9.6% ± 17%	48% ± 16%	52% ± 25%	40% ± 28%	48% ± 26%	44% ± 25%	51% ± 14%
	6.0 mg/kg	2.3% ± 4.8%	0.15% ± 0.094%	0.088% ± 0.14%	59% ± 24%	35% ± 13%	49% ± 15%	39% ± 19%	65% ± 22%	51% ± 19%
MT150AW										
	Dose	Parathymic lymph nodes / Total thoracic lymph nodes			Left mediastinal lymph nodes / Total thoracic lymph nodes			Right mediastinal lymph nodes / Total thoracic lymph nodes		
		3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.
	0.67 mg/kg	3.0% ± 2.4%	9.5% ± 18%	4.3% ± 6.5%	52% ± 28%	34% ± 23%	24% ± 17%	45% ± 29%	57% ± 30%	72% ± 17%
	2.0 mg/kg	1.2% ± 1.4%	3.5% ± 7.7%	6.2% ± 9.8%	65% ± 32%	36% ± 12%	35% ± 34%	34% ± 31%	61% ± 18%	59% ± 32%
	6.0 mg/kg	1.1% ± 1.0%	3.8% ± 3.4%	0.91% ± 0.93%	42% ± 19%	39% ± 11%	61% ± 10%	57% ± 18%	58% ± 13%	38% ± 11%
AMT100										
	Dose	Parathymic lymph nodes / Total thoracic lymph nodes			Left mediastinal lymph nodes / Total thoracic lymph nodes			Right mediastinal lymph nodes / Total thoracic lymph nodes		
		3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.
	0.67 mg/kg	16% ± 6.0%	24% ± 14%	9.7% ± 8.9%	19% ± 18%	39% ± 22%	47% ± 6.7%	65% ± 16%	38% ± 11%	44% ± 10%
	2.0 mg/kg	6.1% ± 6.3%	4.3% ± 4.8%	1.5% ± 2.0%	31% ± 27%	68% ± 23%	61% ± 15%	63% ± 26%	28% ± 25%	38% ± 15%
	6.0 mg/kg	4.1% ± 6.1%	14% ± 32%	3.7% ± 6.6%	55% ± 22%	63% ± 31%	50% ± 24%	41% ± 22%	22% ± 16%	46% ± 21%
MP100										
	Dose	Parathymic lymph nodes / Total thoracic lymph nodes			Left mediastinal lymph nodes / Total thoracic lymph nodes			Right mediastinal lymph nodes / Total thoracic lymph nodes		
		3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.
	0.67 mg/kg	21% ± 18%	23% ± 39%	8.4% ± 16%	14% ± 13%	53% ± 47%	58% ± 29%	65% ± 26%	24% ± 32%	34% ± 32%
	2.0 mg/kg	15% ± 19%	0.93% ± 1.2%	0.13% ± 0.13%	37% ± 26%	88% ± 14%	79% ± 18%	48% ± 13%	11% ± 13%	21% ± 18%
	6.0 mg/kg	2.1% ± 3.4%	14% ± 25%	0.12% ± 0.11%	52% ± 38%	44% ± 18%	60% ± 26%	46% ± 40%	42% ± 31%	40% ± 26%
FTL100										
	Dose	Parathymic lymph nodes / Total thoracic lymph nodes			Left mediastinal lymph nodes / Total thoracic lymph nodes			Right mediastinal lymph nodes / Total thoracic lymph nodes		
		3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.
	0.67 mg/kg	7.8% ± 4.6%	50% ± 26%	4.6% ± 4.3%	41% ± 14%	5.3% ± 10%	53% ± 10%	52% ± 18%	44% ± 18%	43% ± 9.5%
	2.0 mg/kg	17% ± 37%	32% ± 35%	21% ± 29%	53% ± 41%	35% ± 34%	29% ± 25%	30% ± 29%	33% ± 18%	50% ± 21%
	6.0 mg/kg	11% ± 20%	21% ± 11%	22% ± 42%	42% ± 39%	11% ± 15%	47% ± 42%	36% ± 38%	32% ± 34%	37% ± 32%
TTOS3 without coating										
	Dose	Parathymic lymph nodes / Total thoracic lymph nodes			Left mediastinal lymph nodes / Total thoracic lymph nodes			Right mediastinal lymph nodes / Total thoracic lymph nodes		
		3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.	13 weekafter i.t.
	0.67 mg/kg	9.1% ± 6.5%	1.5% ± 0.60%	9.9% ± 16%	37% ± 21%	58% ± 18%	71% ± 18%	54% ± 20%	41% ± 19%	19% ± 19%
	2.0 mg/kg	4.2% ± 5.5%	2.2% ± 1.5%	15% ± 32%	69% ± 15%	26% ± 23%	58% ± 36%	26% ± 14%	72% ± 23%	28% ± 14%
	6.0 mg/kg	16% ± 33%	1.6% ± 2.5%	0.14% ± 0.065%	46% ± 34%	66% ± 6.3%	42% ± 18%	38% ± 24%	32% ± 6.6%	58% ± 18%
TTOS3 with coating										
	Dose	Parathymic lymph nodes / Total thoracic lymph nodes			Left mediastinal lymph nodes / Total thoracic lymph nodes			Right mediastinal lymph nodes / Total thoracic lymph nodes		
		3 day after i.t.	4 week after i.t.	13 weekafter i.t.	3 day after i.t.	4 week after i.t.		3 day after i.t.	4 week after i.t.	13 weekafter i.t.
	0.67 mg/kg	2.3% ± 1.3%	6.8% ± 15%	1.2% ± 1.5%	43% ± 20%	50% ± 19%	69% ± 29%	55% ± 22%	43% ± 26%	29% ± 28%
	2.0 mg/kg	2.2% ± 2.3%	2.1% ± 4.4%	4.6% ± 10%	69% ± 15%	72% ± 7.6%	62% ± 13%	28% ± 15%	26% ± 6.1%	34% ± 14%
	6.0 mg/kg	4.1% ± 5.9%	1.6% ± 2.4%	3.0% ± 4.3%	56% ± 15%	59% ± 22%	59% ± 22%	40% ± 18%	40% ± 23%	38% ± 20%