

**Table S1:** Disposition of the animals used in this study.

Group	Starting animal number	Animals entered into the study <sup>a</sup>	Animals sacrificed at 3 weeks	Animals sacrificed at 1 year	Initial number of animals for the 2-year end-point	Survival to week 73 <sup>b</sup>	Survival to week 105	Mean survival time (weeks)
Untreated	30	30	5	5	20	19	15	101.80 ± 2.166
Vehicle	30	30	5	5	20	19	13	100.95 ± 1.858
r-nTiO <sub>2</sub> (0.25 mg)	30	30	5	5	20	20	14	102.60 ± 1.003
r-nTiO <sub>2</sub> (0.50 mg)	30	29	5	5	19	19	17	104.16 ± 0.637
POT (0.25 mg)	30	28	5	5	18	17	9	99.89 ± 2.289
POT (0.50 mg)	30	29	5	5	19	16	11	92.89 ± 4.098
MWCNT-7 (0.50 mg)	30	30	5	5	20	14	8	87.73 ± 4.635*

<sup>a</sup> Four rats died during TIPS administration: 1 rat in the 0.50 mg r-nTiO<sub>2</sub> group, 2 rats in the 0.25 POT group, and 1 rat in the 0.50 mg POT group.

<sup>b</sup> Prior to the first treatment-related death at week 73, an additional 12 rats died from non-treatment related causes. These 12 rats were excluded from the study.

\* Different from the Vehicle Control at p<0.05.

**Table S2:** Non-treatment-related deaths prior to week 73.

Group	Animal number	Cause of Death
Untreated	1	Leukemia (day 426)
Vehicle	1	Food clogging (day 478)
r-nTiO <sub>2</sub> (0.25 mg)	0	
r-nTiO <sub>2</sub> (0.50 mg)	1	Died during TIPS administration of the test material.
POT (0.25 mg)	3	2 rats died during TIPS administration of the test material. 1 rat died due to food clogging (day 481).
POT (0.50 mg)	4	1 rat died during TIPS administration of the test material. 1 rat died from urethral obstruction (day 334). 1 rat died from a skin fibroma (day 350). 1 rat died from unknown causes (day 407).
MWCNT-7 (0.50 mg)	6	1 rat died from a brain tumor (day 304). 1 rat died from leukemia (day 463). 4 rats died due to food clogging (days 372, 414, 465, 484).

**Table S3:** Final body weights.

Group	Animals Surviving to week 105	Body weights at week 105
Untreated	15	448.3 ± 23.3
Vehicle	13	427.4 ± 25.4*
r-nTiO <sub>2</sub> (0.25 mg)	14	425.7 ± 24.5
r-nTiO <sub>2</sub> (0.50 mg)	17	437.8 ± 55.5
POT (0.25 mg)	9	447.1 ± 23.7
POT (0.50 mg)	11	413.1 ± 36.1
MWCNT-7 (0.50 mg)	8	407.1 ± 25.8

\* Different from the Vehicle Control at p<0.05.

**Table S4:** Neoplastic lesions found in individual rats.

Group	Animals with tumors	Lung Tumors	Pleural Mesotheliomas	Time of Death
Untreated	3	Bronchiolo-alveolar adenocarcinoma		TS (week 105)
		Bronchiolo-alveolar adenocarcinoma		TS (week 105)
		Bronchiolo-alveolar adenocarcinoma		TS (week 105)
Vehicle	1	Bronchiolo-alveolar adenoma		TS (week 105)
r-nTiO <sub>2</sub> (0.25 mg)	2	Bronchiolo-alveolar adenoma		TS (week 105)
		Bronchiolo-alveolar adenoma		TS (week 105)
r-nTiO <sub>2</sub> (0.50 mg)	2	Bronchiolo-alveolar adenoma		TS (week 105)
		Bronchiolo-alveolar adenoma		TS (week 105)
POT (0.25 mg)	4	Bronchiolo-alveolar adenoma	Visceral mesothelioma	MS (week 94)
		Squamous cell carcinoma		TS (week 105)
			Parietal mesothelioma	MS (week 98)
			Parietal mesothelioma	TS (week 105)
POT (0.50 mg)	2	Bronchiolo-alveolar adenocarcinoma		TS (week 105)
		Bronchiolo-alveolar adenocarcinoma	Parietal mesothelioma	FD (week 75)
MWCNT-7 (0.50 mg)	7	Bronchiolo-alveolar adenoma		TS (week 105)
		Bronchiolo-alveolar adenocarcinoma		FD (week 73)
		Bronchiolo-alveolar adenocarcinoma		FD (week 92)
		Bronchiolo-alveolar adenocarcinoma		TS (week 105)
		Bronchiolo-alveolar adenocarcinoma		TS (week 105)
		Bronchiolo-alveolar adenocarcinoma	Parietal mesothelioma	MS (week 91)
			Parietal mesothelioma	FD (week 92)

TS: Terminal sacrifice  
MS: Moribund sacrifice  
FD: Found dead

**Table S5:** Incidence of other tumors.

Group	Animals examined	Leydig cell tumors	Leukemia/ Lymphoma	Subcutaneous fibroma	Preputial gland tumors	Pituitary tumors	Other
Untreated	19	10	1	2	5	0	Renal cortex adenoma (1)
Vehicle	19	11	1	3	1	4	
r-nTiO <sub>2</sub> (0.25 mg)	20	11	1	3	6	2	Oligodendroglioma (1)
r-nTiO <sub>2</sub> (0.50 mg)	19	12	1	3	3	3	Undifferentiated pancreatic carcinoma (1)
POT (0.25 mg)	17	8	2	4	2	2	Renal cortex adenocarcinoma (1) Undifferentiated pancreatic carcinoma (1) Diaphragmatic carcinoma (1) Nasal cavity squamous cell carcinoma (1)
POT (0.50 mg)	16	7	0	3	1	2	Undifferentiated pancreatic carcinoma (1) Nasal cavity squamous cell carcinoma (2)
MWCNT-7 (0.50 mg)	14	8	2	2	2	2	Anaplastic Meningeal sarcoma (1)

**Table S6:** Absolute organ weights (grams).

Group	Animals examined	Lungs	Brain	Heart	Liver	Kidneys	Spleen
Untreated	15	1.36 ± 0.10	2.15 ± 0.03	1.16 ± 0.06	14.52 ± 0.85	2.99 ± 0.20	1.11 ± 0.36
Vehicle	13	1.30 ± 0.07	2.13 ± 0.06	1.12 ± 0.08	13.54 ± 1.42 <sup>#</sup>	2.84 ± 0.23	0.94 ± 0.14
r-nTiO <sub>2</sub> (0.25 mg)	14	1.36 ± 0.08	2.15 ± 0.02	1.15 ± 0.10	13.97 ± 1.47	2.95 ± 0.19	1.11 ± 0.22
r-nTiO <sub>2</sub> (0.50 mg)	17	1.34 ± 0.06	2.13 ± 0.04	1.16 ± 0.12	14.12 ± 1.70	3.00 ± 0.23	1.13 ± 0.36
POT (0.25 mg)	9	1.35 ± 0.07 <sup>a</sup>	2.11 ± 0.05	1.15 ± 0.13	14.68 ± 1.97	3.05 ± 0.49 <sup>a</sup>	1.13 ± 0.25
POT (0.50 mg)	11	1.35 ± 0.09	2.13 ± 0.03	1.10 ± 0.05	13.47 ± 2.11	2.83 ± 0.11	1.08 ± 0.44
MWCNT-7 (0.50 mg)	8	1.94 ± 0.73 <sup>*</sup>	2.16 ± 0.04	1.16 ± 0.07	14.89 ± 2.05	2.99 ± 0.23	2.45 ± 2.84

\* : Significantly different from vehicle group at p < 0.05.

# : Significantly different from untreated group at p < 0.05.

a : n=8, one organ was omitted.

**Table S7:** Relative organ weights (expressed as percent body weight).

Group	Animals examined	Lungs	Brain	Heart	Liver	Kidneys	Spleen
Untreated	15	0.31 ± 0.03	0.48 ± 0.03	0.26 ± 0.02	3.24 ± 0.18	0.67 ± 0.05	0.25 ± 0.09
Vehicle	13	0.31 ± 0.02	0.50 ± 0.03	0.26 ± 0.02	3.17 ± 0.31	0.67 ± 0.06	0.22 ± 0.03
r-nTiO <sub>2</sub> (0.25 mg)	14	0.32 ± 0.03	0.51 ± 0.03	0.27 ± 0.03	3.28 ± 0.31	0.69 ± 0.04	0.26 ± 0.06
r-nTiO <sub>2</sub> (0.50 mg)	17	0.31 ± 0.03	0.49 ± 0.05	0.27 ± 0.02	3.25 ± 0.37	0.69 ± 0.08	0.26 ± 0.08
POT (0.25 mg)	9	0.30 ± 0.02 <sup>a</sup>	0.47 ± 0.02	0.26 ± 0.03	3.28 ± 0.40	0.68 ± 0.11 <sup>a</sup>	0.25 ± 0.06
POT (0.50 mg)	11	0.33 ± 0.04	0.52 ± 0.05	0.27 ± 0.02	3.27 ± 0.51	0.69 ± 0.07	0.26 ± 0.11
MWCNT-7 (0.50 mg)	8	0.48 ± 0.19 <sup>*</sup>	0.53 ± 0.03 <sup>*</sup>	0.28 ± 0.02 <sup>*</sup>	3.66 ± 0.45 <sup>**</sup>	0.74 ± 0.05 <sup>*</sup>	0.61 ± 0.72

\* : Significantly different from vehicle group at p < 0.05.

a : n=8, one organ was omitted.

**Table S8.** Non-neoplastic lesions in the lung and pleura .

Group	Untreated	Vehicle	r-nTiO <sub>2</sub> 0.25 mg	r-nTiO <sub>2</sub> 0.50 mg	POT 0.25 mg	POT 0.50 mg	MWCNT-7 0.50 mg
Number of animals	19	19	20	19	17	16	14
Alveolar type II epithelial cell hyperplasia	2	2	0	2	7	10 <sup>**</sup>	14 <sup>***</sup>
Bronchiolar hyperplasia	0	0	0	0	0	0	3
Alveolar macrophages <sup>a</sup>	0	0	0	0	4 <sup>*</sup>	13 <sup>***</sup>	14 <sup>**</sup>
Focal fibrosis in the lung	0	0	0	0	4 <sup>*</sup>	10 <sup>***</sup>	14 <sup>***</sup>
Granulomatous change in the lung	0	0	0	0	0	0	14 <sup>***</sup>
Mesothelial cell hyperplasia	0	0	0	0	4 <sup>*</sup>	7 <sup>**</sup>	10 <sup>***</sup>

<sup>a</sup>

Alveolar macrophages were scored as +, ++, +++. The numbers of rats with scores of ++ and +++ are shown.

\*\*\*\*\* Different from both the Untreated and the Vehicle Control at p<0.05, p<0.01, p<0.001, respectively.

**Table S9:** LDH and Total Protein found in the pleural lavage fluid of individual rats.

Group	Tumor	LDH (U/L)	Total protein (µg/ml)
Untreated		5.12	292.79
		5.38	335.62
		8.00	351.13
		8.69	310.83
		9.46	359.14
Vehicle		4.90	430.76
		5.23	375.98
		7.39	266.13
		8.18	292.12
		13.74	537.92
r-nTiO <sub>2</sub> (0.25 mg)	Bronchiolo-alveolar adenoma	3.89	215.04
		5.10	373.28
		5.95	332.94
		11.33	475.65
		14.78	3234.02
r-nTiO <sub>2</sub> (0.50 mg)		5.22	275.45
		5.77	343.68
		6.21	331.60
		6.96	155.07
		11.15	842.98
POT (0.25 mg)		4.37	66.26
		5.01	104.01
		5.14	914.28
		5.64	400.28
		16.74	1112.18
POT (0.50 mg)		5.53	238.22
		6.18	351.07
		6.64	375.98
		6.76	409.07
		6.77	231.59
MWCNT-7 (0.50 mg)		5.96	324.89
		7.39	360.49
		7.50	321.54
		7.59	660.98
		10.66	2726.85