吸入全身暴露を基軸としたナノ材料の毒性評価体系の構築とMWCNTからの知見

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鳥獣人物戯画より

背　景

- 革新的物質・素材で、過去のものとなってしまったもの
  - アスベスト
  - PCB（ポリ塩化ビフェニール）
  - カドミウム（メッキ）
  - ……
- 共通点＝体内・環境中で物理化学的に安定性 (biodurability・persistency)
  - 急性毒性が弱い　Low acute toxicity
  - 慢性毒性のために使用禁止となった

    Banned because of chronic toxicity

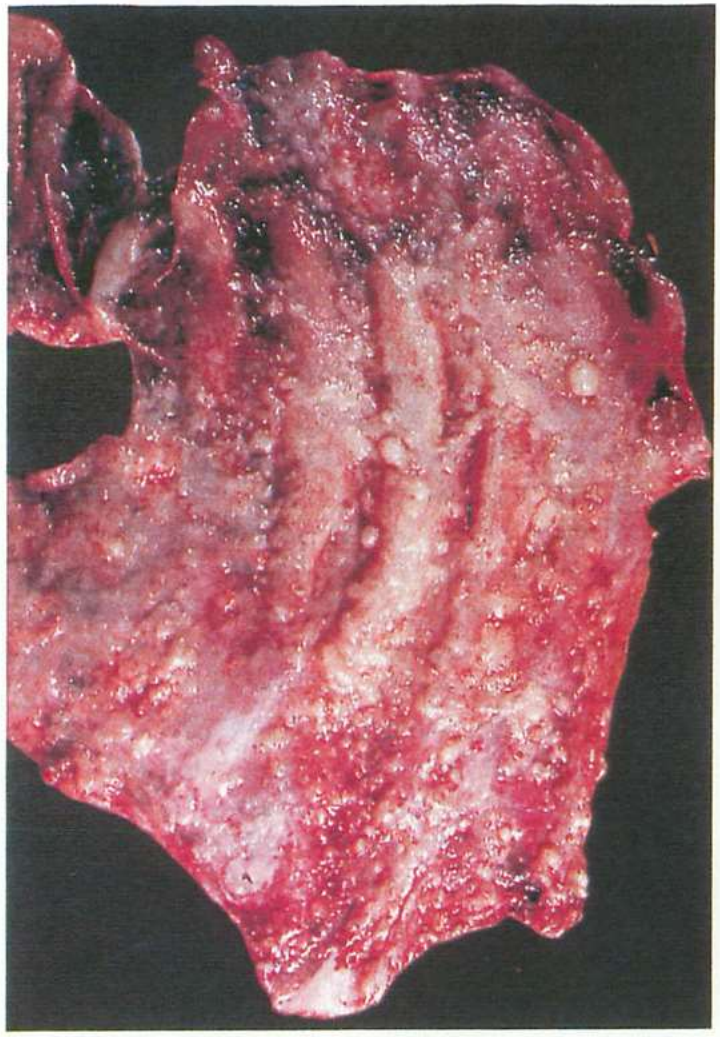


Figure 4-3

MALIGNANT MESOTHELIOMA

Malignant pleural mesothelioma appears as multiple small tumor nodules. (Fig. 4-7 from Fascicle 15, 3rd Series.)

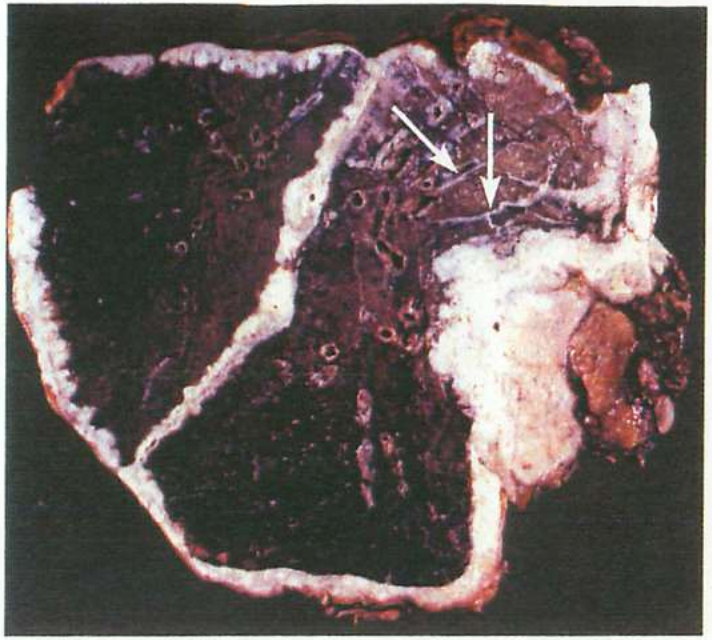


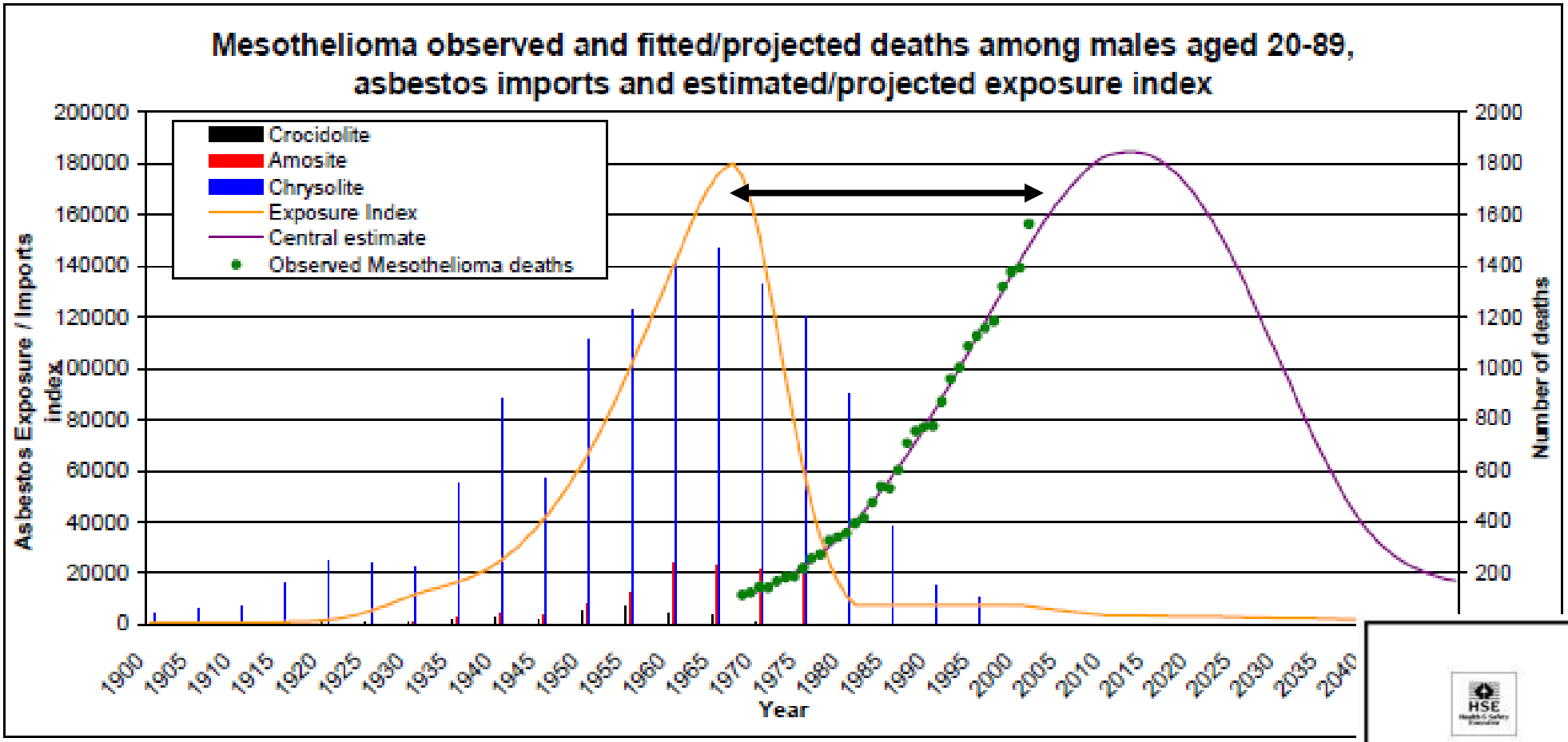
Figure 4-4

MALIGNANT MESOTHELIOMA

The tumor almost completely encases the lung and extends along the major fissure. Tumor also grows into the lung along the interlobular septa, surrounding small vessels and airways (arrows).

localized rather than diffuse disease should make one hesitate before diagnosing a diffuse malignant mesothelioma, although sometimes diffuse microscopic disease is present that is not apparent grossly. Similarly, the presence of disease thought to be benign on gross examination indicates a need for caution, although very

Figure 3



4. Discussion

繊維発癌の基礎　スタントンーポットの仮説

Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestoses and Other Fibrous Minerals [1,2]

Mearl F. Stanton, [3,4] Maxwell Layard, [5,6] Andrew Tegeris, [7] Eliza Miller, [3,8] Margaret May, [3,4] Elizabeth Morgan, [7,9] *and* Alroy Smith [5]

mercial crocidolite. Samples crocid 6, 7, 8, 11, 12, and 13 were all prepared in our laboratory by various milling, sedimentation, and flotation methods from a single lot of standard UICC crocidolite designated crocid 5. Differences in dimension were the result of

South African crocidolite and separated by centrifugation to obtain mutually exclusive size ranges from the same sample (*24*). The remaining sample, crocid 2, was

TABLE 1.—*Summary of 72 experiments with different fibrous materials*

Expt No.	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg, ≤0.25 μm × >8 μm	Expt No.	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg, ≤0.25 μm × >8 μm
1	Titanate 1	21/29	95±4.7	4.94	37	Halloy 1	4/25	20±9.0	0
2	Titanate 2	20/29	100	4.70	38	Halloy 2	5/28	23±9.3	0
3	Si carbide	17/26	100	5.15	39	Glass 8	3/26	19±10.3	3.01
4	Dawson 5	26/29	100	4.94	40	Crocid 11	4/29	19±8.5	0
5	Tremolite 1	22/28	100	3.14	41	Glass 19	2/28	15±9.0	0
6	Tremolite 2	21/28	100	2.84	42	Glass 9	2/28	14±9.4	1.84
7	Dawson 1	20/25	95±4.8	4.66	43	Alumin 6	2/28	13±8.8	0.82
8	Crocid 1	18/27	94±6.0	5.21	44	Dawson 6	3/30	13±6.9	0
9	Crocid 2	17/24	93±6.5	4.30	45	Dawson 2	2/27	12±7.9	0
10	Crocid 3	15/23	93±6.9	5.01	46	Wollaston 2	2/25	12±8.0	0
11	Amosite	14/25	93±7.1	3.53	47	Crocid 12	2/27	10±7.0	3.73
12	Crocid 4	15/24	86±9.0	5.13	48	Attapul 2	2/29	11±7.5	0
13	Glass 1	9/17	85±13.2	5.16	49	Glass 10	2/27	8±5.6	0
14	Crocid 5	14/29	78±10.8	3.29	50	Glass 11	1/27	8±5.5	0
15	Glass 2	12/31	77±16.6	4.29	51	Titanate 3	1/28	8±8.0	0
16	Glass 3	20/29	74±8.5	3.59	52	Attapul 1	2/29	8±5.3	0
17	Glass 4	18/29	71±9.1	4.02	53	Talc 1	1/26	7±6.9	0
18	Alumin 1	15/24	70±10.2	3.63	54	Glass 12	1/25	7±5.4	0
19	Glass 5	16/25	69±9.6	3.00	55	Glass 13	1/27	6±5.7	0
20	Dawson 7	16/30	68±9.8	4.71	56	Glass 14	1/25	6±5.5	0
21	Dawson 4	11/26	66±12.2	4.01	57	Glass 15	1/24	6±5.9	1.30
22	Dawson 3	9/24	66±13.4	5.73	58	Alumin 7	1/25	5±5.1	0
23	Glass 6	7/22	64±17.7	4.01	59	Glass 16	1/29	5±4.4	0
24	Crocid 6	9/27	63±13.9	4.60	60	Talc 3	1/29	4±4.3	0
25	Crocid 7	11/26	56±11.7	2.65	61	Talc 2	1/30	4±3.8	0
26	Crocid 8	8/25	53±12.9	0	62	Talc 4	1/29	5±4.9	0
27	Alumin 2	8/27	44±11.7	2.95	63	Alumin 8	1/28	3±3.4	0
28	Alumin 3	9/27	41±10.5	2.47	64	Glass 21	2/47	6±4.4	0
29	Crocid 9	8/27	33±9.8	4.25	65	Glass 22	1/45	2±2.3	0
30	Wollaston 1	5/20	31±12.5	0	66	Glass 17	0/28	0	0
31	Alumin 4	4/25	28±12.0	2.60	67	Glass 18	0/115	0	0
32	Crocid 10	6/29	37±13.5	3.09	68	Crocid 13	0/29	0	0
33	Alumin 5	4/22	22±9.8	3.73	69	Wollaston 4	0/24	0	0
34	Glass 20	4/25	22±10.0	0	70	Talc 5	0/30	0	0
35	Glass 7	5/28	21±8.7	2.50	71	Talc 6	0/30	0	3.30
36	Wollaston 3	3/21	19±10.5	0	72	Talc 7	0/29	0	0

(1) Titanate 1 — 95%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5					3.75	4.11			
>.50-1.5				3.75		4.87			
>.25-.50	3.57	4.41	4.79	4.11	4.87		6.17	4.44	
>.10-.25	3.87	5.08	5.34		6.17				
>.05-.10	3.27	5.02	5.02		4.44				
>.01-.05									

(2) Titanate 2 — 100%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5					3.70	3.40			
>.50-1.5				3.70		4.18			
>.25-.50	3.70	4.18	4.52	3.40	4.18		4.48		
>.10-.25	3.88	4.99	5.07		4.48				
>.05-.10	4.25	4.91	4.78		4.31				
>.01-.05	3.40								

(3) Si Carbide — 100%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0					1.82	1.35			
>1.5-2.5				2.25	1.82	1.65	1.35		
>.50-1.5	2.92	3.08	3.03	2.04	1.95				
>.25-.50	3.29	3.89	4.20	3.24	1.35				
>.10-.25	0.81	4.01	4.19	4.40					
>.05-.10		4.21	4.41	4.56					
>.01-.05	3.78	4.48	4.54	4.74					
				4.70					

(4) Dawson 5 — 100%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5				1.87	3.02				
>.50-1.5		2.18	1.87	3.50					
>.25-.50	3.24	4.23	4.25		4.53				
>.10-.25		2.83	3.73		4.93				
>.05-.10									
>.01-.05									

(5) Tremolite 1 — 100%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5				3.14	3.14	3.14			
>.50-1.5	3.84	4.47	3.92	3.92					
>.25-.50	4.10	4.35	3.14		3.14				
>.10-.25	4.20	4.14	3.44		3.44				
>.05-.10	3.69	3.54	3.14		3.14				
>.01-.05									

(6) Tremolite 2 — 100%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5				2.54	3.01				
>.50-1.5		3.14	2.84	2.54					
>.25-.50		4.05	3.68	3.77					
>.10-.25	3.44	3.86	3.38		3.31				
>.05-.10	4.09	4.04	3.38		2.84				
>.01-.05	3.14	2.84							

(7) Dawson 1 — 95%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0					2.14				
>1.5-2.5	1.44	1.44	3.00	1.75					
>.50-1.5	1.92	1.92	2.22	3.68					
>.25-.50	1.75	3.16	3.32		4.25				
>.10-.25	2.62	3.70	3.90		4.66				
>.05-.10	3.40	3.62	3.62		2.62				
>.01-.05	3.57	3.57							

(8) Crocid. 1 — 94%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5				4.07					
>.50-1.5			4.07		4.56				
>.25-.50	5.75	5.69	4.67		5.15				
>.10-.25	6.52	5.62	4.67		4.37				
>.05-.10	5.87	4.67							
>.01-.05									

(9) Crocid. 2 — 93%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5									
>.50-1.5	3.53	4.53	4.37	4.30					
>.25-.50	4.22	4.83	4.70		4.22				
>.10-.25	5.55	5.57	4.73		4.00				
>.05-.10	5.71	4.96			4.00				
>.01-.05	4.57	3.83							

(10) Crocid. 3 — 93%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5					4.10	4.10			
>.50-1.5				4.10		4.40			
>.25-.50	6.12	5.71	4.95		5.01				
>.10-.25	6.52	5.84	4.10						
>.05-.10	5.62	4.58	4.10						
>.01-.05									

(11) Amosite — 93%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0					2.13				
>1.5-2.5				2.13	2.43	2.13			
>.50-1.5	2.13	3.17	3.36	3.54	2.61				
>.25-.50	3.13	3.64	3.56		3.72				
>.10-.25	3.53	3.76	3.31		3.47				
>.05-.10	2.98	2.98	3.03		2.61				
>.01-.05									

(12) Crocid. 4 — 86%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5									
>.50-1.5		2.76	3.24	3.84	3.06				
>.25-.50		4.24	3.61		4.36				
>.10-.25	3.24	4.33	4.50		4.92				
>.05-.10	2.76	4.31	4.53		4.70				
>.01-.05	3.24	3.36	3.54		3.06				

(13) Glass 1 (M0L) — 85%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5									
>.50-1.5		2.23	2.53	3.23	3.08				
>.25-.50		3.08			4.95				
>.10-.25		2.93	3.35		4.53				
>.05-.10			3.93		4.79				
>.01-.05			3.46		4.65				

(14) Crocid. 5 — 78%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0					2.81				
>1.5-2.5				2.81	2.81				
>.50-1.5	3.59	4.19	3.42	3.77	2.81				
>.25-.50	4.35	4.35	3.66		3.59				
>.10-.25	4.84	4.65	3.77		3.29				
>.05-.10	4.74	4.63	3.42						
>.01-.05	4.42	4.26	2.81						

(15) Glass 2 (M6D) — 77%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5									
>.50-1.5		2.91	3.21	3.99	3.61				
>.25-.50		3.38	2.91		4.11				
>.10-.25		3.69	3.61		4.02				
>.05-.10		4.08	3.69		3.81				
>.01-.05	3.51	3.51	3.21		3.38				

(16) Glass 3 (KL) — 74%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									0.67
>2.5-4.0			0.67	1.52	0.97				
>1.5-2.5		1.45	0.67	2.03	2.19				
>.50-1.5		2.95	2.40	3.42	2.74				
>.25-.50	2.55	3.16			3.63				
>.10-.25	3.03	3.16	3.33		3.03				
>.05-.10	2.85	4.09	3.76		3.25				
>.01-.05	3.03	3.73	3.03		3.03				
μm	>.01-1	>1-4	>4-8	>8-64	>64				

(17) Glass 4 (M6L) — 71%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0					1.53	1.23			
>1.5-2.5				1.84	2.76	2.13			
>.50-1.5	2.81	2.05	2.59	3.70	2.90				
>.25-.50	2.44	2.44	3.16		3.39				
>.10-.25	2.44	[illegible]	[illegible]		3.62				
>.05-.10	2.44	3.44	3.56		3.70				
>.01-.05		3.44	3.35		3.14				
	>.01-1	>1-4	>4-8	>8-64	>64				

(18) Alumin. 1 — 70%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0					1.20				
>4.0-8.0				1.10	1.80	0.80			
>2.5-4.0		1.20	1.82	1.90	1.40				
>1.5-2.5			1.61	2.17	1.58				
>.50-1.5	3.12	2.26	1.93	2.78	2.21				
>.25-.50			0.80		2.42				
>.10-.25			2.57		3.51				
>.05-.10					2.73				
>.01-.05			1.73		2.68				

Diameter

Length

TEXT-FIGURE 1.—Fiber distribution by common log of the number of particles per microgram in each of 34 dimensional categories.

Diameter

(10) Crocid. 3 — 93%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5					4.10	4.10			
>.50-1.5				4.10		4.40			
>.25-.50	6.12	5.71	4.95		5.01				
>.10-.25	6.52	5.84	4.10						
>.05-.10	5.62	4.58	4.10						
>.01-.05									

(13) Glass 1 (M0L) — 85%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									
>2.5-4.0									
>1.5-2.5									
>.50-1.5		2.23	2.53	3.23	3.08				
>.25-.50		3.08			4.95				
>.10-.25		2.93	3.35		4.53				
>.05-.10			3.93		4.79				
>.01-.05			3.46		4.65				

(16) Glass 3 (KL) — 74%

Diameter	>8.0	>4.0-8.0	>2.5-4.0	>1.5-2.5	>.50-1.5	>.25-.50	>.10-.25	>.05-.10	>.01-.05
>8.0									
>4.0-8.0									0.67
>2.5-4.0			0.67	1.52	0.97				
>1.5-2.5		1.45	0.67	2.03	2.19				
>.50-1.5		2.95	2.40	3.42	2.74				
>.25-.50	2.55	3.16			3.63				
>.10-.25	3.03	3.16	3.33		3.03				
>.05-.10	2.85	4.09	3.76		3.25				
>.01-.05	3.03	3.73	3.03		3.03				
μm	>.01-1	>1-4	>4-8	>8-64	>64				

TEXT-FIGURE 1.—Fiber distribution by common log of th

(19) Glass 5 (KW) 69%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	2.48	1.80	1.29	2.42
> .25-.50	1.06	0.67	1.70	2.75
> .10-.25			1.67	2.71
> .05-.10			1.67	2.51
> .01-.05				2.21

> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
0.06	0.06	0.06	0.06
0.36	0.76	0.06	1.06
0.06	1.06	1.41	1.98
1.41	1.98	2.51	1.77
2.51	1.77	3.11	2.72
3.11	2.72		

(20) Dawson, 7 68%

(21) Dawson, 4 66%

(22) Dawson, 3 66%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	3.33	3.07	2.69	2.29
> .25-.50	4.87	4.38	4.50	4.18
> .10-.25	5.31	4.41	4.74	3.91
> .05-.10	5.29	4.88	5.18	5.85
> .01-.05	5.14	4.28	5.17	5.90

> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
1.39			
2.29			
3.33			
4.87			
5.31			
5.29			
5.14			
2.28			
1.40			
1.70			
3.10			
2.71			

(23) Glass 64%

(25) Crocid. 7 56%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	2.02	0.91	1.69	1.86
> .25-.50	2.34	1.69	2.05	2.25
> .10-.25	2.51	1.91	1.86	2.29
> .05-.10	2.05	1.91	9.91	
> .01-.05	0.91	9.91		

> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
0.91	1.21	1.51	2.25
1.86	2.29	2.34	2.51
2.02	2.29	2.05	4.55
4.45	5.08	5.61	5.23

(26) Crocid 53%

(28) Alumin. 3 41%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	1.75	1.19	1.09	1.59
> .25-.50	2.61	2.33	2.42	2.36
> .10-.25	2.41	2.19	0.97	0.97
> .05-.10	1.59	0.97	1.27	
> .01-.05				

> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
1.72			
1.75	0.19		
1.82			
1.70			
0.67			
3.13			
3.43			
4.51			
5.24			
5.48			

(29) Crocid 33%

(31) Alumin. 4 28%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	2.37	1.88	2.15	2.80
> .25-.50	2.83	2.15	2.48	2.30
> .10-.25	2.29	1.98	2.15	2.37
> .05-.10	2.29		2.48	1.28
> .01-.05	2.29		2.15	0.98

> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
1.75			
1.98			
2.92	2.83	2.45	2.75
3.57	3.01	3.19	2.83
2.29	1.99	2.29	
2.29			
2.69			
3.79			
4.89			
5.03			
5.13			
4.96			

(32) Crocid 37%

(34) Glass 20 (RT) 22%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5				
> .25-.50				
> .10-.25				
> .05-.10				
> .01-.05				

> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
0.88			
0.98			
3.00			
3.24			
3.24			
2.50			
2.20			

(35) Glass 21%

μm > .01-.1 > .1-.4 > .4-.8 > .8-6.4 > 6.4

TEXT-FIGURE 1 (continued).—Fiber distribution by common log of

(37) Halloy. 1 20%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5				
> .25-.50		5.28		
> .10-.25		5.95	4.95	
> .05-.10	6.47	6.58	8.18	
> .01-.05	6.07	6.21		

(38) Halloy. 2 23%

		4.51
		4.51
6.36	6.47	
6.16	6.14	
6.33	6.89	

(39) Glass 8 (KUP)

(40) Crocid. 11 19%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	2.15	1.72	2.38	3.03
> .25-.50	2.50	2.42	2.98	1.72
> .10-.25			1.90	1.42
> .05-.10				
> .01-.05				

(41) Glass 19 (RD) 15%

	1.56
	2.16
2.56	2.92
2.67	2.37
2.43	1.26

(43) Alumin. 6 13%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	0.37	0.12	1.22	0.97
> .25-.50	0.22		0.48	0.82
> .10-.25	1.84		0.67	1.54
> .05-.10	0.82		0.70	1.49
> .01-.05			1.44	0.63

(44) Dawson. 6 13%

6.17	6.47
6.96	6.86
7.86	6.78

(46) Wollaston. 2 12%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	2.40	2.78	3.32	2.78
> .25-.50		3.18	3.43	3.18
> .10-.25		3.18	3.32	2.78
> .05-.10				
> .01-.05				

(47) Crocid. 12 10%

2.27	
2.87	3.31
3.31	3.73
4.00	4.21
4.00	4.00
3.67	3.50

(49) Glass 10 (MOS) 8%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	2.72	2.46	2.97	3.43
> .25-.50	1.76	2.99	2.37	1.17
> .10-.25	2.46	2.76	3.69	3.37
> .05-.10				
> .01-.05				

(50) Glass 11 (K2P) 8%

2.89	
3.84	
4.12	4.53
4.28	3.02
4.11	
3.91	2.89

(52) Amaput. 1 8%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5		5.12		
> .25-.50		5.48	4.64	
> .10-.25	5.75	6.50	4.94	
> .05-.10	6.62	6.65		
> .01-.05	6.96	6.65		

(53) Talc 1 7%

3.64	
4.02	
4.00	4.56
4.15	3.97
4.19	3.91
3.70	3.27

μm > .01-.1 > .1-.4 > .4-.8 > .8-6.4 > 6.4

Length

TEXT-FIGURE 1 (continued).—Fiber distribution by common log of the number

(55) Glass 13 (KFP) 6%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	2.03	2.67	2.89	3.20
> .25-.50		2.03	2.73	1.92
> .10-.25			0.92	
> .05-.10				
> .01-.05				

(56) Glass 14 (P2P) 6%

	2.00		
1.85	2.21	1.06	
2.30	2.08	1.70	
2.28	0.91	0.69	
2.56	2.51	1.21	0.81
1.21			
2.38	1.29		
1.56	0.81		

(57) Glass 15 (Y2P) 6%

	1.06		
1.94	2.12		
2.58	1.74		
3.42	2.09	1.60	
3.12	1.80		

(58) Alumin. 7 5%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	1.27	1.19	2.52	0.02
> .25-.50	1.64	1.28	2.52	1.19
> .10-.25		2.15	1.43	0.31
> .05-.10			0.31	
> .01-.05				

(59) Glass 16 (M8S) 5%

			1.37
2.21	2.75	2.90	
3.17	3.43	3.59	
3.41	2.92	3.46	2.81
3.83	2.48		
3.81			
3.85	2.45	2.14	

(60) Talc 3 4%

	2.81		
	4.24		
4.13	4.85		
3.76	3.58		
3.81	3.81		
3.28	3.41		
	2.81		

(61) Talc 2 4%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	2.68	2.76	2.58	3.06
> .25-.50	2.56	3.21	2.45	2.45
> .10-.25			2.28	1.98
> .05-.10				
> .01-.05				

(62) Talc 4 5%

		3.32	
	4.19	3.32	
4.06	4.81	3.79	
3.40	4.58	3.02	
4.38	4.22		
3.62	3.32		

(63) Alumin. 8 3%

		2.25	
	2.42	2.34	
	2.87	1.70	
2.72	2.46		
2.86	2.12		
2.71	1.99		
2.22			

(64) Glass 21 (S1) 6%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	1.15	1.15	1.15	1.46
> .25-.50	1.46	2.38	1.85	2.06
> .10-.25		2.00	1.63	1.46
> .05-.10				
> .01-.05				

(65) Glass 22 (S2) 2%

	1.17		
1.47	1.17		
1.77	2.07	1.87	
1.17	2.25	1.77	
1.87	1.47		

(66) Glass 17 (M8S) 0%

	2.45		2.85
4.43	4.83	4.38	3.79
5.17	4.88	1.87	
5.60	4.73	3.58	
5.45	4.28		
5.16			

(67) Glass 18 (YW) 0%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5	0.89	0.92	0.80	1.00
> .25-.50	0.34	0.40	0.30	0.11
> .10-.25				1.10
> .05-.10				
> .01-.05				

(68) Crocid. 13 0%

2.98			
2.98			
4.00	3.16		
4.30	4.46	2.68	
4.68	4.00		
4.50	3.63		
4.68	2.68		
4.31			

(69) Wollaston. 4 0%

			1.43
			1.56
	1.43	1.86	
	1.25	0.95	1.80
1.43	2.07	1.98	1.91
	1.86	0.95	
0.95	0.95		
0.95			

(70) Talc 5 0%

Diameter	> 8.0	> 4.0-8.0	> 2.5-4.0	> 1.5-2.5
> .50-1.5			3.43	4.33
> .25-.50			4.33	4.98
> .10-.25			4.56	4.30
> .05-.10			4.27	3.90
> .01-.05			3.97	3.60

(71) Talc 6 0%

		3.25	
	3.25	3.25	
	3.95	3.56	
4.63	4.88	3.56	3.25
4.83	4.43	3.25	3.56
4.68	3.95		
4.65	3.85	3.56	3.25
4.10	3.25		

(72) Talc 7 0%

	4.37		
4.95	5.09	3.67	
5.33	4.93	3.67	
5.18	4.37		
5.14	4.63	3.67	
4.82			

μm > .01-.1 > .1-.4 > .4-.8 > .8-6.4 > 6.4

Length

TEXT-FIGURE 1 (continued).—Fiber distribution by common log of the number of particles per microgram in each of 54 dimensional

Dose–Response Relationship of Fibrous Dusts in Intraperitoneal Studies

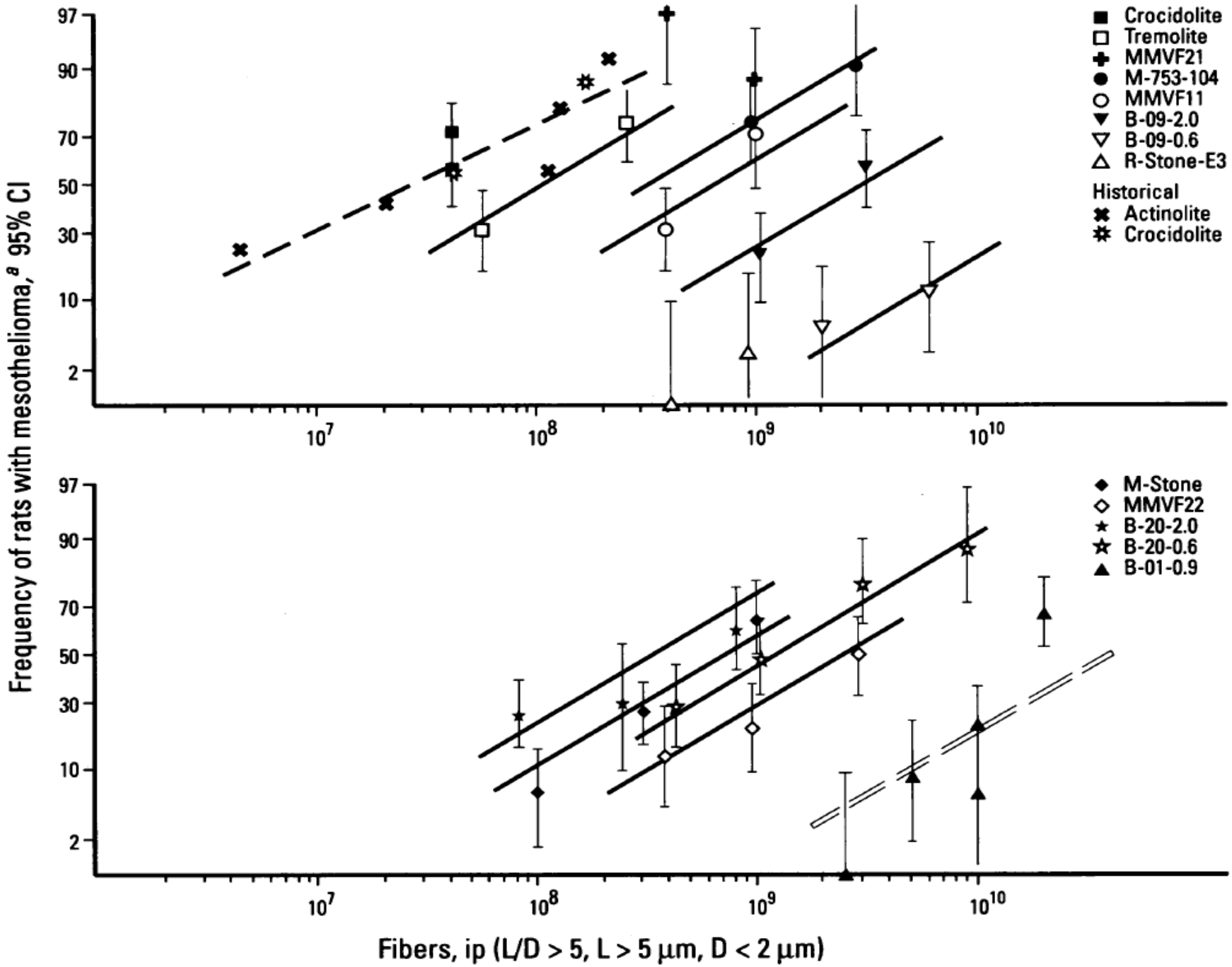
Environ Health Perspect 105(Suppl 5):1253–1256 (1997)

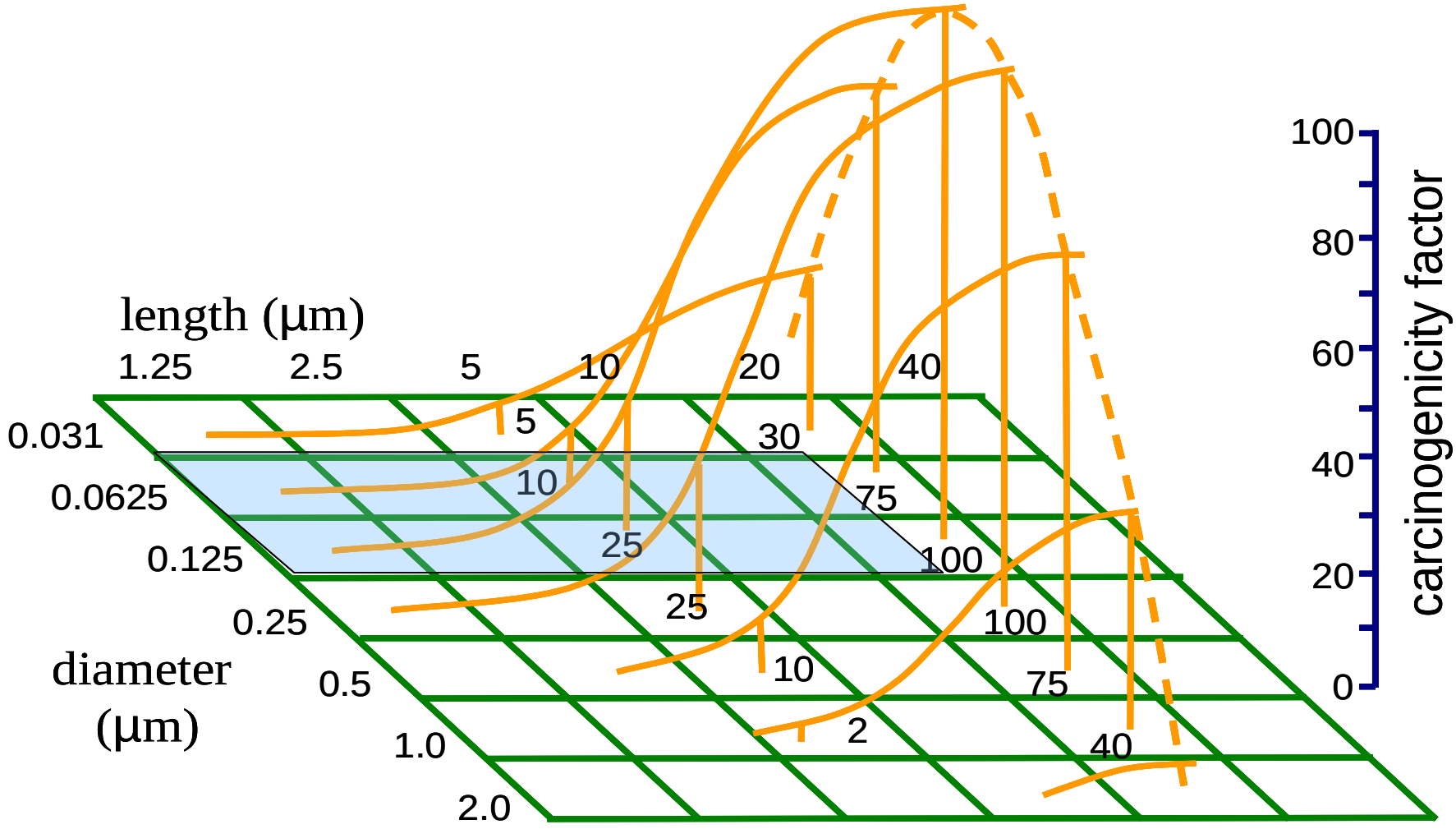
Markus Roller,[1] Friedrich Pott,[1] Kenji Kamino,[2] Gerhard-Heinrich Althoff,[1] and Bernd Bellmann[3]

Table 1. Fibrous dusts and mass doses applied in a series of carcinogenicity studies from 1990 to 1992 (number of injections × dust mass/injection, mg).

Fibrous dusts containing relatively long and thick fibers[a]	Fibrous dusts containing relatively short and thin fibers[b]
Glass fibers[c] B-01-0.9 (5×25, 10×25, 20×25, 40×25)	
B-09-2.0 (3×50, 9×50)	B-09-0.6 (2×50, 6×50)
B-20-2.0 (1×6, 1×18, 2×30)	B-09-0.6 (1×3.5, 1×8.5, 1×25, 3×25)
Glass[d] MMVF11 (2×35, 6×30)	Glass fibers[d] M-753-104 (1×17, 1×50)
Stone[d] MMVF21 (2×30, 5×30)	
Slag[e] MMVF22 (1×20, 1×50, 3×50)	Asbestos
M-Stone (1×8.5, 1×25.5, 2×42.5)	Crocidolite (5×0.1)
R-Stone-Experimental 3 (4×28.5, 9×28.5)	Tremolite (1×3.3, 1×15)

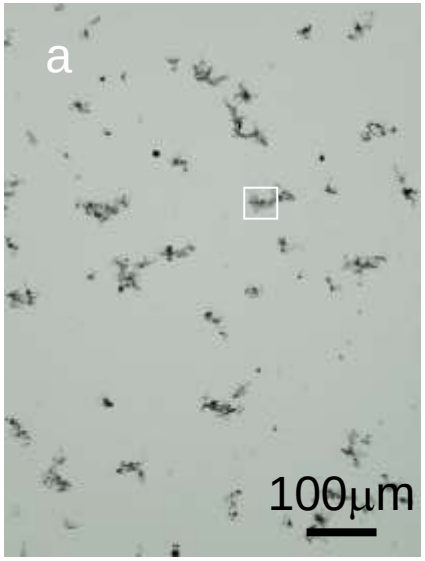
[a]Particles with aspect ratio > 5/1, median length 8–17 μm, median diameter 0.7–1.2 μm. [b]Particles with aspect ratio > 5/1, median length 2–4 μm, median diameter 0.2–0.5 μm. [c]All B-prefix fibers are glass fibers. The first number (B-01, B-09, B-20) represents a code for the chemical composition. The composition of B-20 is similar to stone fibers MMVF21. The second number indicates the nominal median diameter of the original sample. [d]The designations MMVF11 and -21 originate from the Thermal Insulation Manufacturers Association (TIMA, Stamford, CT). TIMA made the samples available for scientific purposes. The dusts were prepared from the thinnest fraction of typical commercial insulation wools and were also used in inhalation experiments in the laboratories of Research and Consulting Company (RCC), Geneva, Switzerland. Glass fibers M-753-104 are produced as microfibers, i.e., with a relatively small diameter and a chemical composition similar to MMVF11. [e]The chemical composition of this dust sample, bought in 1990 from Manville Technical Center (Denver, CO), is practically identical to the slag-wool designated MMVF22 in inhalation experiments carried out in the RCC laboratories, Switzerland.

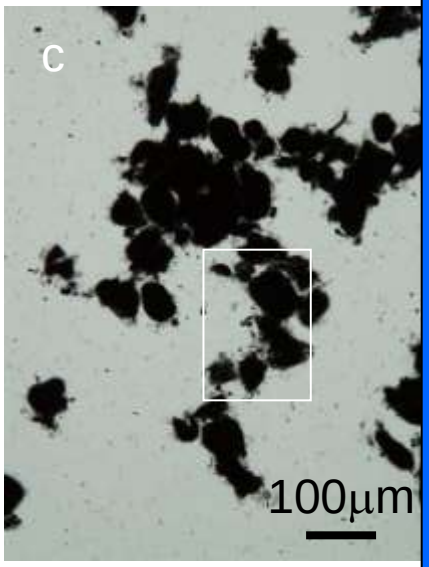

Frequency of rats with mesothelioma,[a] 95% CI
97
90
70
50
30
10
2
10^7
10^8
10^9
10^{10}
Crocidolite
Tremolite
MMVF21
M-753-104
MMVF11
B-09-2.0
B-09-0.6
R-Stone-E3
Historical
Actinolite
Crocidolite
M-Stone
MMVF22
B-20-2.0
B-20-0.6
B-01-0.9
Fibers, ip (L/D > 5, L > 5 μm, D < 2 μm)



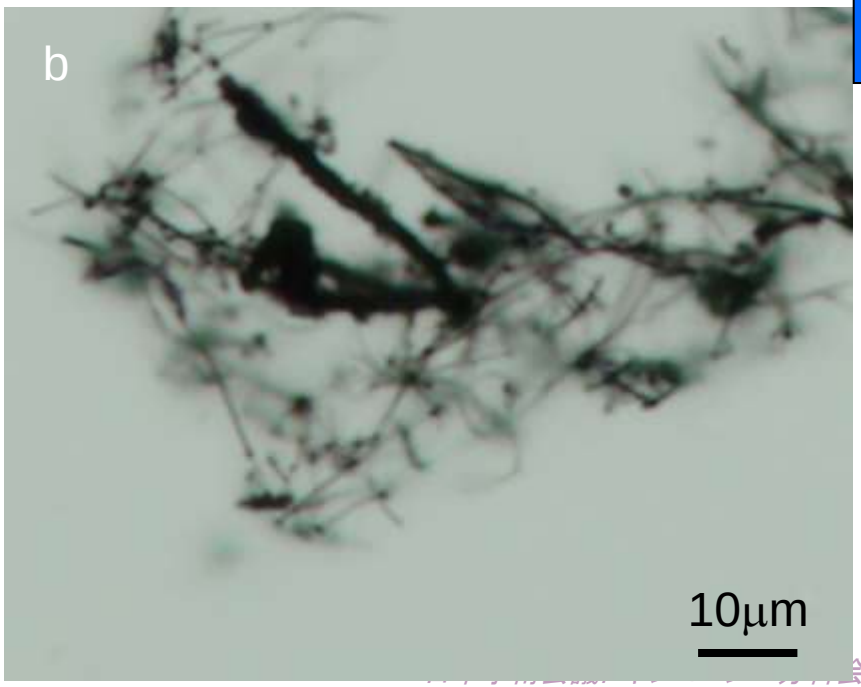
Hypothesis on the carcinogenic potency of a fibre as a function of its size with some data on “carcinogenicity factors”. From: Pott (1978).

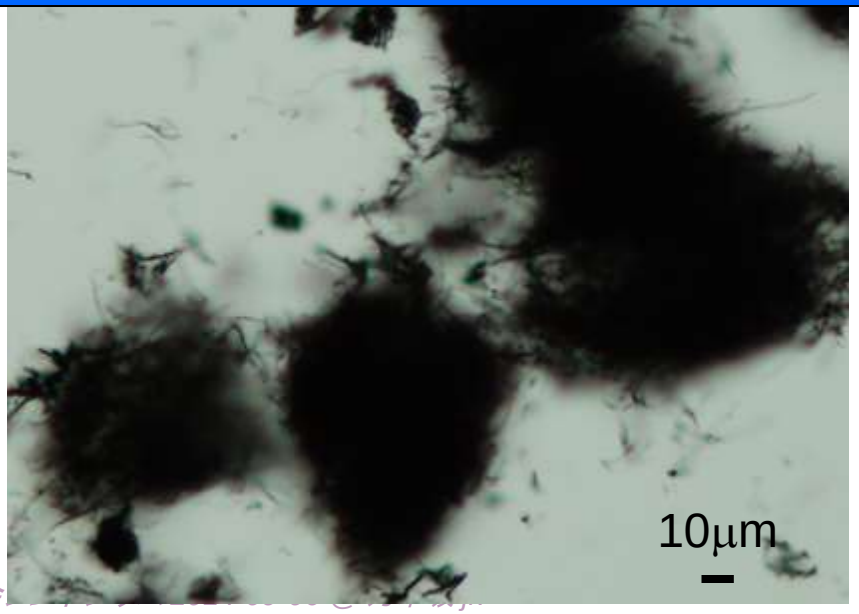
MWCNT (Mitsui)

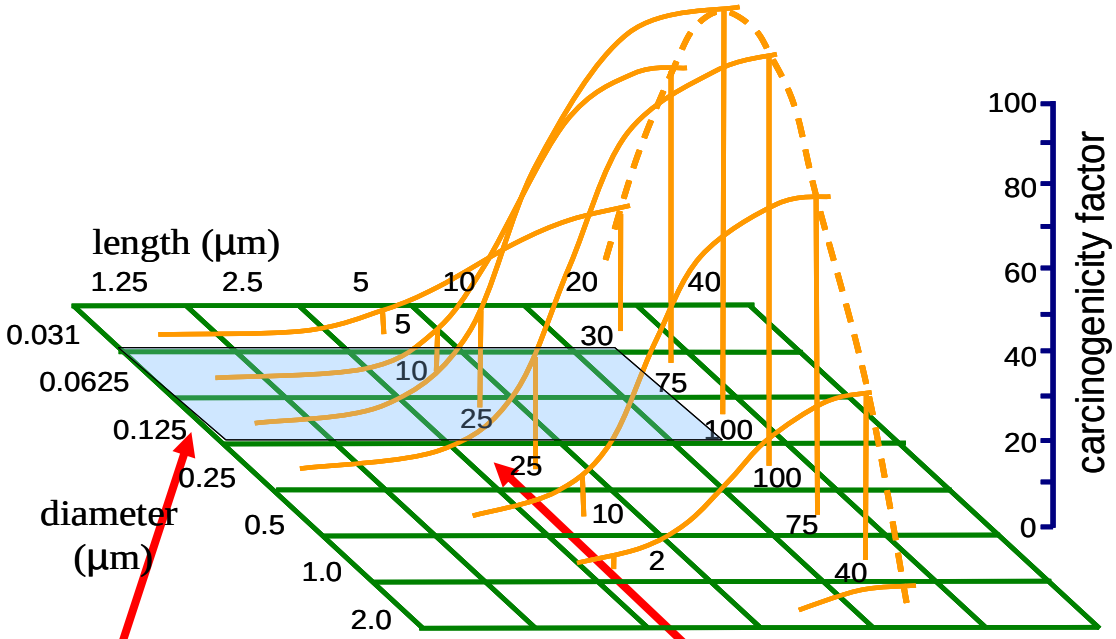




asbestos（crocidolite, 青アスベスト）

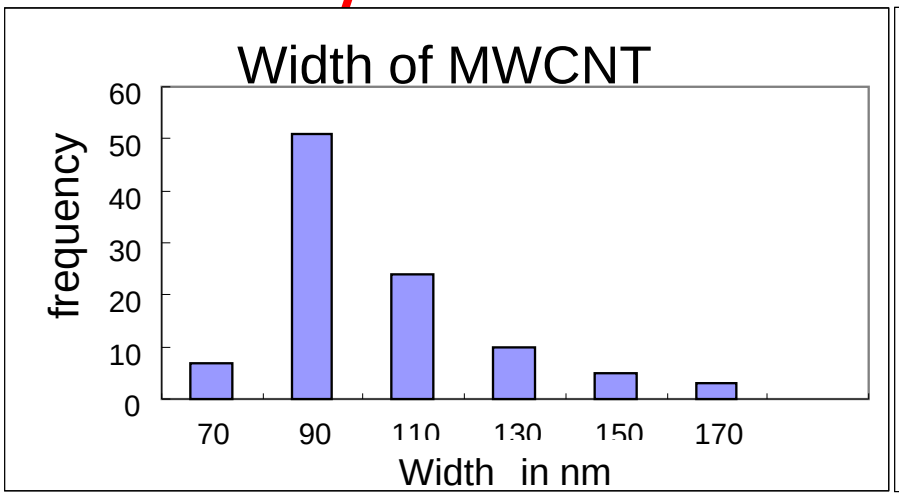


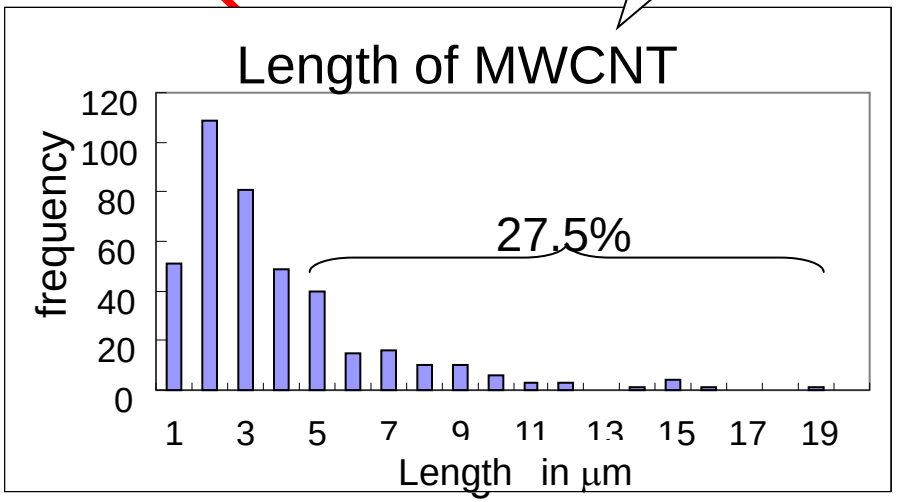




Hypothesis on the carcinogenic potency of a fibre as a function of its size with some data on "carcinogenicity factors". From: Pott (1978).

Measured at the Tokyo Metropolitan Institute of Public Health





MWCNT：3mg/animal

＝ 1.06 X10^9 fiber/mouse ＝ 1.86 X10^8 WHO fiber/mouse)

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Original Article

Induction of mesothelioma in p53+/– mouse by intraperitoneal application of multi-wall carbon nanotube

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Cancer Science
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Dose-dependent mesothelioma induction by intraperitoneal administration of multi-wall carbon nanotubes in p53 heterozygous mice

Atsuya Takagi,[1] Akihiko Hirose,[2] Mitsuru Futakuchi,[3] Hiroyuki Tsuda[4] and Jun Kanno[1,5]

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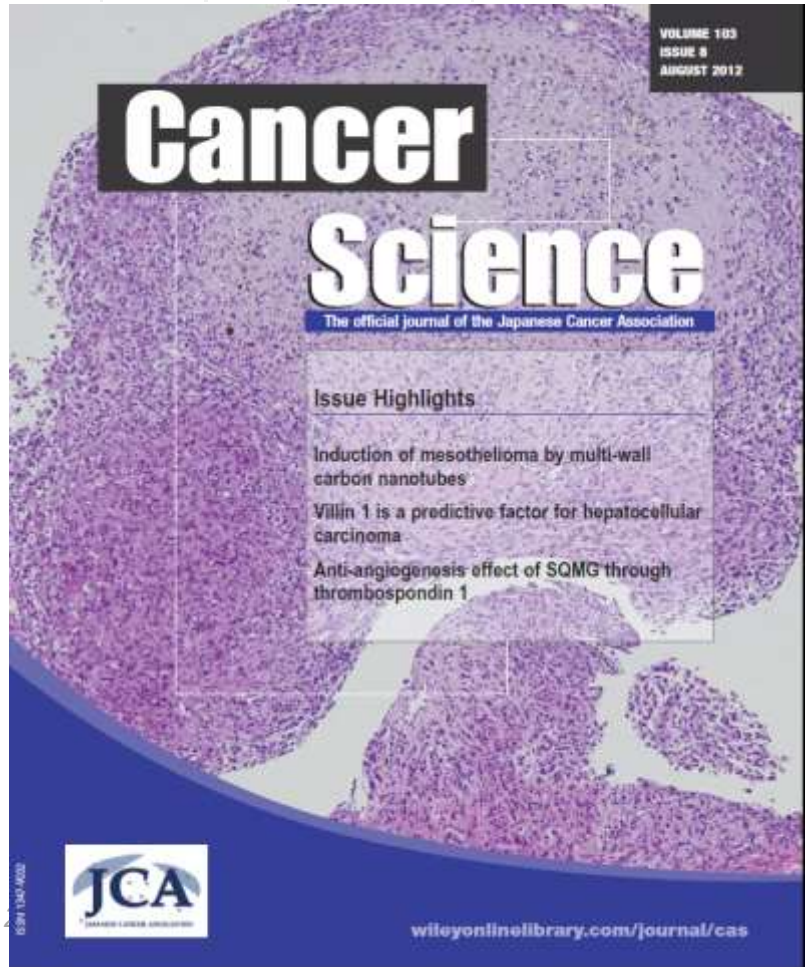
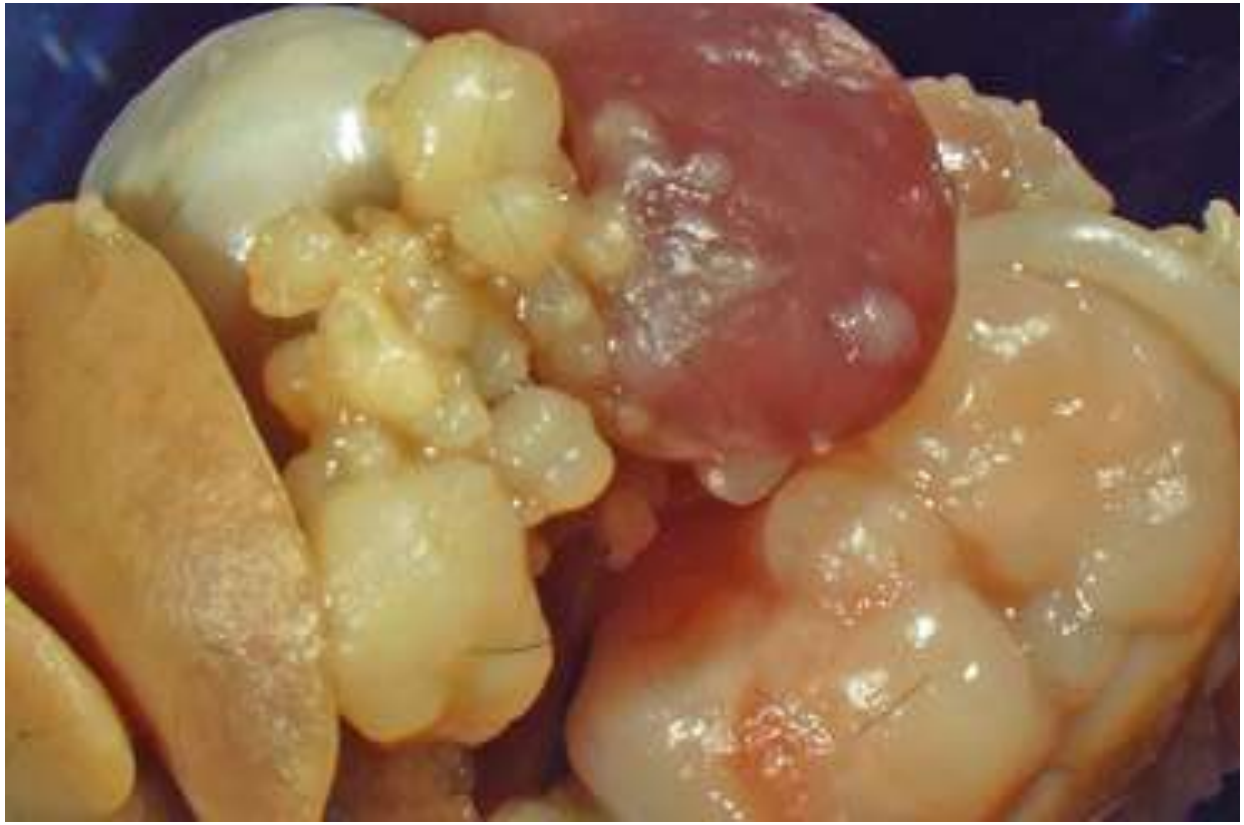
Three doses

300 μg/animal = $1x10^8$ fiber /animal
30 μg/animal = $1x10^7$ fiber /animal
3 μg/animal = $1x10^6$ fiber /animal



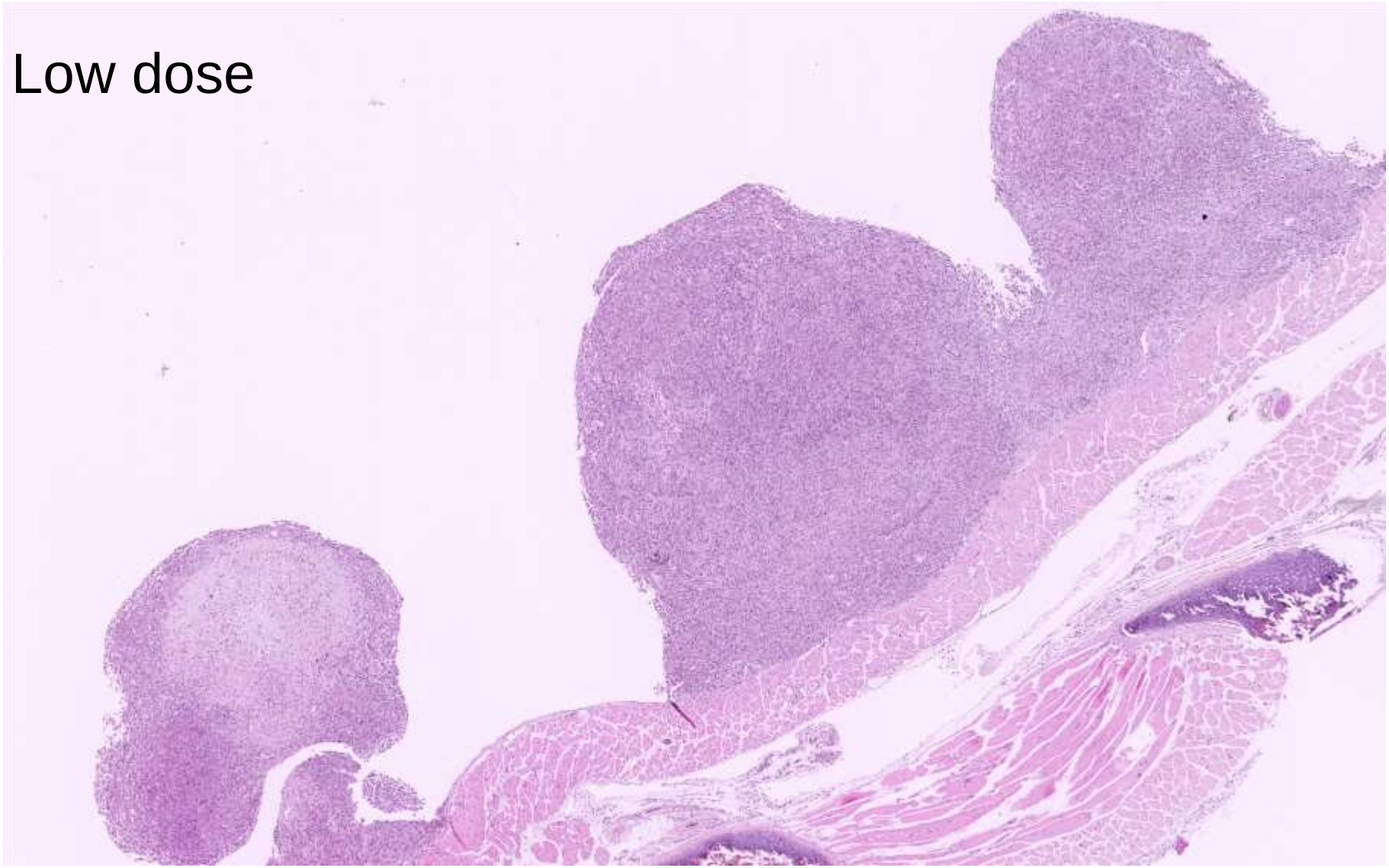
Low dose group #19

3 μg/animal = 1/1,000 of the first study



Takagi et al. Cancer Science, 2012

Low dose



NANOTOXICOLOGY

The asbestos analogy revisited

Direct injection of long multiwalled carbon nanotubes into the abdominal cavity of mice produces asbestos-like pathogenic behaviour. What does this finding mean for nanotube safety?

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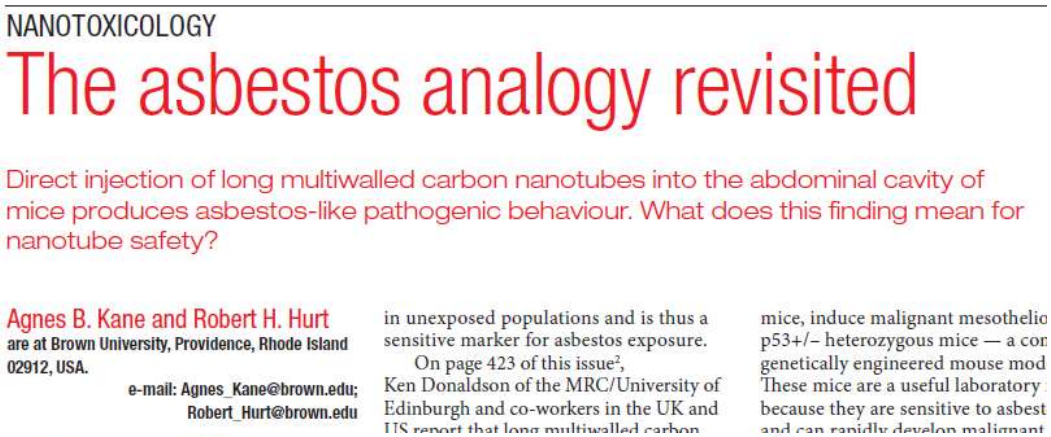
The possibility that carbon nanotubes would show asbestos-like behaviour in the human body was raised ten years ago with a call for appropriate research[1]. Exposure to asbestos is known to cause mesothelioma — cancer of the lining of the lungs (pleura) and abdominal cavity (peritoneum). The nanotube and asbestos analogy relies on several points of material similarity: small fibre diameter, long length and chemical stability in physiological environments (biopersistence). There are also differences between these two fibrous materials, such as their chemical composition and surface properties, so the validity and usefulness of the nanotube and asbestos analogy have been unclear. Two recent studies provide important new insight into the possibility that carbon nanotubes may indeed induce mesothelioma — a disease that is rare in unexposed populations and is thus a sensitive marker for asbestos exposure.

On page 423 of this issue[2], Ken Donaldson of the MRC/University of Edinburgh and co-workers in the UK and US report that long multiwalled carbon nanotubes (MWNTs) injected directly into the abdominal cavity of mice induce inflammation, formation of nodular lesions called granulomas and early fibrosis or scarring in the mesothelial lining. Shorter nanotubes had much less of an effect, as did carbon black nanoparticles used as a non-fibrous reference material. A seven-day exposure did not induce mesothelioma, but the distribution and severity of these early inflammatory and granulomatous lesions are similar to those induced by long fibres of brown asbestos (amosite), which is known to induce significant toxicity and carcinogenicity in longer-term animal studies.

Another recent study[3] by Jun Kanno of the National Institute of Health Sciences in Japan and colleagues from the Tokyo Metropolitan Institute of Public Health shows that MWNTs, also injected into the abdominal cavity of mice, induce malignant mesotheliomas in p53+/– heterozygous mice — a common genetically engineered mouse model. These mice are a useful laboratory model because they are sensitive to asbestos and can rapidly develop malignant mesothelioma following repeated exposure to asbestos fibres.

Using commercial MWNTs from the same suppliers as Donaldson and co-workers, the Japanese team observed granulomas and fibrosis in the mesothelial lining as well as tumours in 88% of the MWNT-treated mice after 25 weeks, in comparison with 79% in mice injected with crocidolite, a particularly potent form of asbestos. Minimal mesothelial reactions and no mesotheliomas were produced by the same mass dose of (non-fibrous) C_{60} fullerene. The authors conclude that asbestos fibres and MWNTs may have similar carcinogenic potential on the basis of their fibrous geometry, biopersistence and ability to generate tissue-damaging free radicals.

Both of these reports identify key physical properties of carbon nanotubes that may be relevant for potential toxicity



NANOTOXICOLOGY

The asbestos analogy revisited

Direct injection of long multiwalled carbon nanotubes into the abdominal cavity of mice produces asbestos-like pathogenic behaviour. What does this finding mean for nanotube safety?

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in unexposed populations and is thus a sensitive marker for asbestos exposure.

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In the case of carbon nanotubes and other engineered nanoproducts, we are still within a 'window of opportunity' to develop safe material design and manufacturing strategies before commercialization becomes widespread.

TOXICOLOGICAL SCIENCES 110(2), 442–448 (2009)
doi:10.1093/toxsci/kfp100
Advance Access publication May 8, 2009

発癌性が認められないことが十分に予想される実験

Absence of Carcinogenic Response to Multiwall Carbon Nanotubes in a 2-Year Bioassay in the Peritoneal Cavity of the Rat

Julie Muller,* Monique Delos,† Nadtha Panin,* Virginie Rabolli,* François Huaux,* and Dominique Lison*,[1]

*Industrial Toxicology and Occupational Medicine Unit, Catholic University of Louvain, 1200 Brussels, Belgium; and †Laboratory of Pathology, University Hospital of Mont-Godinne, Catholic University of Louvain, 5530 Yvoir, Belgium

Received April 8, 2009; accepted April 30, 2009

TABLE 1
Main Physico-chemical Characteristics of the Tested Materials

	Crocidolite[b,c]	MWCNT+[d]	MWCNT−[d]
Metal content (%)[a]	nd		
Al		1.97	0.37
Fe		0.49	<0.01
Co		0.48	<0.01
Specific surface area (m^2/g)	8	299	190
Extent of defects (I_D/I_G)[e]	nd	1.16	0.58
Reactive sites[f], molar enthalpy of adsorption of H_2O_2 (kJ/mmol)	nd	29.2	0.4
Diameter (nm)	330 (2.1)*	11.3 ± 3.9**	11.3 ± 3.9
Length (μm)	2.5 (2.0)	About 0.7	About 0.7

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発癌性が認められないことが十分に予想される実験

Ab rbon Nanotubes in
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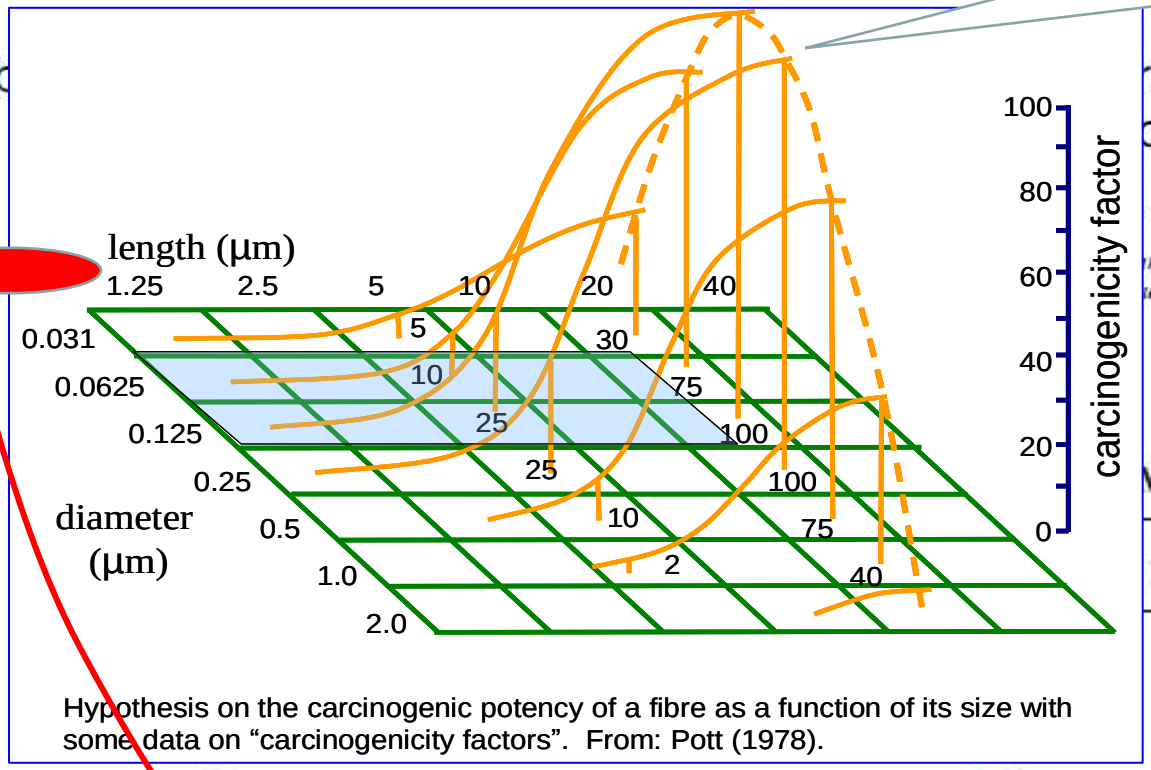
and Dominique Lison*,[1]

nd †Laboratory of Pathology, University
um



Hypothesis on the carcinogenic potency of a fibre as a function of its size with some data on "carcinogenicity factors". From: Pott (1978).

Materials

			MWCNT-[d]
			0.37
			<0.01
Co		0.48	<0.01
Specific surface area (m^2/g)	8	299	190
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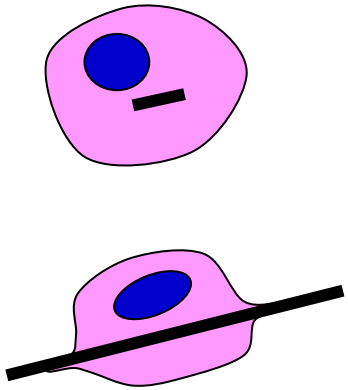
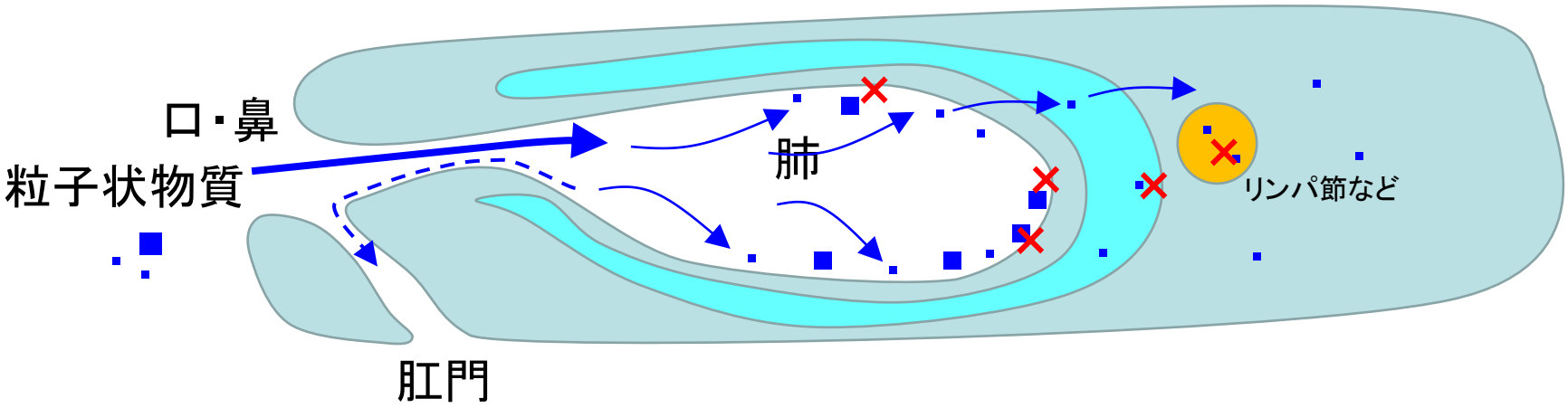
ここでの主役＝マクロファージ（大食細胞）



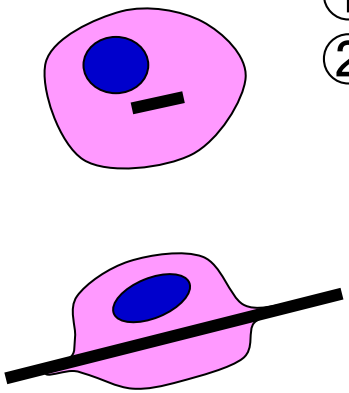
細菌や異物の掃除屋

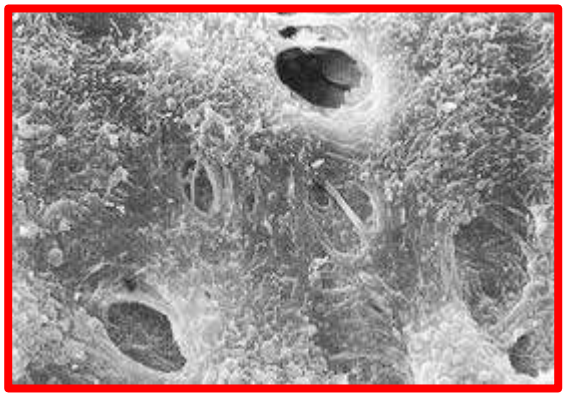
- 食べる
- 強力に分解（過酸化水素、活性酸素、酵素）
- 応援を呼ぶ（サイトカイン、活性酸素等）：炎症、肉芽腫、線維化
- 運ぶ：リンパ節などへ、（胸腔経由、リンパ管、血管経由）
- 処理しきれない時の反応
  - ①原因の隔離肉芽腫・瘢痕化
  - ②くすぶり続ける：Frustrated phagocytosis：発癌



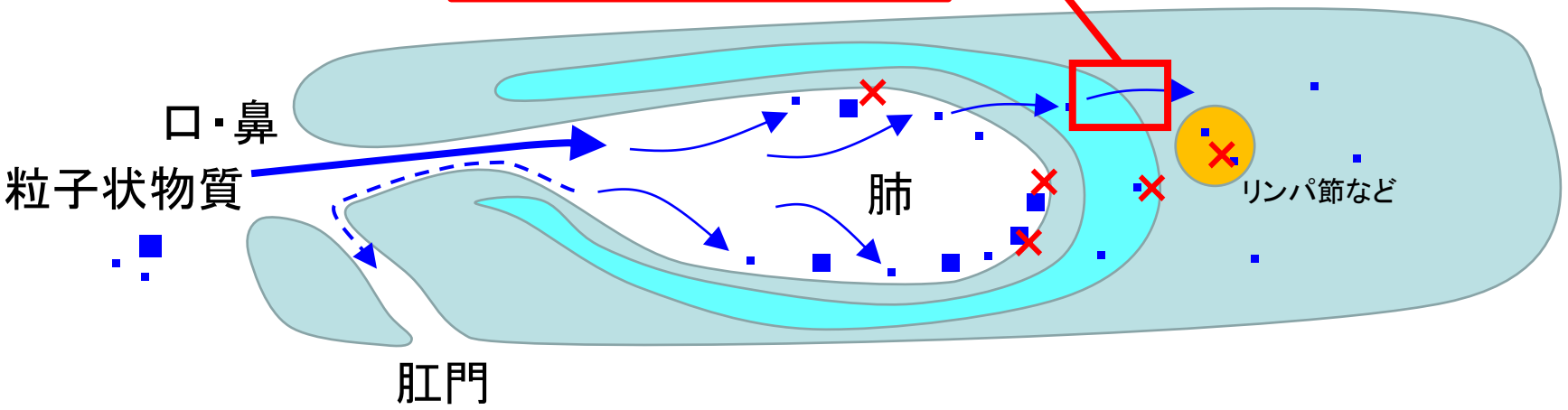
ここでの主役＝マクロファージ（大食細胞）
繊維の長さとの関係では、、

①マクロファージの大きさとの関係：貪食できるサイズを超えているか
②胸膜面の排水口の直径よりも長いか(Pleural Stomata)



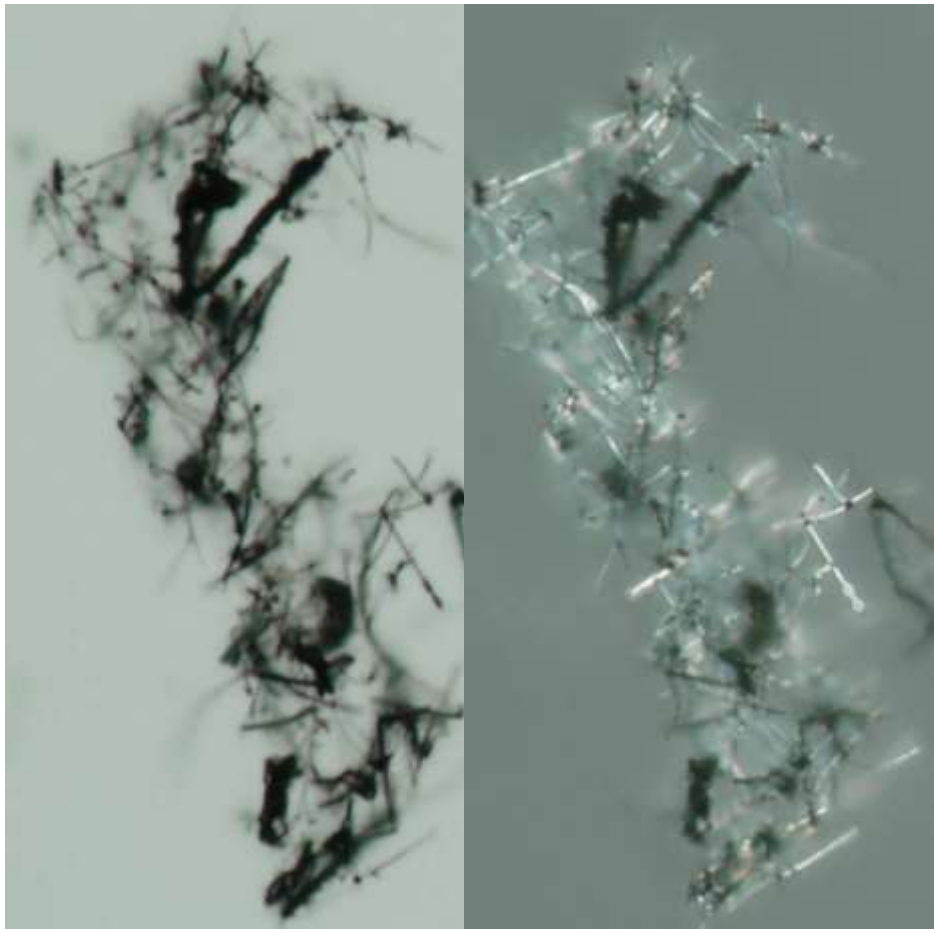


~Φ10μm



短めのMWCNTは全身に広がる
（リンパ管や血管を介して）

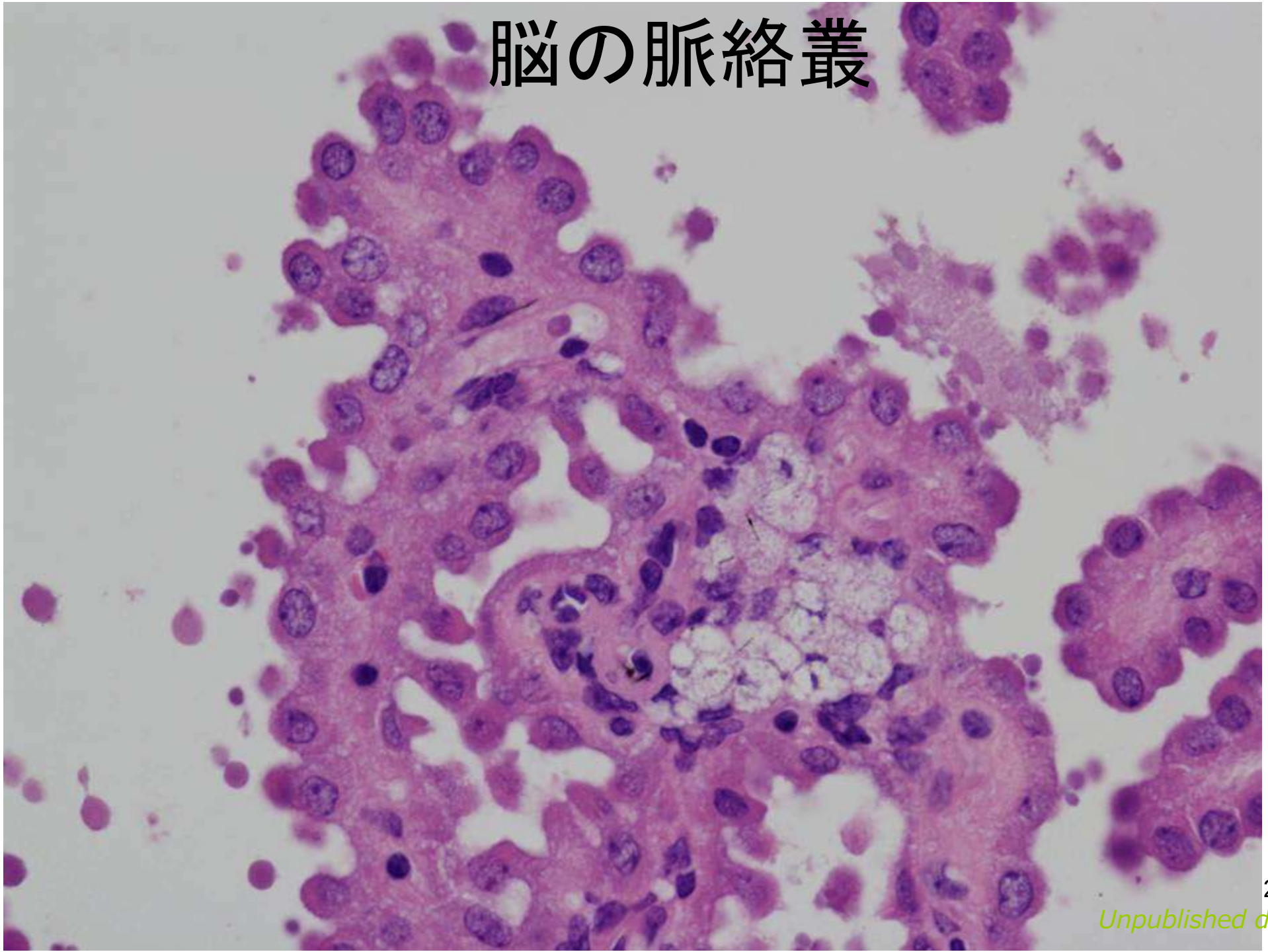
偏光顕微鏡



MWNT-7は複屈折性あり

Unpublished data

脳の脈絡叢



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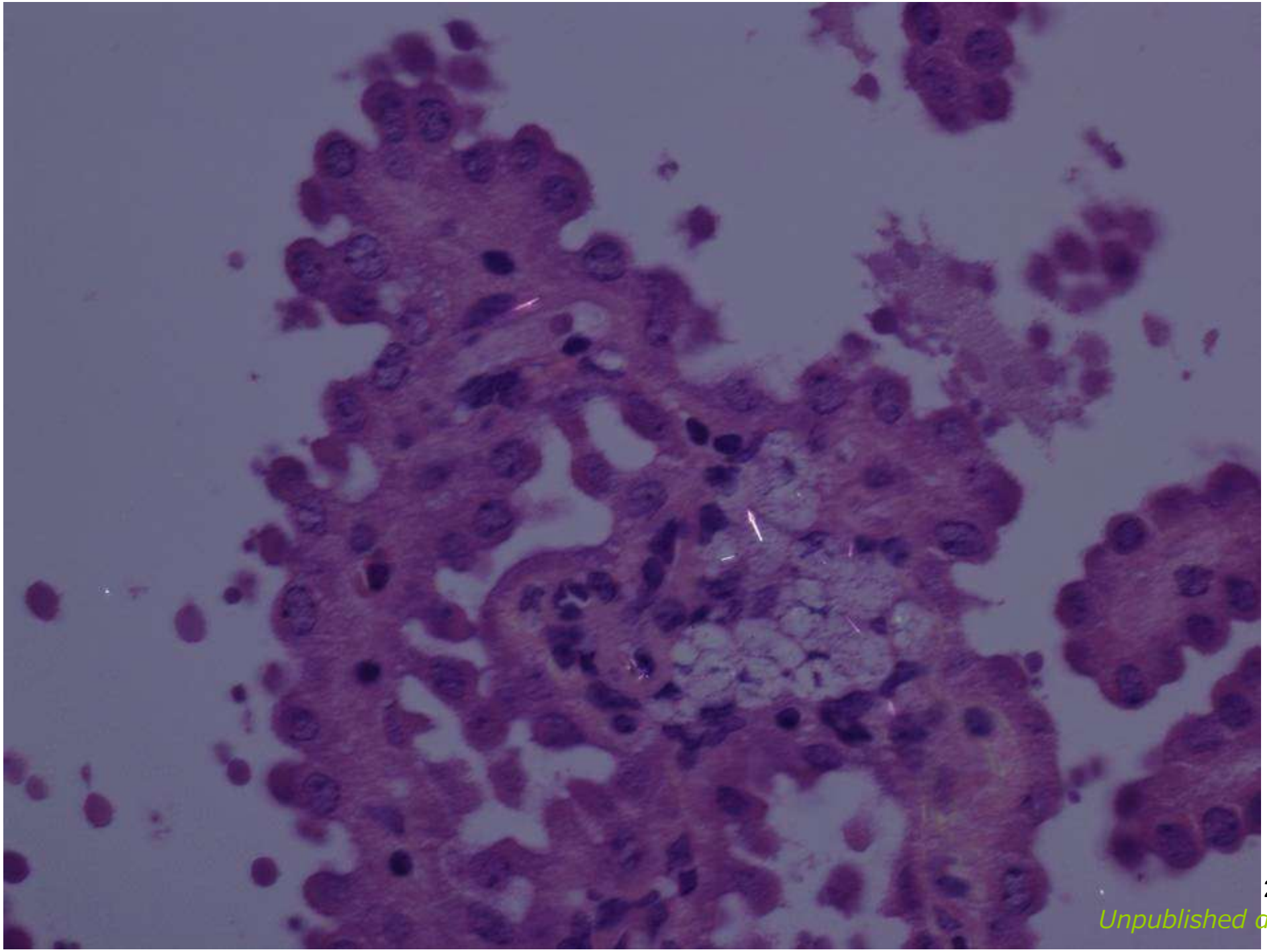

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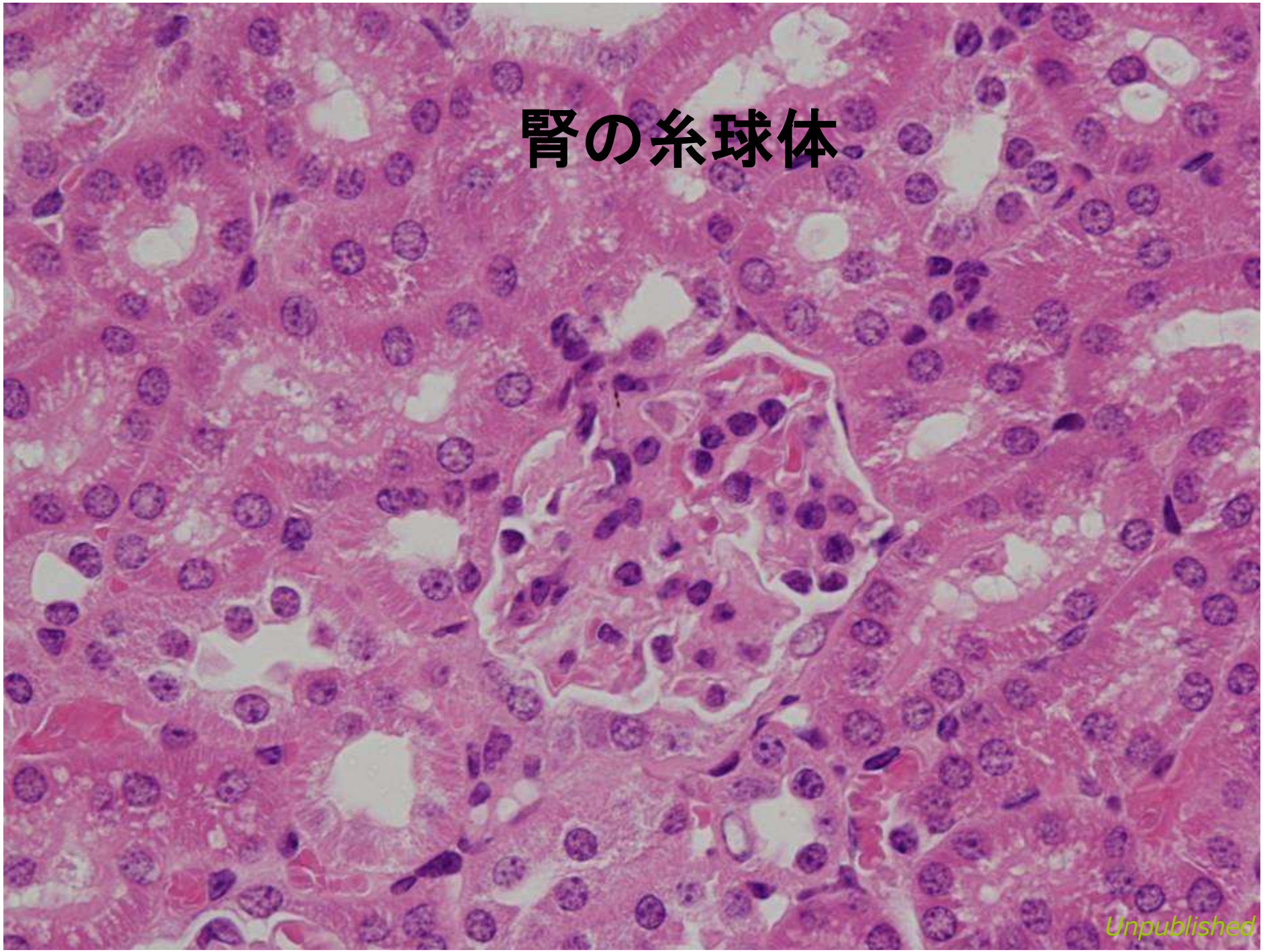
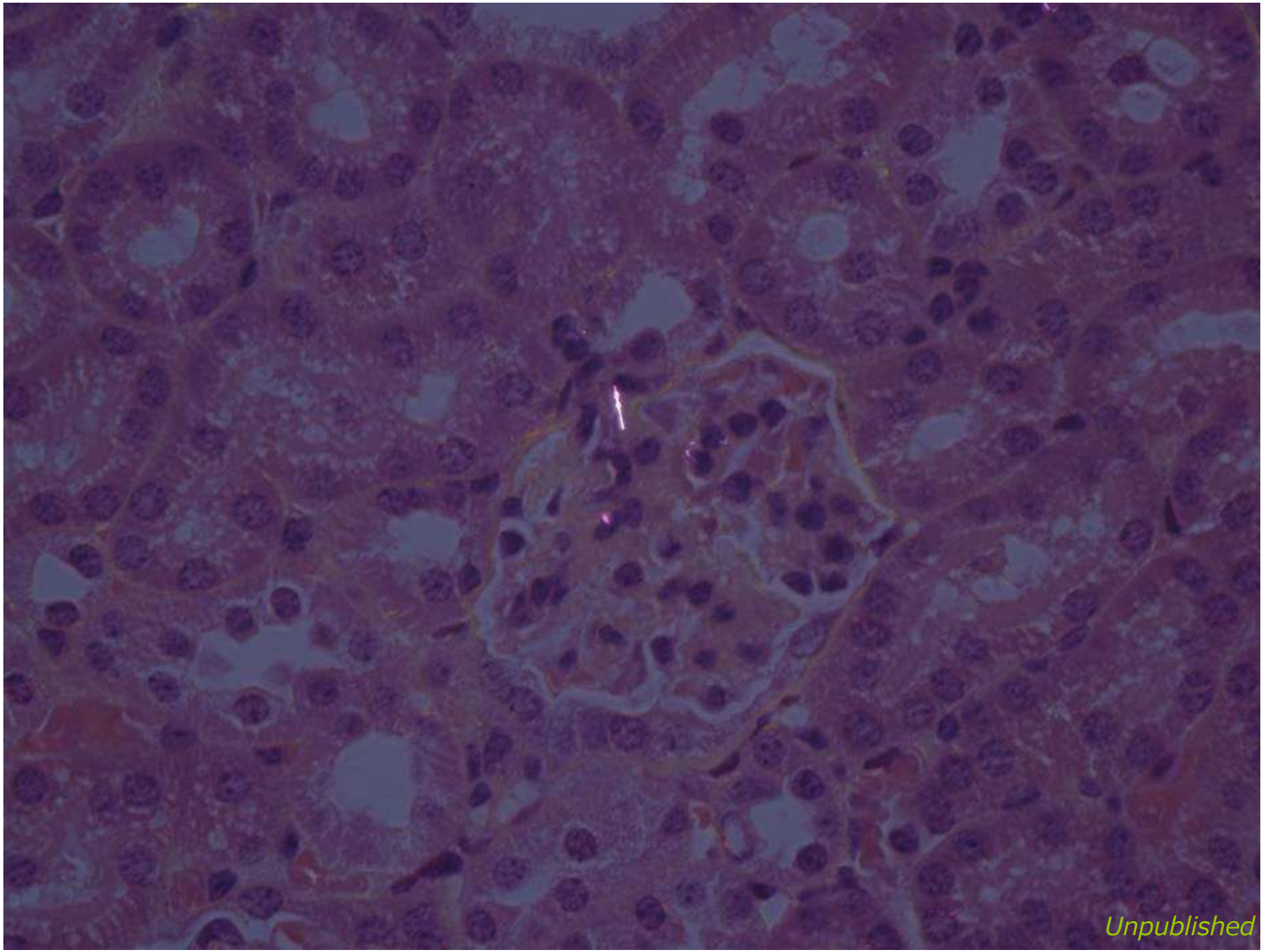




Unpublished data

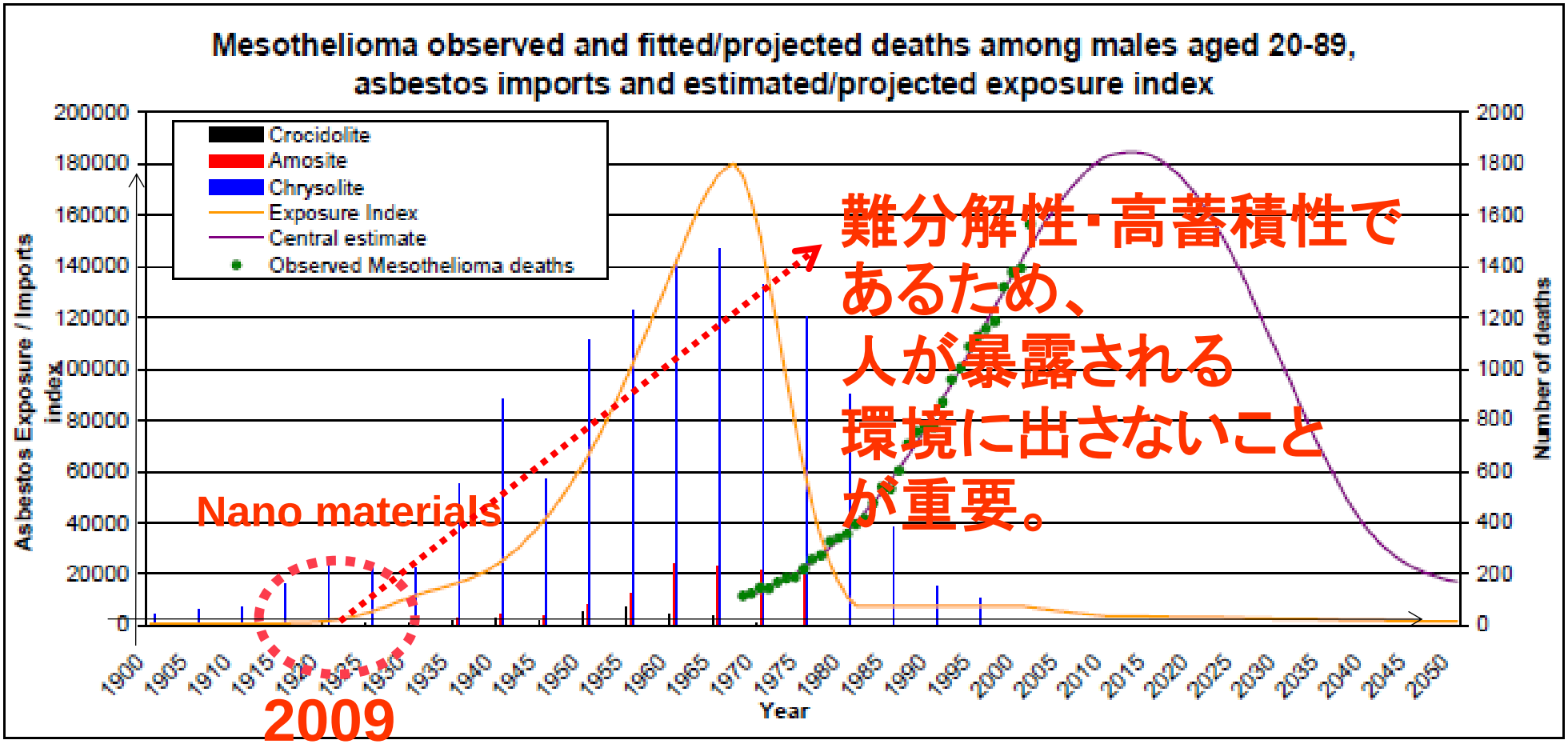
毒性まとめ：MWCNT

- Stanton仮説により発癌性が予測される長さと太さを持ったMWCNTには中皮腫発癌性があると結論付ける「蓋然性」がある。

- 凝集などによって出来たMWCNTの大きな塊は、肉芽腫や線維化を起こす。これは、中皮腫発癌とは直結しない。しかし、肉芽腫の形成と繊維化は、体にとって有害であり、非発癌性の毒性である。

- それよりも短いMWCNTは、全身に血行性に広がる。このことによる毒性はまだ調べられていない。

Figure 3



4. Discussion

ナノマテリアルの毒性評価

- わかっていること
  - 難分解性のものが多いゆえに、急性毒性は弱い
- わかっていないこと
  - ナノマテリアルの吸収と分布
  - 慢性毒性

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毒性研究の方向性

1. メカニズムがある程度、既知の場合　＝ごく限られている
    - ・繊維発癌 – 腹腔内投与モデル
    - ・全身分布（血行性・リンパ行性） – 腹腔内投与モデル

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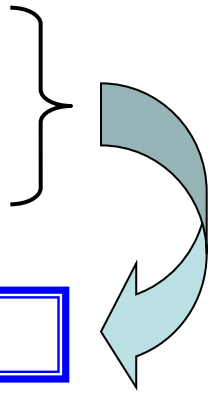
---

2. メカニズムが未知の場合
   人で想定される暴露経路*による動物実験

→ 有害性同定
→ メカニズム同定（推定）
→ 用量相関データ取得

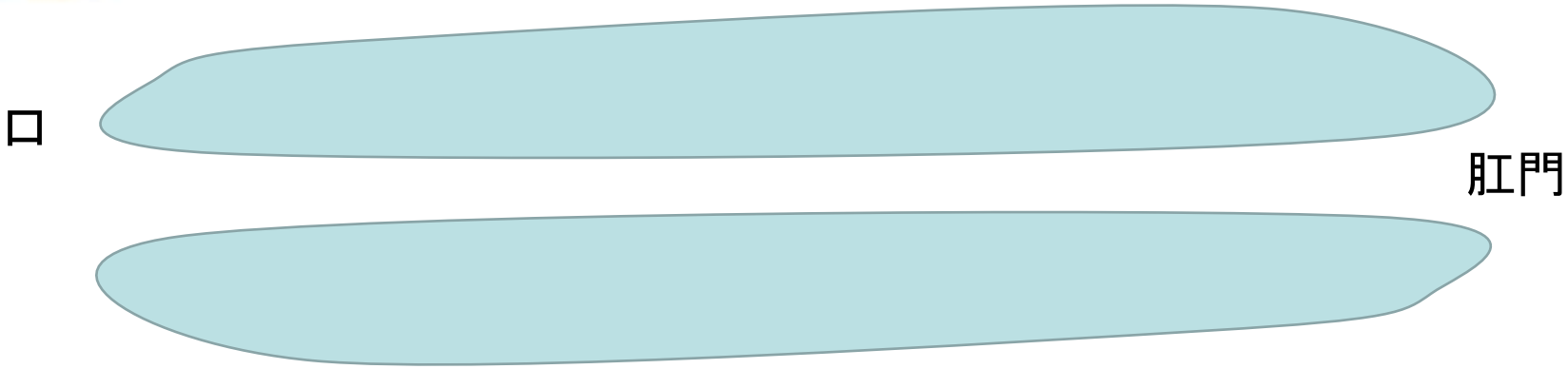


人における毒性と用量相関性を推定

*：吸入 (全身, 気管内), 経皮, 経口

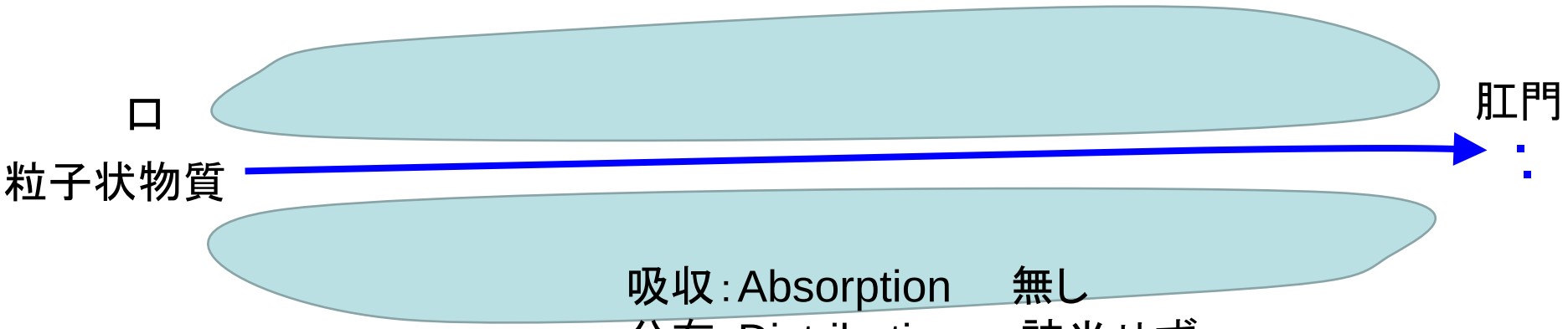
暴露経路基礎　経口

- 経口暴露:消化管

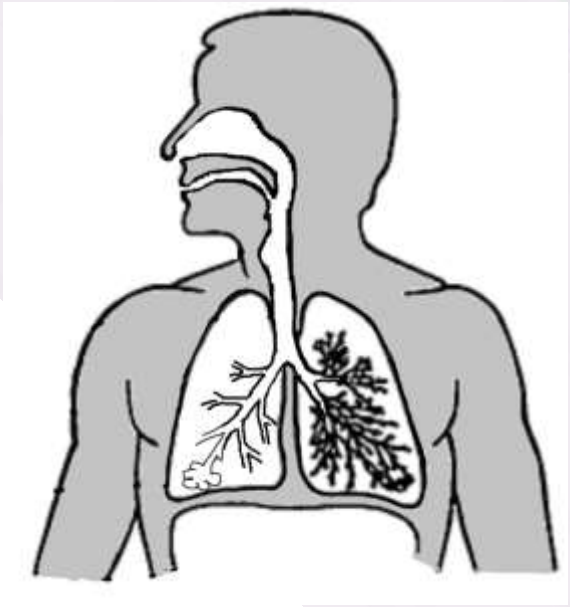


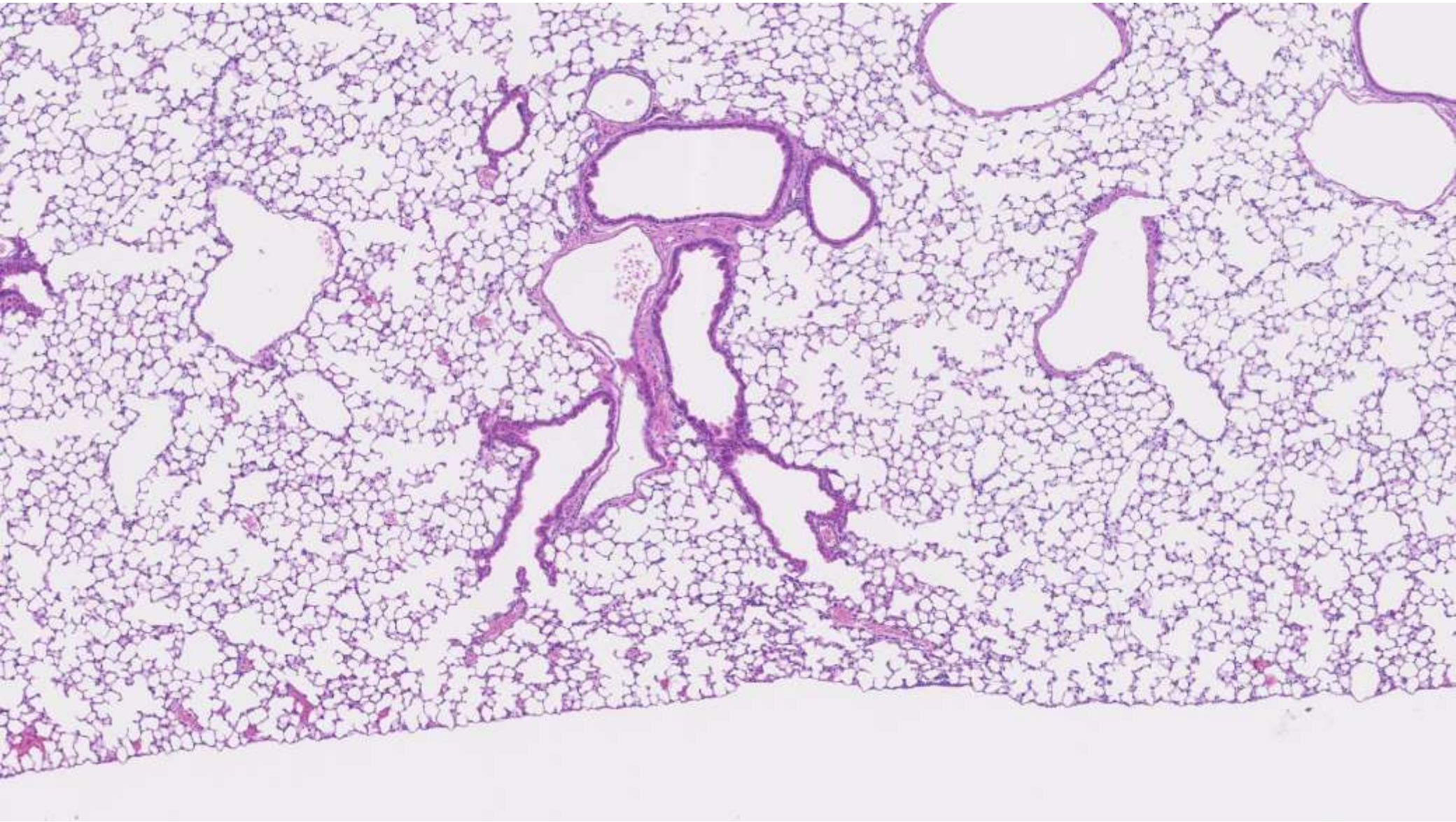
実際に:

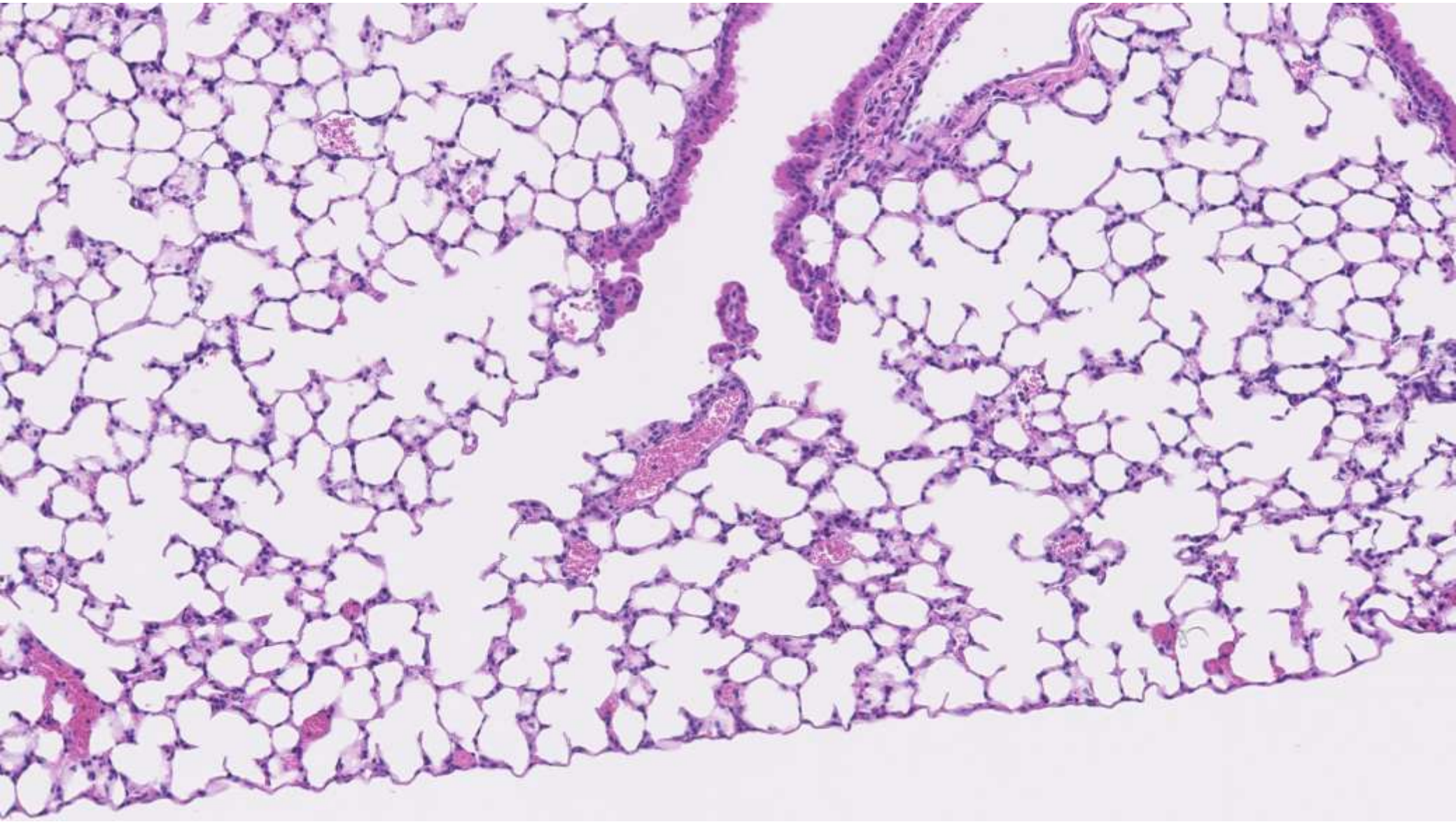
- アスベストを水に懸濁して飲ませた場合、毒性なし(アスベスト水道管の問題)
- 二酸化チタン(非ナノ)を懸濁して飲ませた場合、毒性なし(食用色素)

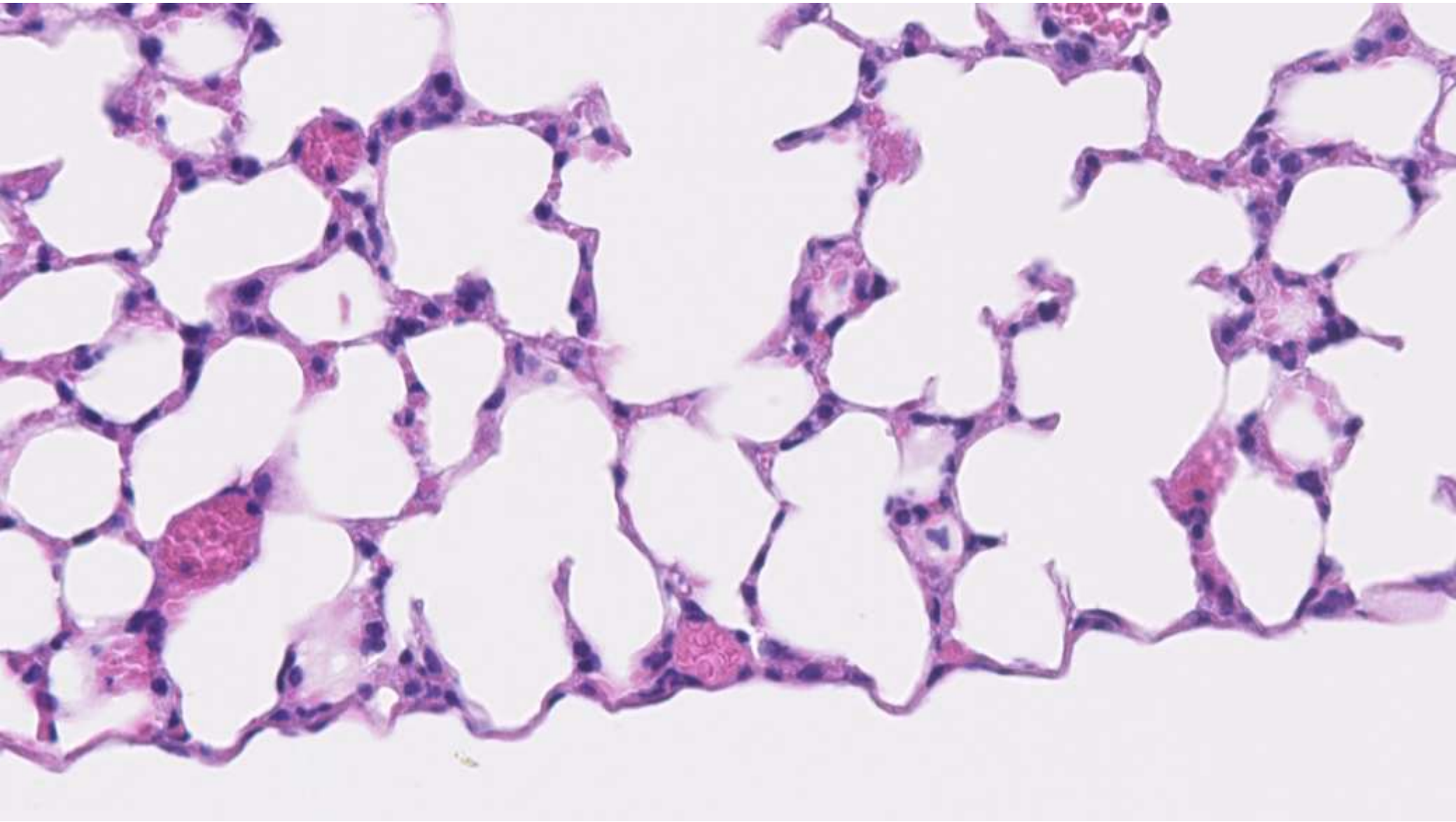


- 吸入暴露:肺～胸腔

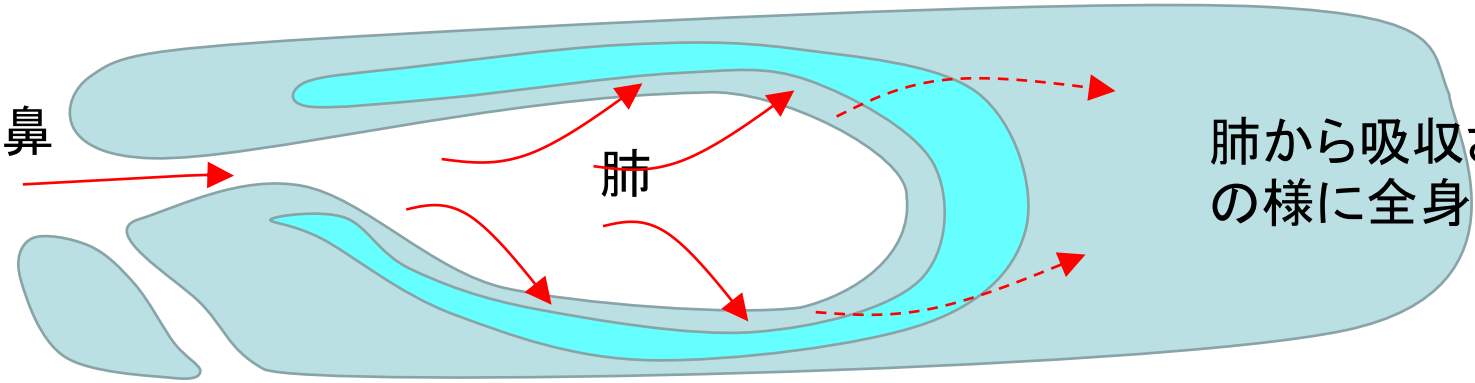








- 吸入暴露：肺～胸腔



吸収：Absorption　有り
分布：Distribution　有り
代謝：Metabolism　有り
排泄：Excretion　有り

毒性研究の方向性

1. メカニズムがある程度、既知の場合　＝ごく限られている
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---

2. メカニズムが未知の場合
   人で想定される暴露経路*による動物実験

→ 有害性同定
→ メカニズム同定（推定）
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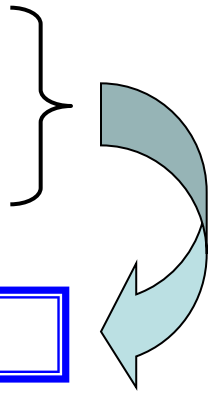

人における毒性と用量相関性を推定

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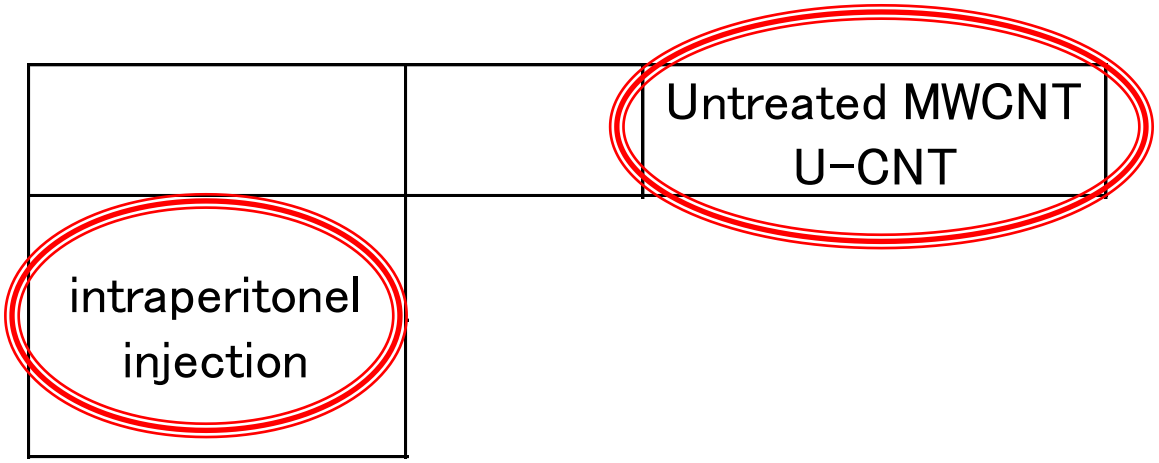
   → 有害性同定
   → メカニズム同定（推定）
   → 用量相関データ取得

SWCNT
Shorter MWCNT
Other CNT
Nano Metals
TiO_2
ZnO
Fullerene whiskers
Etc.

人における毒性と用量相関性を推定

*：吸入 (全身, 気管内), 経皮, 経口

ここまでのお話の内容



Mitsui MWNT-7

+ proposal

ここからのお話の内容

		Untreated MWCNT U-CNT	Taquann MWCNT T-CNT
intraperitonel injection			
whole body inhalation			

Mitsui MWNT-7

+ proposal

		Untreated MWCNT U-CNT	Taquann MWCNT T-CNT
intraperitonel injection	p53−/+	Mesothelioma	Mesothelioma
	wild	Not Planned	Mesothelioma & Fibrosis
whole body inhalation	p53−/+	Not Planned	Ongoing
	wild	Not Planned	Ongoing

		Untreated MWCNT U-CNT	Taquann MWCNT T-CNT
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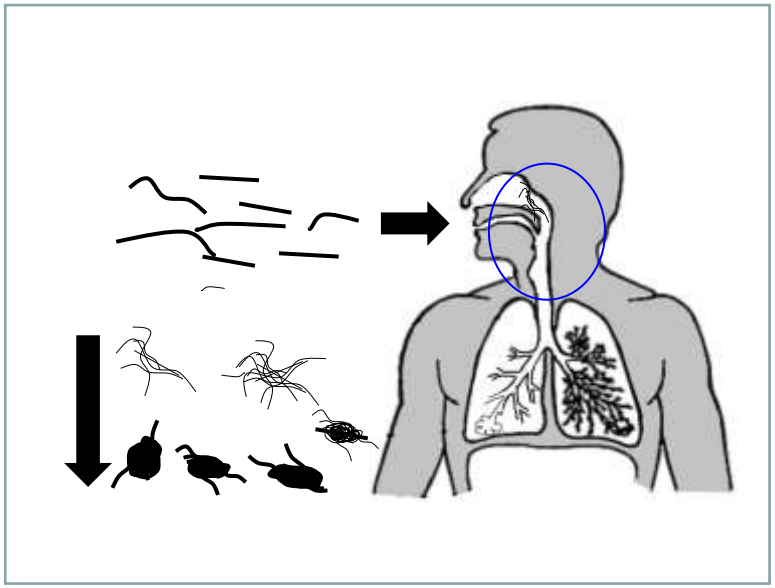
whole body inhalation	p53-/+	Not Planned	Ongoing
	wild	Not Planned	Ongoing

Human

Exposure Chamber
=Rigorous agitation



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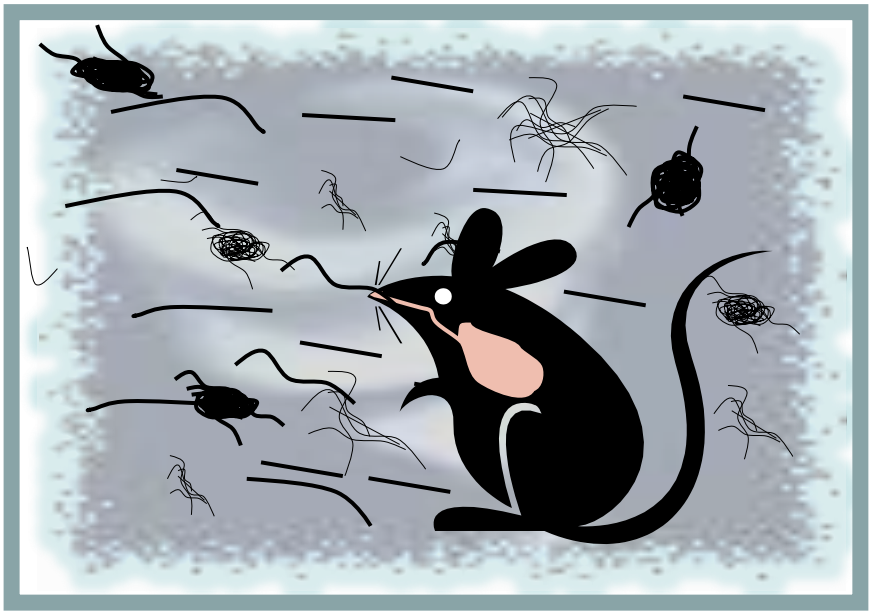
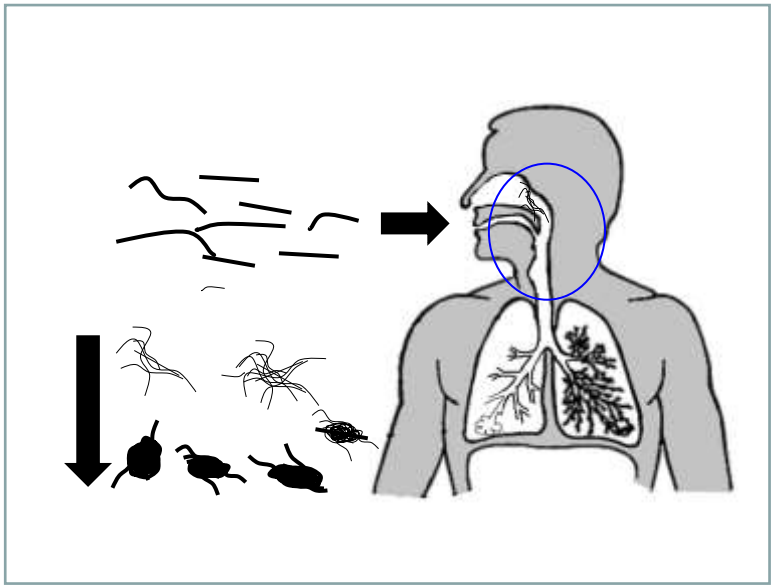


Aerosol with aggregates/agglomerates

Human

Exposure Chamber
=Rigorous agitation



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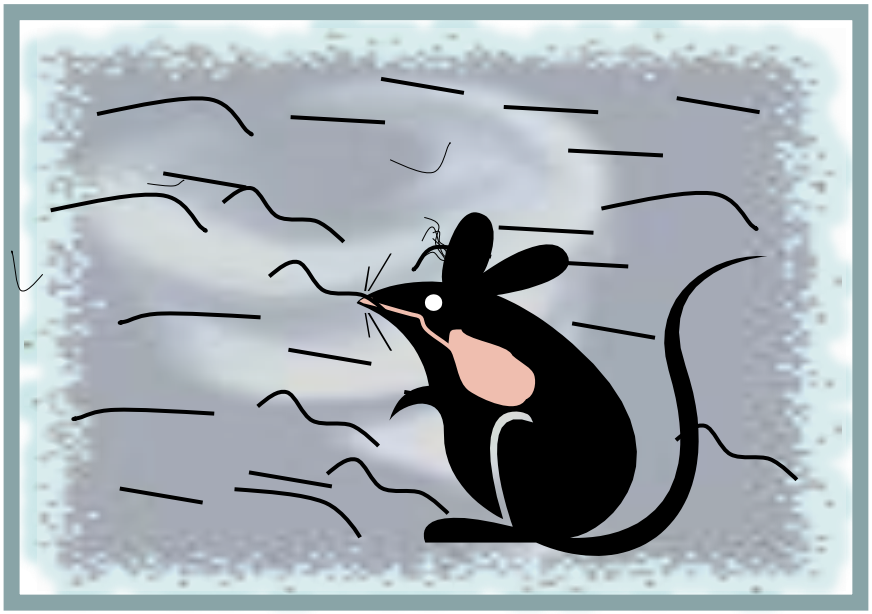


Aerosol without aggregates/agglomerates

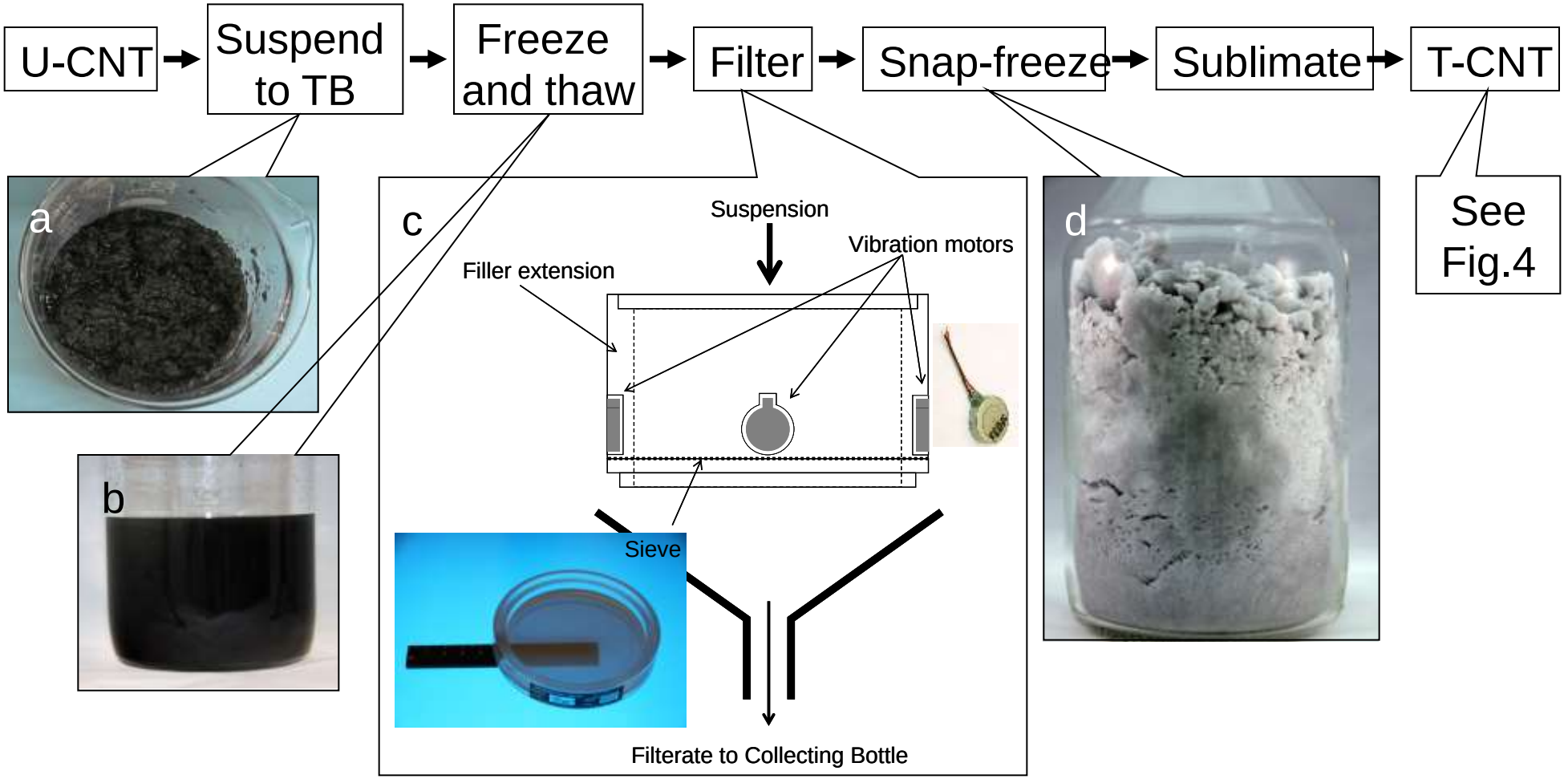
Taquann method (outline)

Based on two idea of

- 液相での濾過 : Liquid phase dispersion and filtration using volatile dispersant.
- 臨界点乾燥による再凝集の阻止 : Critical point drying to avoid aggregation by surface tension.

高度に分散した単繊維の MWCNT を精確に分取することが出来る。

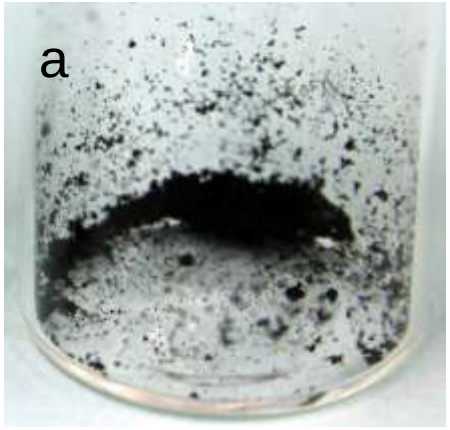
Figure 1

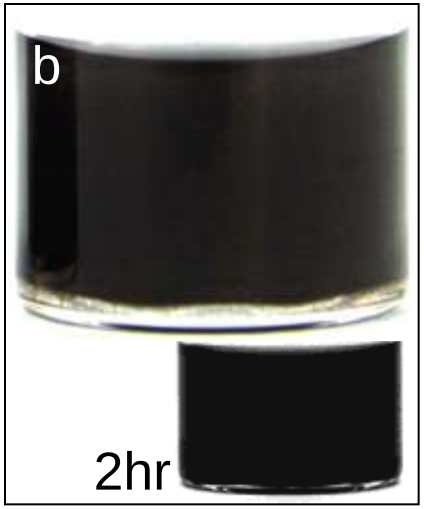


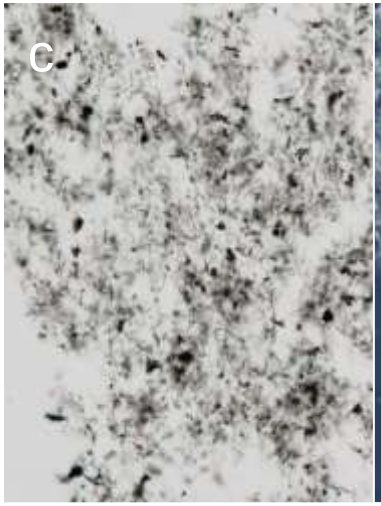
Taquahashi et al., J Tox Sci 38:619-628, 2013

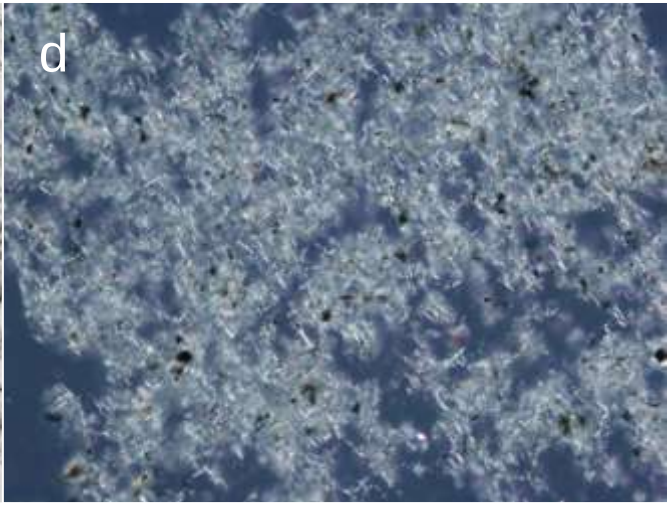
Figure 4

T-CNT

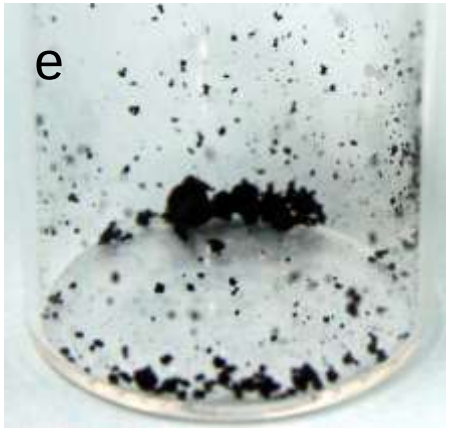


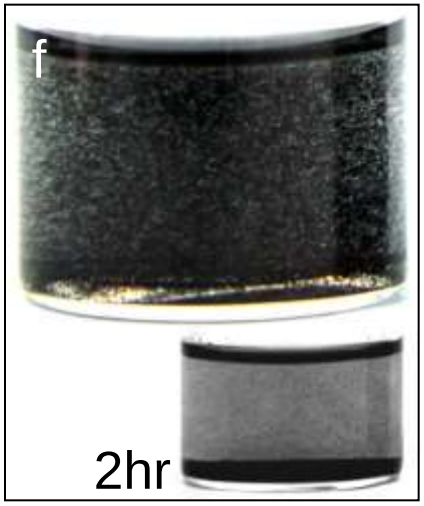


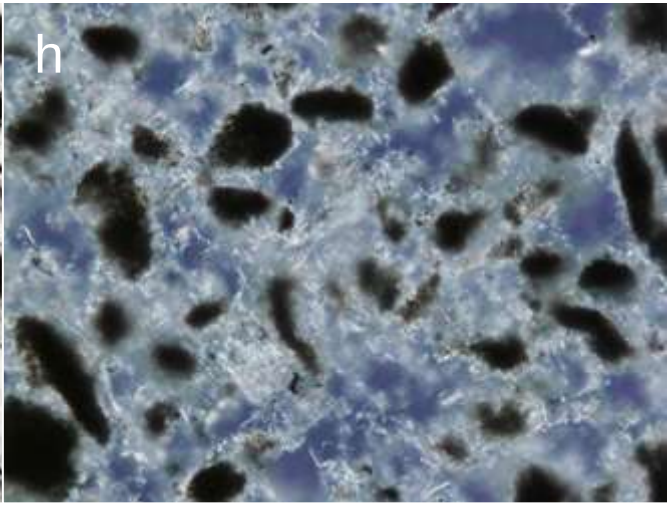




U-CNT

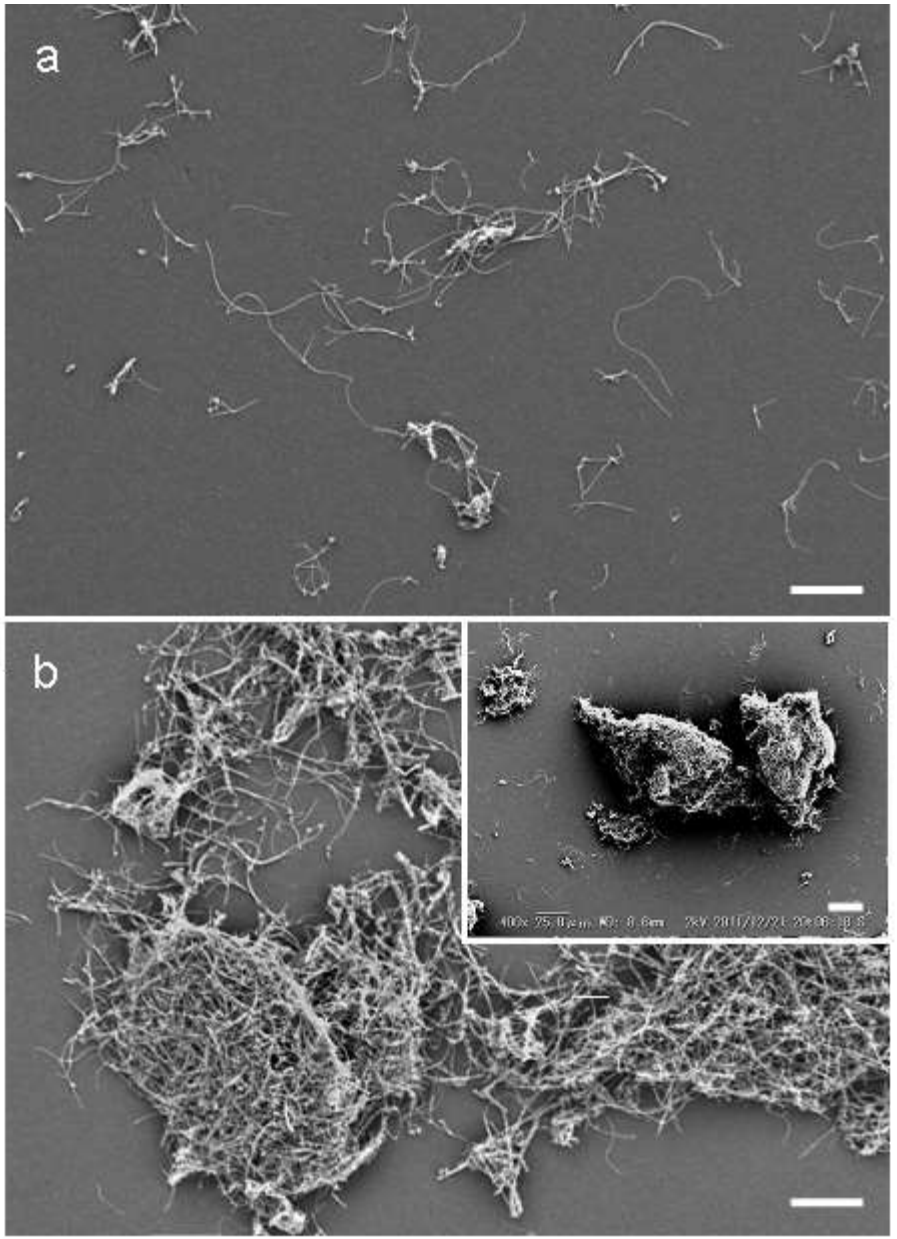






T-CNT（SEM x1,000）
単繊維が観察される。

U-CNT（SEM x1,000）
大型の凝集体・凝固体が多数認められる

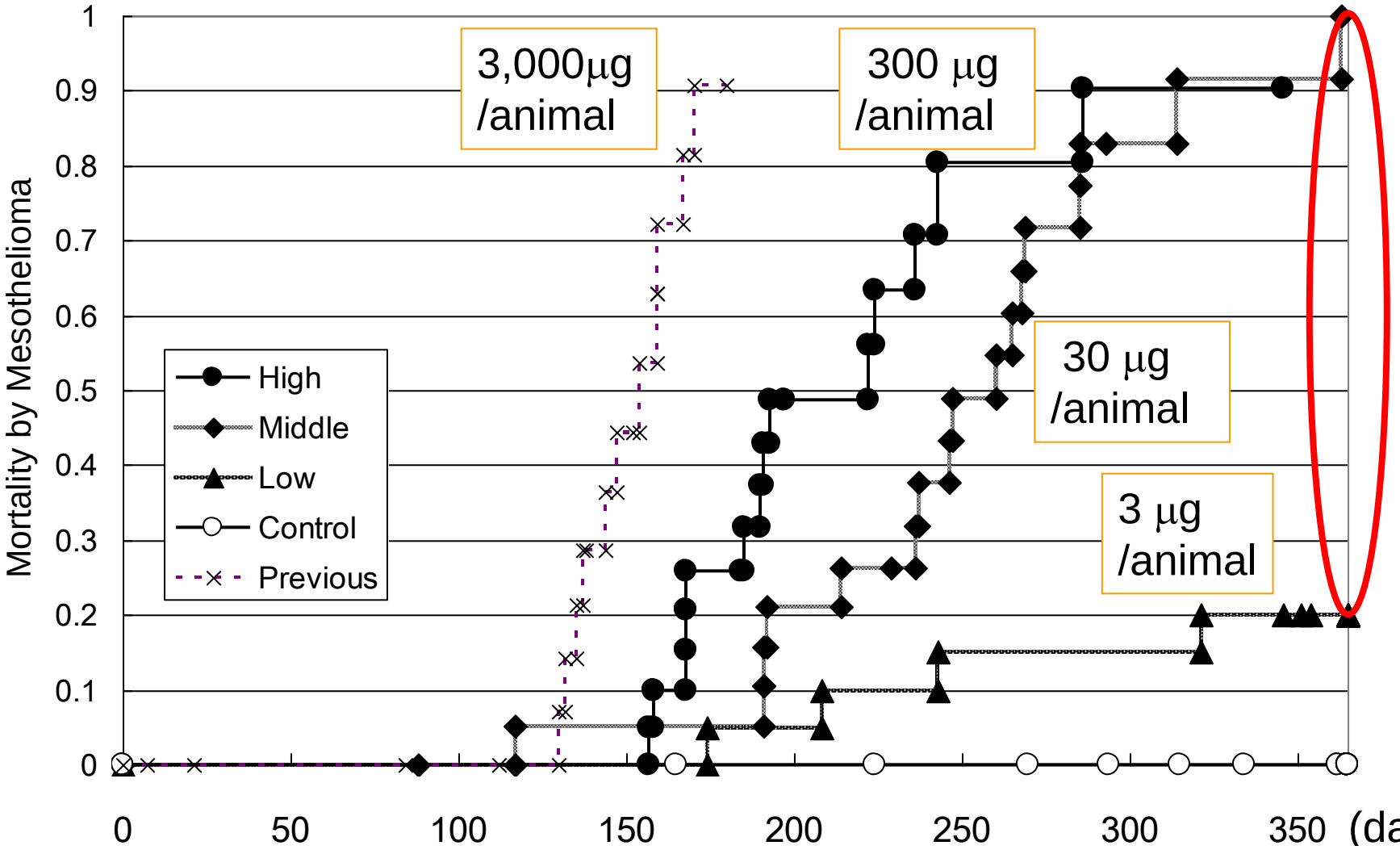


SEM x400

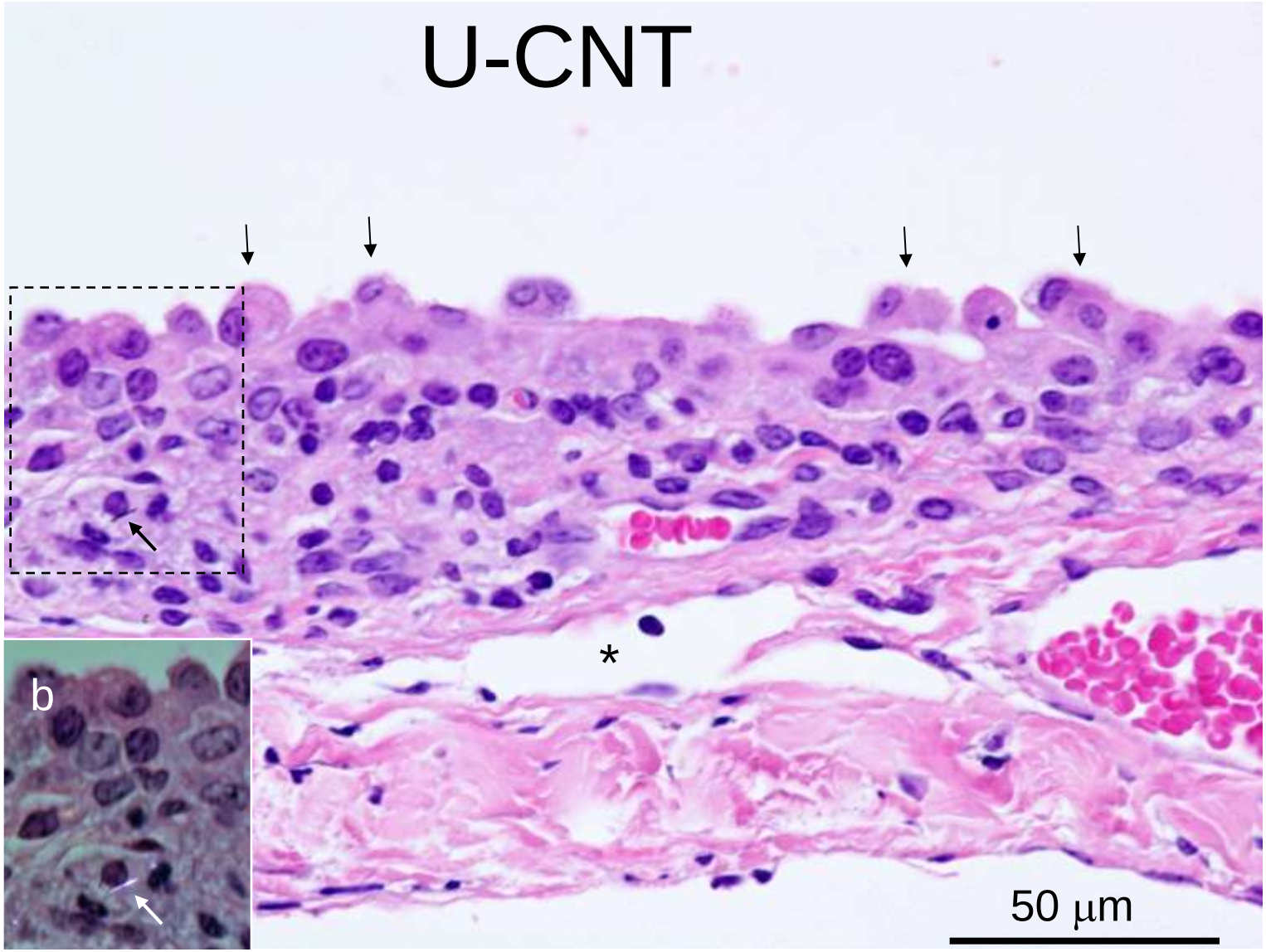
scale bars 10 μm

Comparison of yield / weight of sample

		Untreated MWCNT U-CNT	Taquann MWCNT T-CNT
intraperitonel injection	p53−/+	Mesothelioma	Mesothelioma
	wild	Not Planned	Mesothelioma & Fibrosis
whole body inhalation	p53−/+	Not Planned	Ongoing
	wild	Not Planned	Ongoing



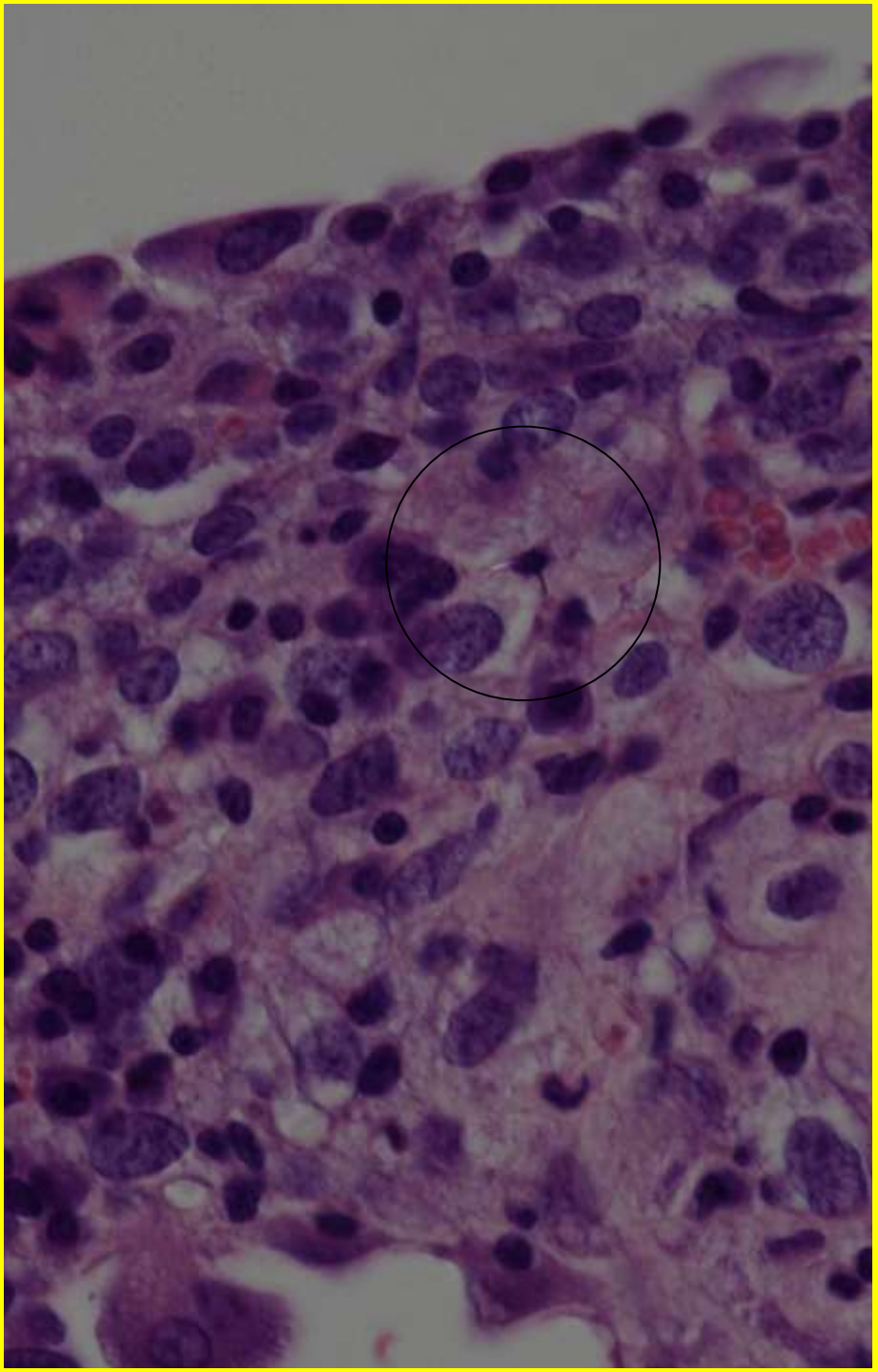
Takagi et al. Cancer Science, 2012

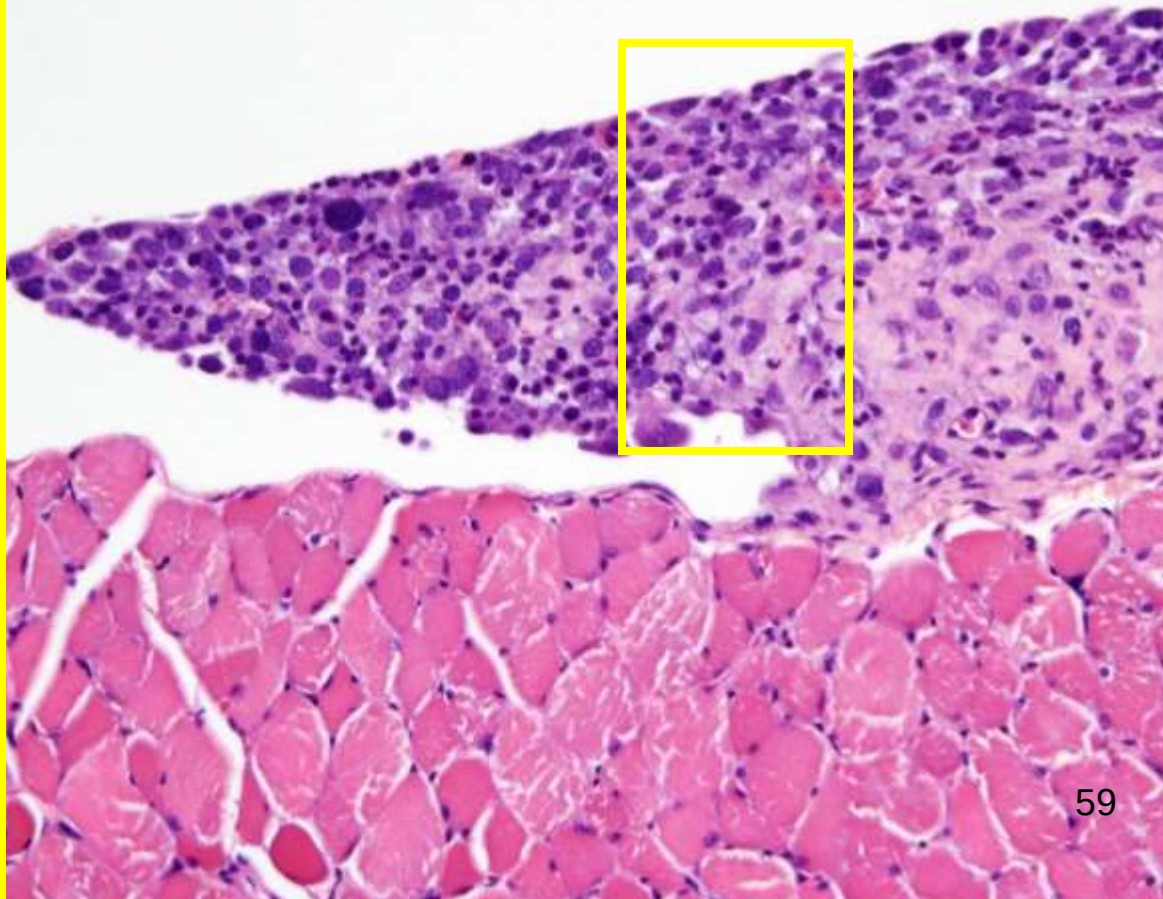


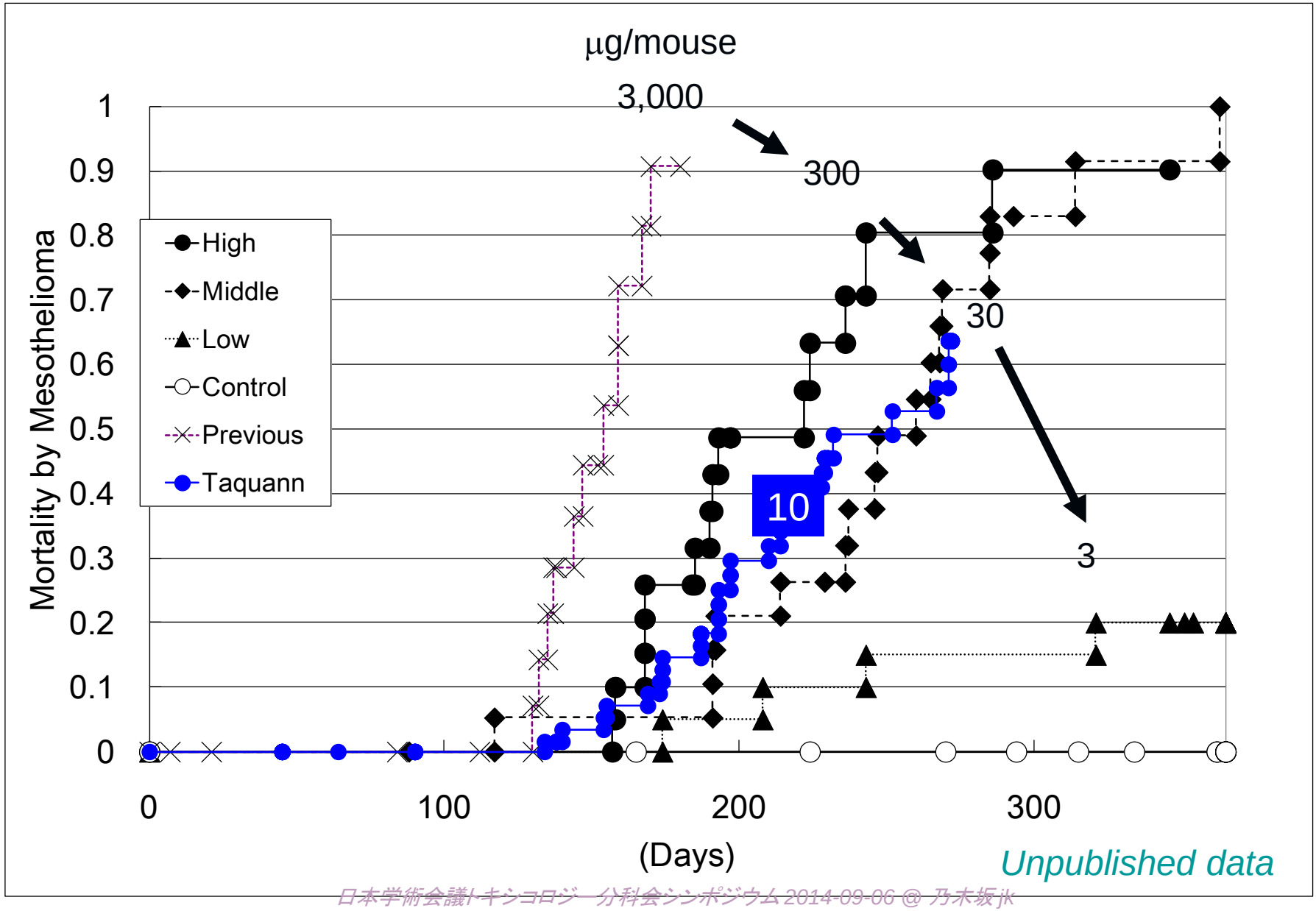
Takagi et al. Cancer Science, 2012

Unpublished data

T-CNT

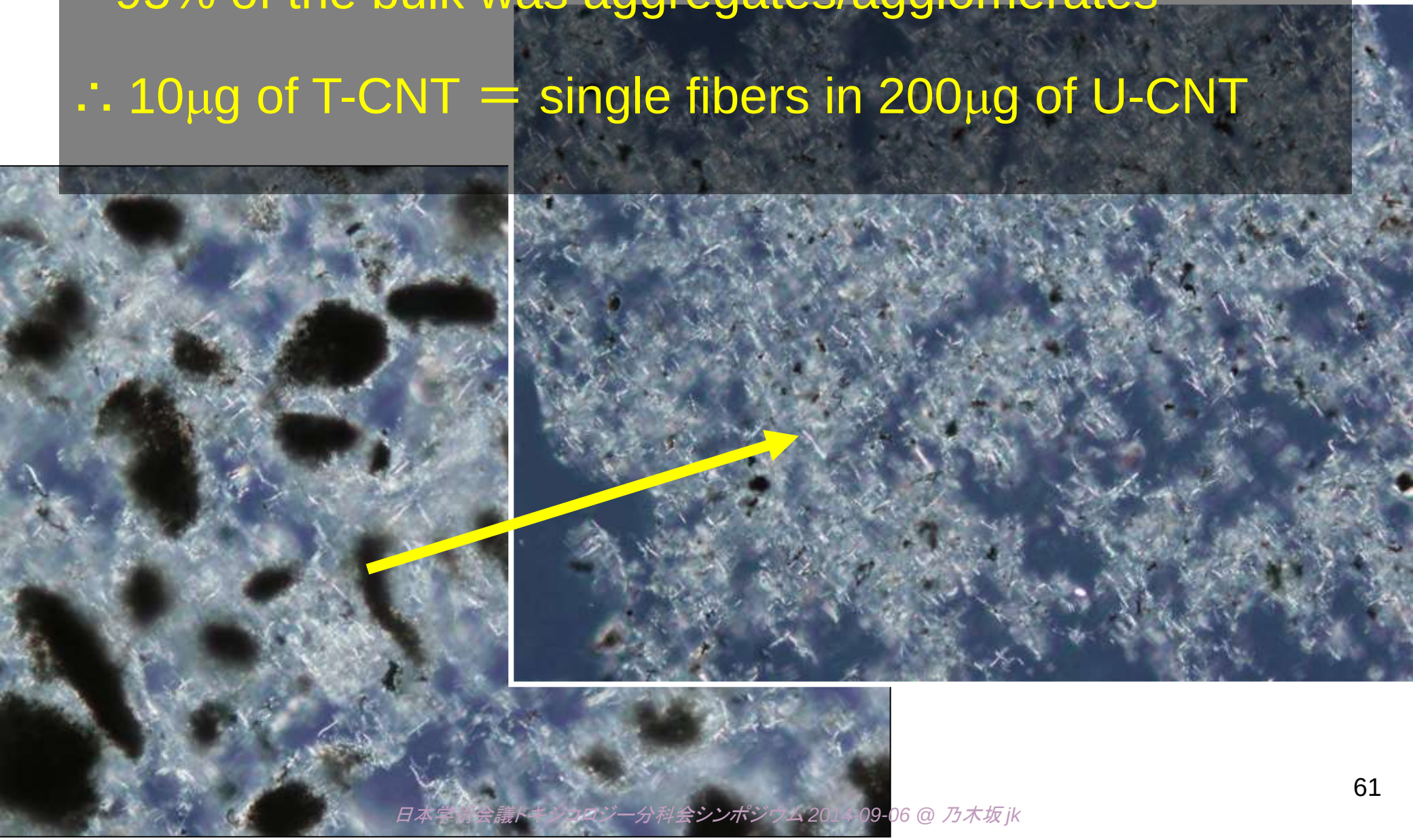


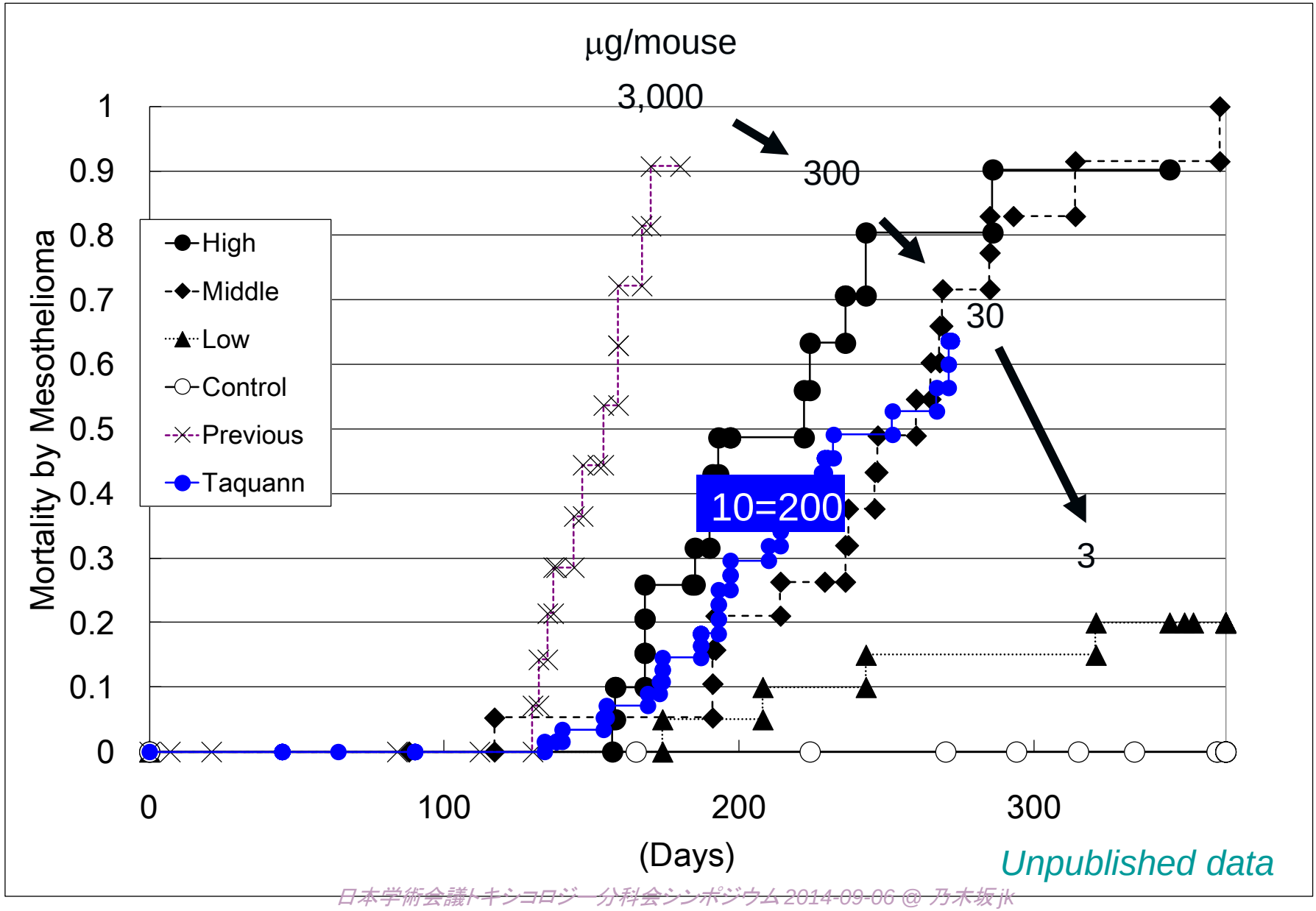



μg/mouse
3,000
300
30
10
3
Mortality by Mesothelioma
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
High
Middle
Low
Control
Previous
Taquann
0
100
200
300
(Days)
Unpublished data

Taquann-MWCNT is 5% in weight of bulk MWCNT
95% of the bulk was aggregates/agglomerates

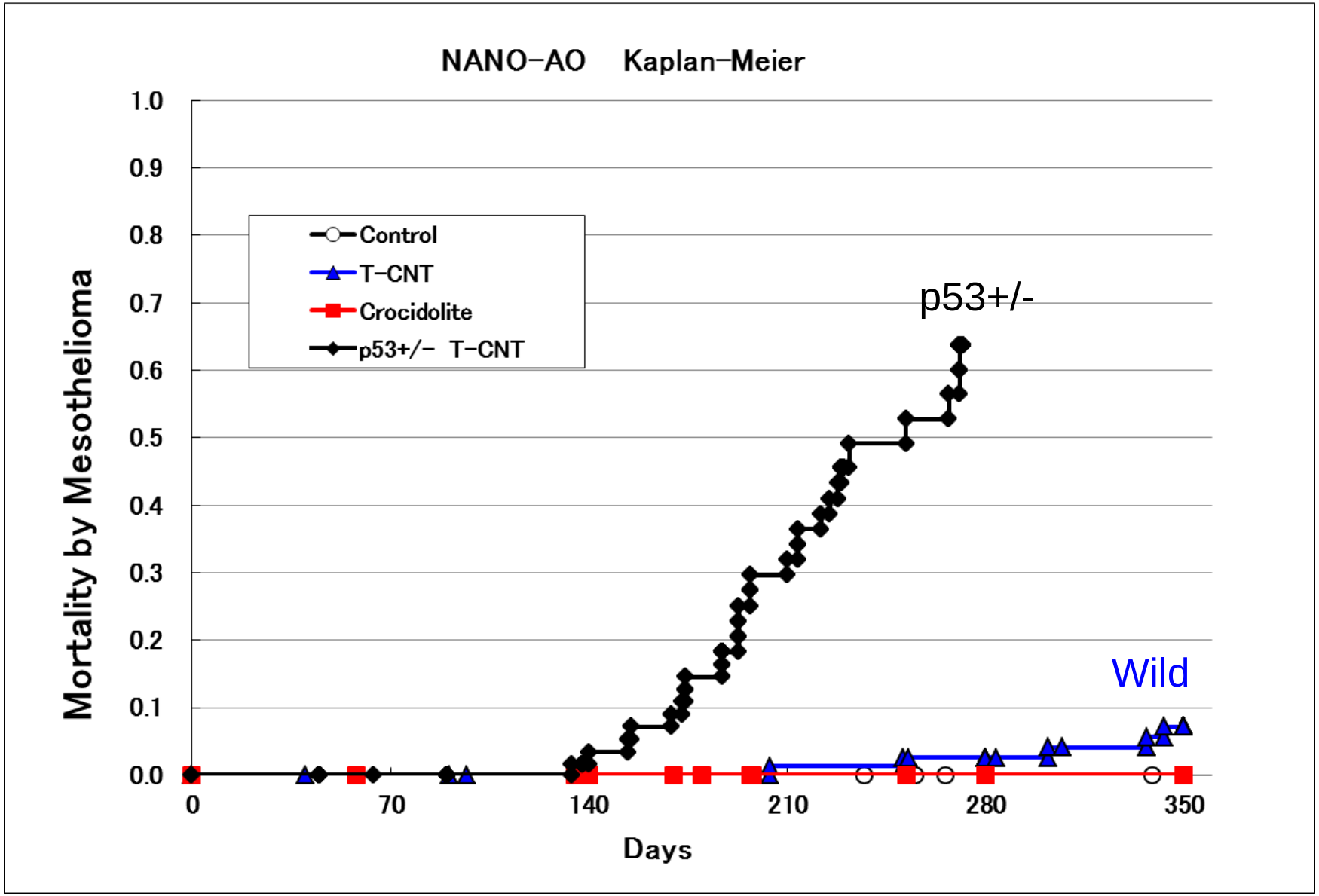
∴ 10μg of T-CNT ＝ single fibers in 200μg of U-CNT




μg/mouse
3,000
300
30
3
10=200
Mortality by Mesothelioma
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
High
Middle
Low
Control
Previous
Taquann
0
100
200
300
(Days)
Unpublished data

Comparison of yield and peritoneal response

		Untreated MWCNT U-CNT	Taquann MWCNT T-CNT
intraperitonel injection	p53-/+	Mesothelioma	Mesothelioma
	wild	Not Planned	Mesothelioma & Fibrosis
whole body inhalation	p53-/+	Not Planned	Ongoing
	wild	Not Planned	Ongoing


NANO-AO Kaplan-Meier
Mortality by Mesothelioma
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
70
140
210
280
350
Days
Control
T-CNT
Crocidolite
p53+/- T-CNT
p53+/-
Wild

Contents of this presentation

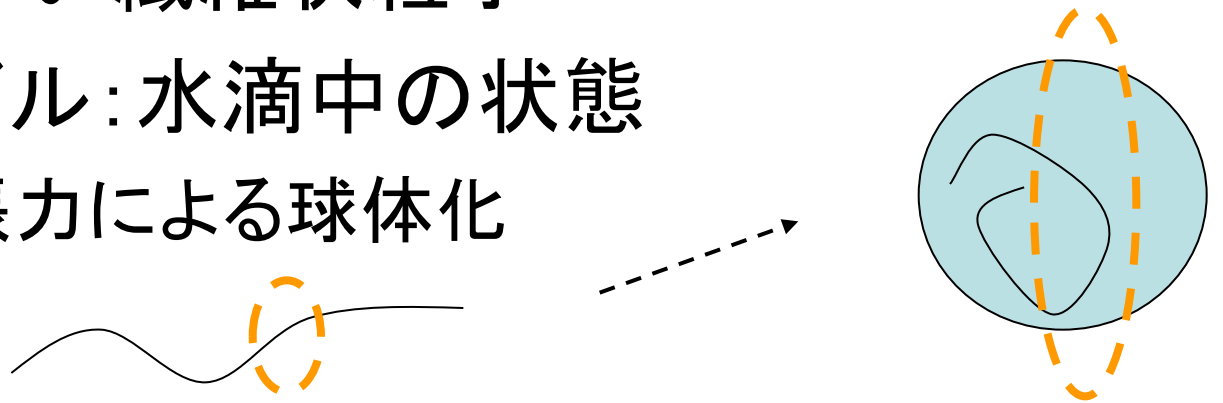
		Untreated MWCNT U-CNT	Taquann MWCNT T-CNT
intraperitonel injection	p53-/+	Mesothelioma	Mesothelioma
	wild	Not Planned	Mesothelioma & Fibrosis
whole body inhalation	p53-/+	Not Planned	Ongoing
	wild	Not Planned	Ongoing

吸入毒性研究の障害

- 粒子状物質の毒性学は相対的に遅れた分野である。
  Particulate Matter (PM) toxicology is a relatively retarded area in toxicology.
  - 難しい Difficult to study
  - 吸入毒性試験ひとつを取っても、施設が非常に少ない。
    Inhalation facility is very limited in number
    - 費用がかかる Expensive
    - 熟練した運転者が必要 Needs highly experienced engineer/researcher to run

Aerodynamic diameter（ ）

- やわらかい繊維状粒子
- エアロゾル：水滴中の状態
  - 表面張力による球体化



- 気相中：
  - 自然な繊維状を維持

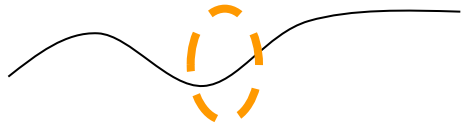
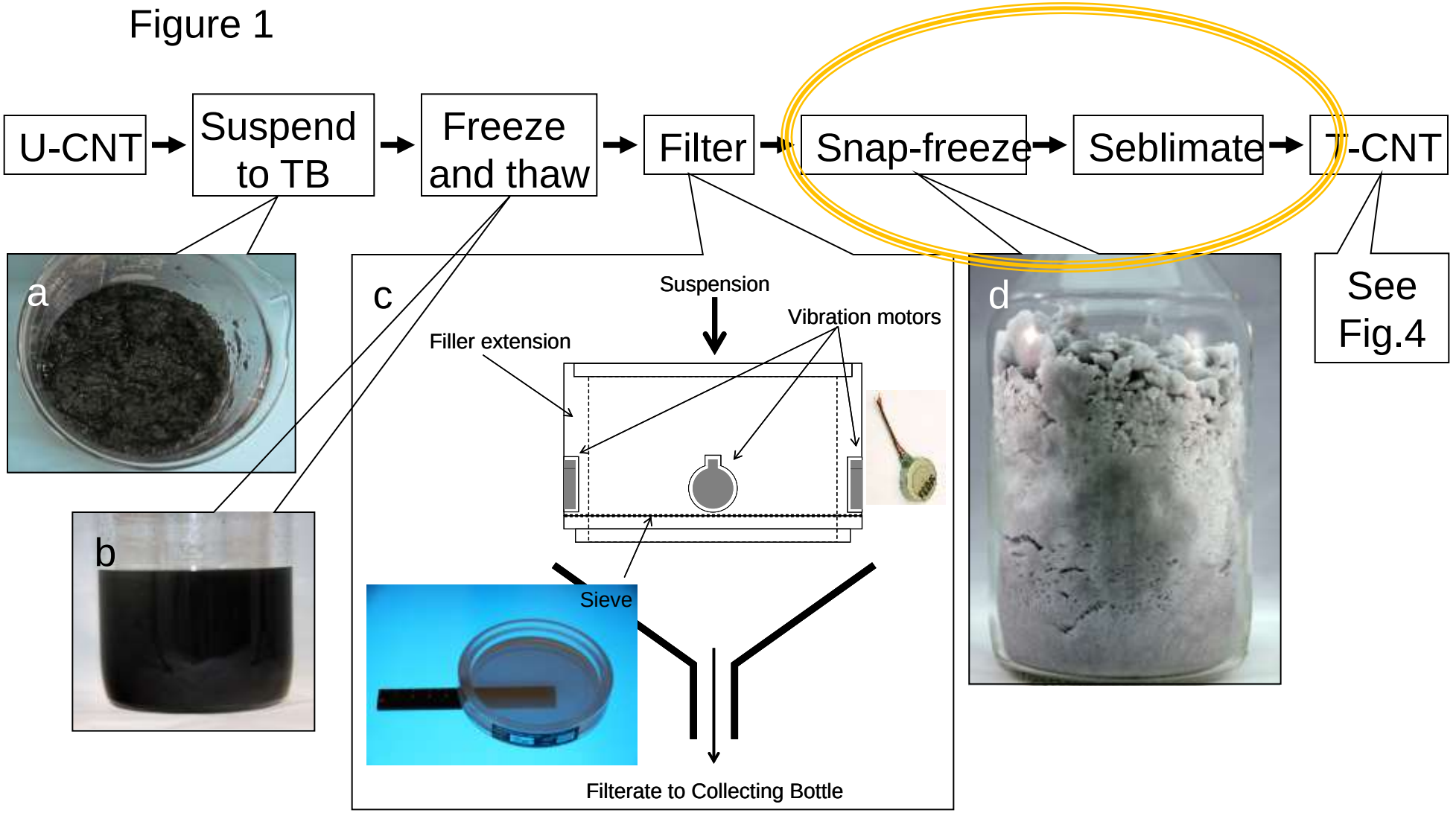
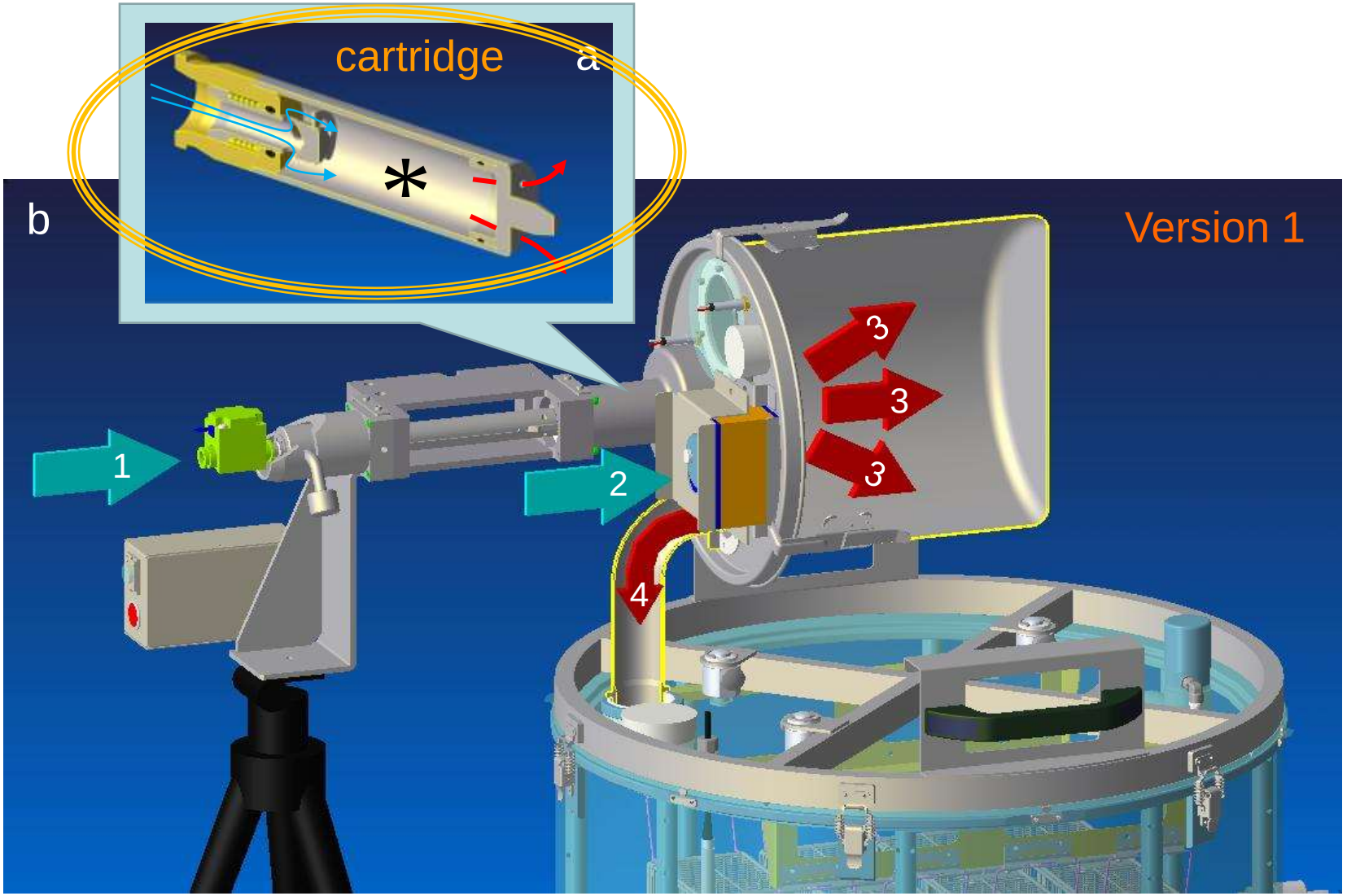


Figure 1



Taquahashi et al., J Tox Sci 38:619-628, 2013

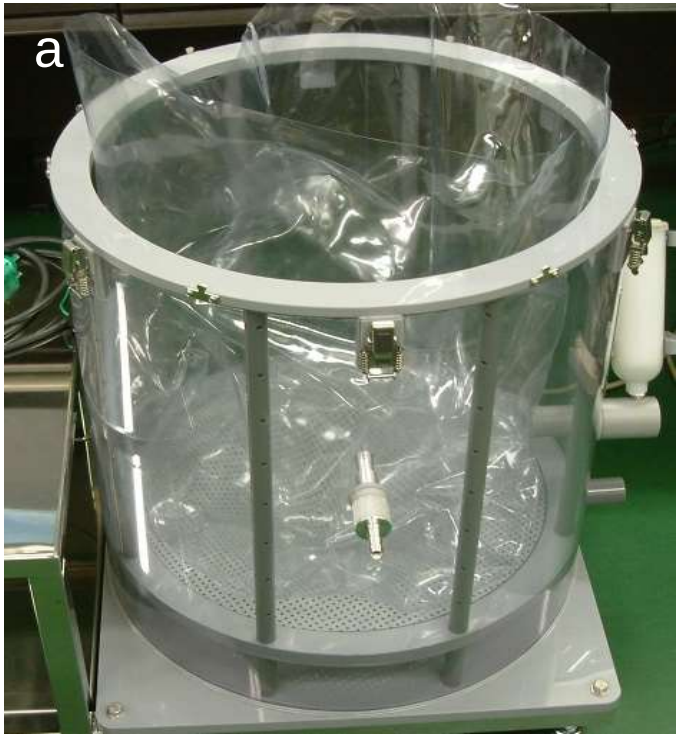


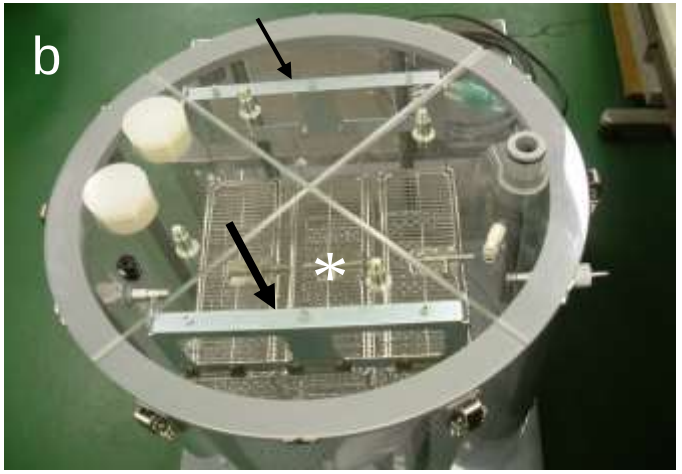
Taquahashi et al., J Tox Sci 38:619-628, 2013

Inhalation chamber

特許出願:「吸入曝露試験装置」
特願2012-148848

Disposable inner (capacity = 16 mice)





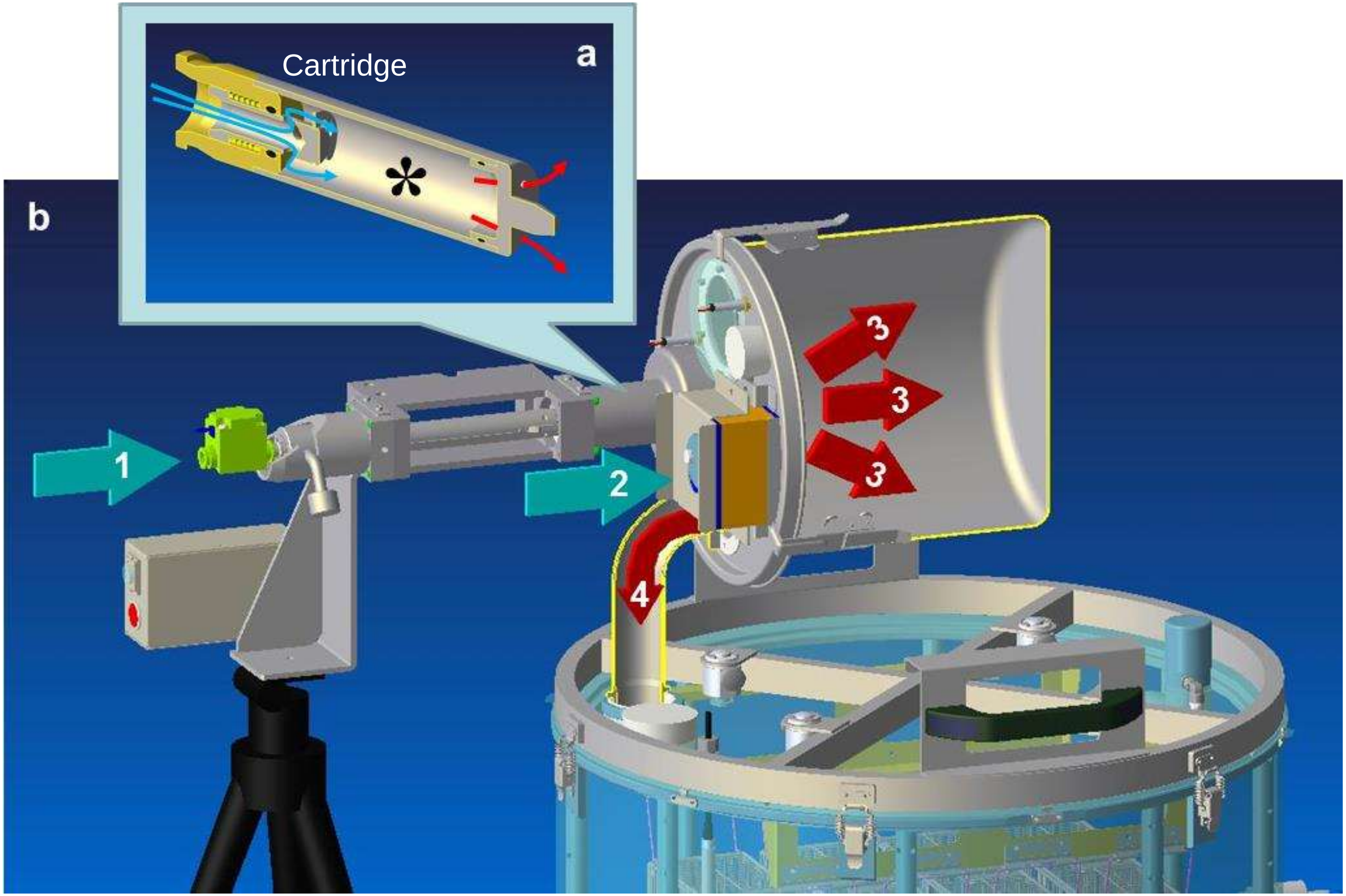
・マウスは16匹収容が可能
・蓋の下部に吊り下げ金具を装着(矢印)
・マウスはステンレス金網製のケージ(*)に収容する

全体像

・インナーチャンバー:導電性樹脂(交換可能)
・アウターチャンバー:アクリル製
・Φ550mm × H550mm、気積:105.5L
・差圧:室内>インナー>インナーとアウター間
差圧により柔軟なインナーチャンバーの形状を保つ


Version 2
2013-10-25

Carrier air flow from subchamber to mainchamber



Taquahashi et al., JTS, 2013

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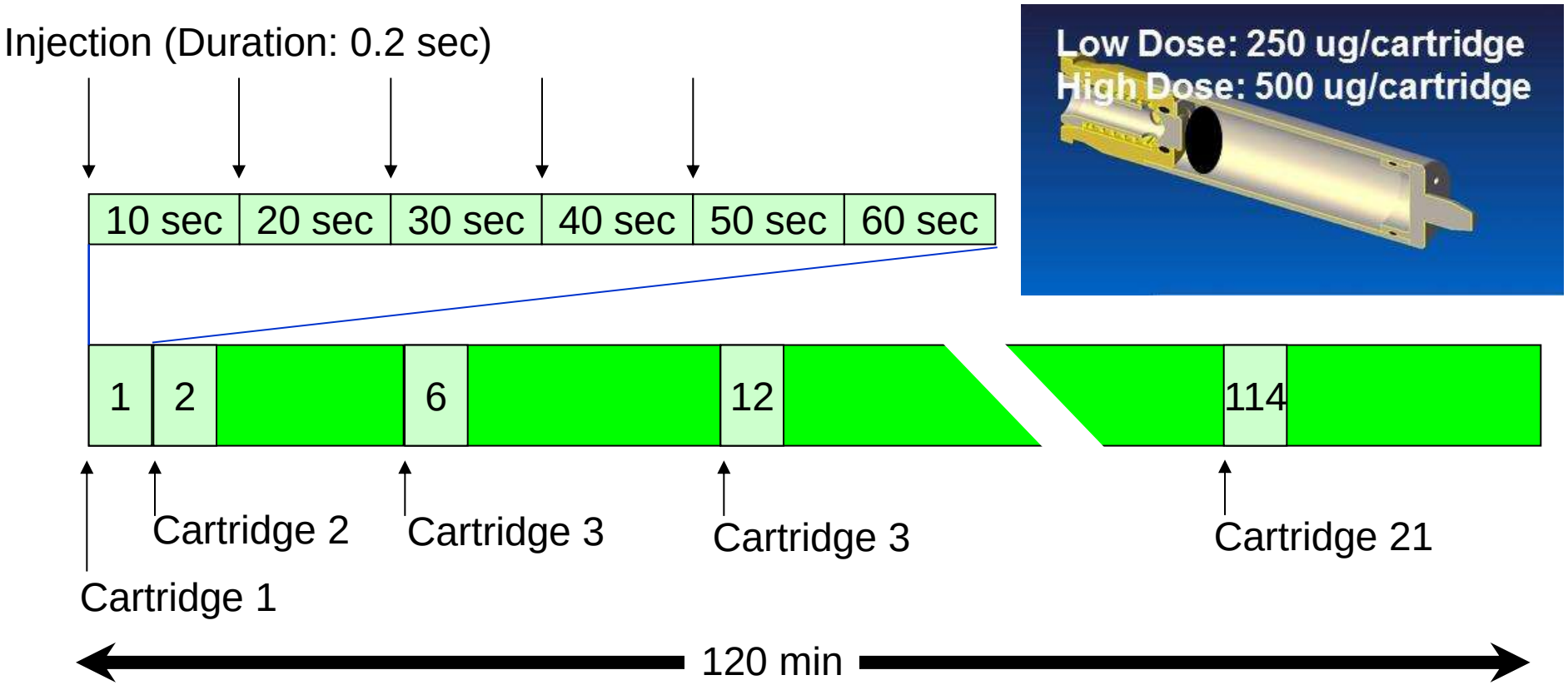
Loading T-CNT to the cartridges

Cartrges
Φ22 mm × H65 mm
Capacity;　23.5mL

A measured amount the collected T-CNT was resuspended to TB

The suspension was dispensed into the cartridges, snap-frozen and sublimated

Aerosol generation procedure



- Twenty-one cartridges were prepared for a two hour exposure experiment
- The compressed air was injected into subchamber (0.8MPa、0.2 sec×5 time,10 sec interval)
- Loading first two in 1 min for an initial boost and then one in every 6 min

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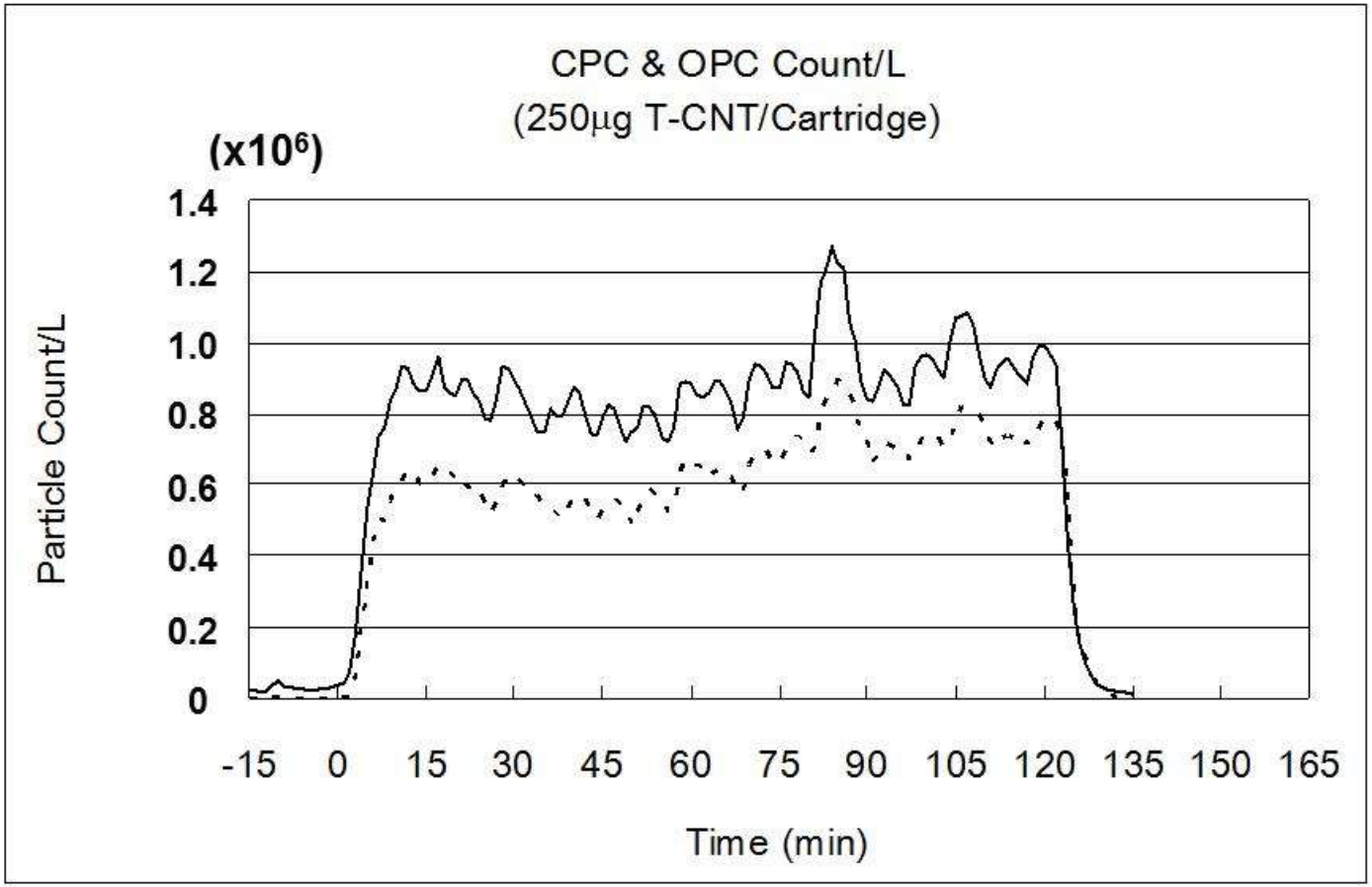
A real time particle counting in Mainchamber

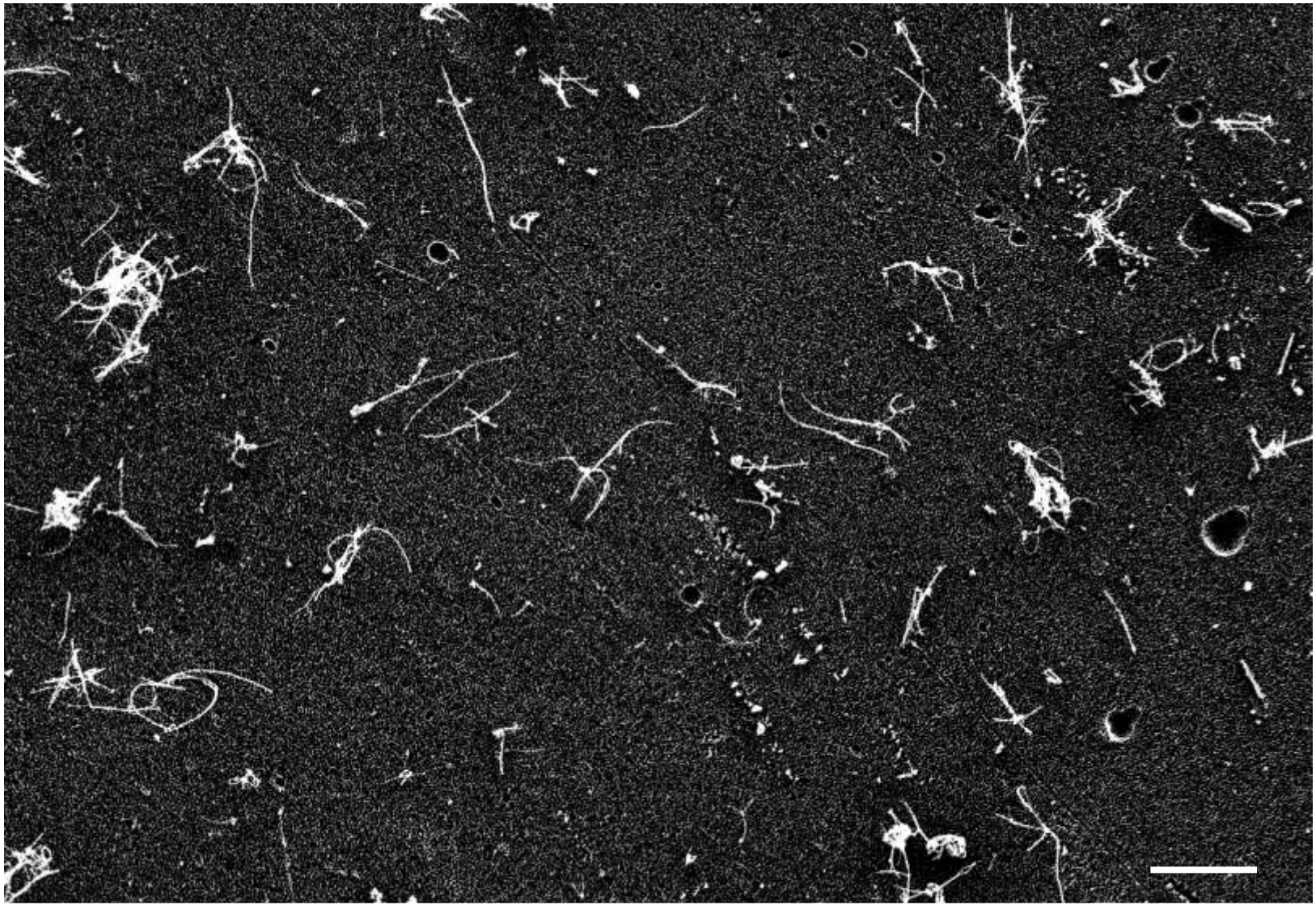


Solid line : CPC Dotted line : OPC

Taquahashi et al., JTS, 2013

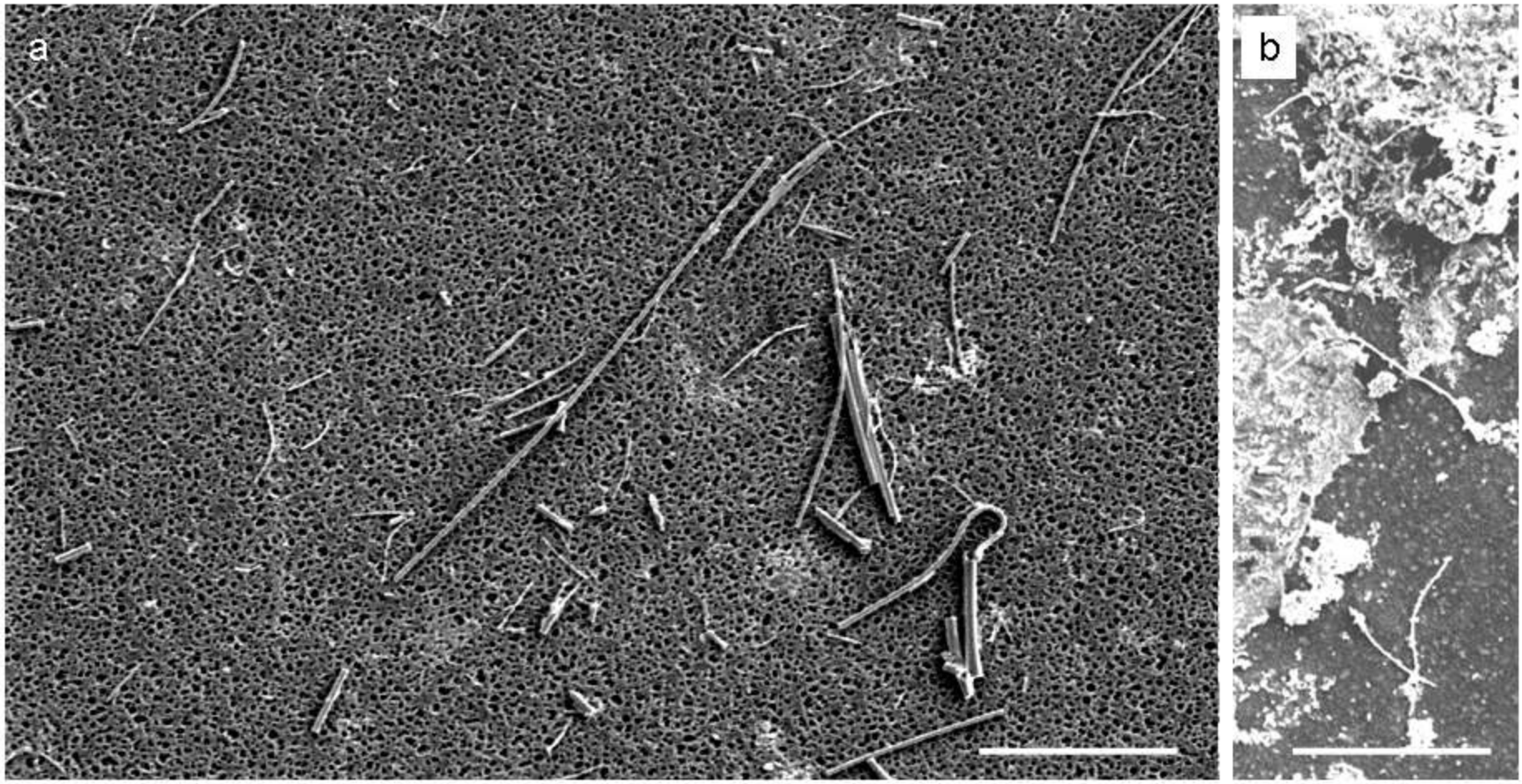
Chamber air sample

Taquahashi et al., J Tox Sci 38:619-628, 2013



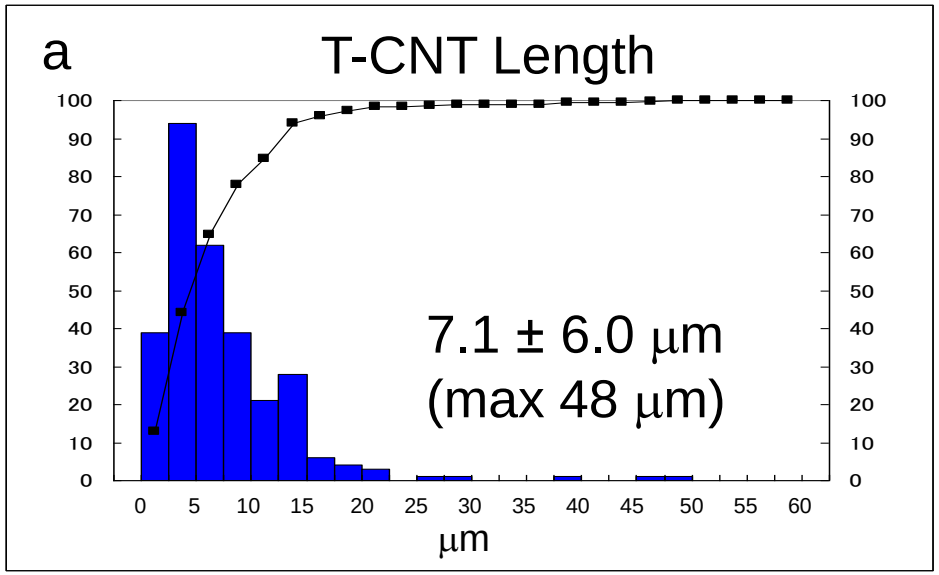
5L/min for 3 minutes SEM x1,000 (scale bars are 10 um).

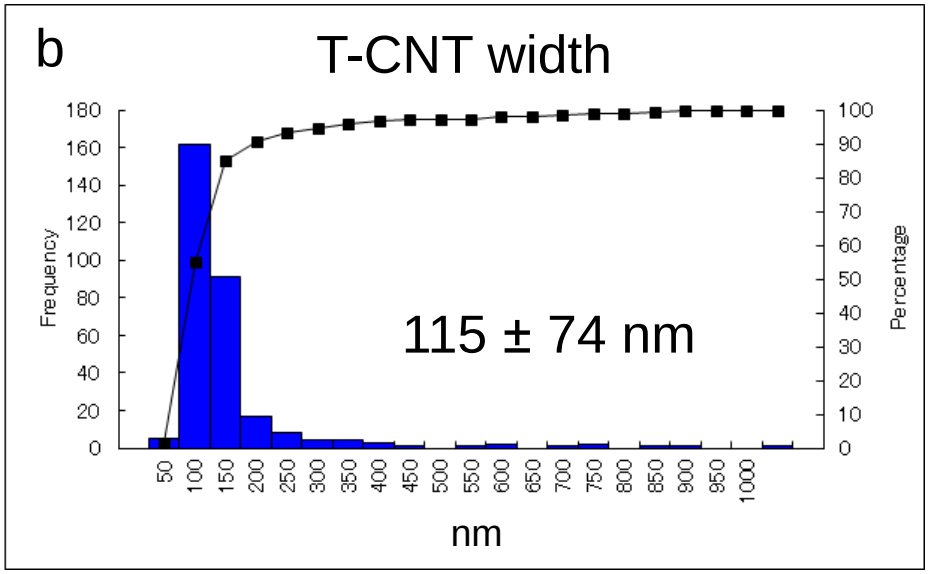
From the lysed lung

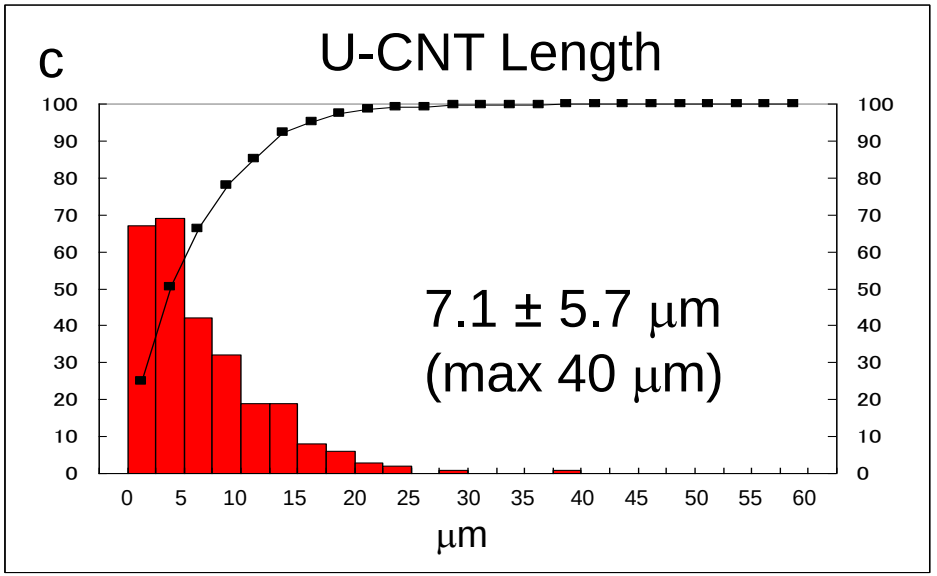


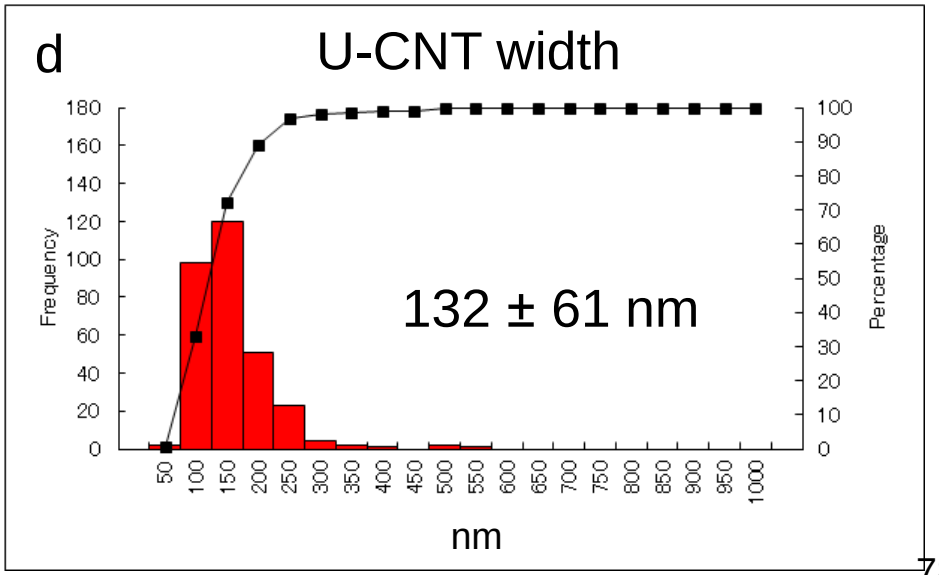
Taquahashi et al., J Tox Sci 38:619-628, 2013

No change in length/width by Taquann Dispersion



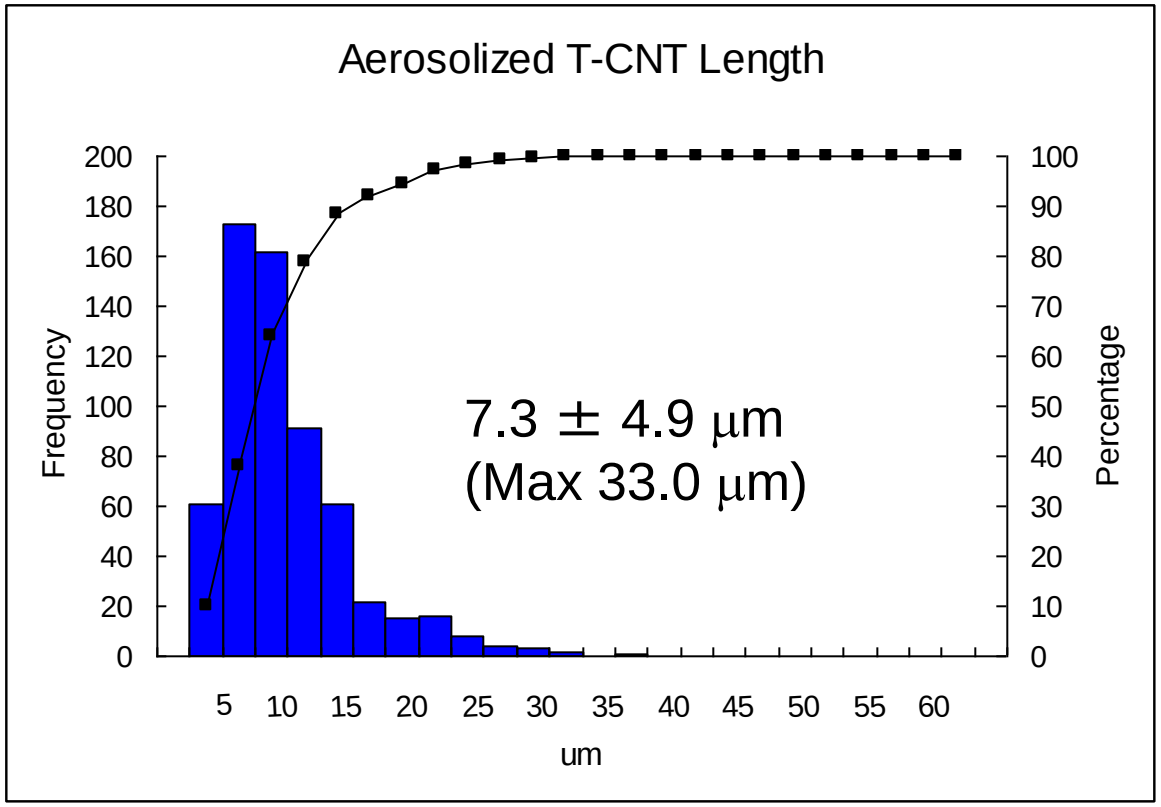






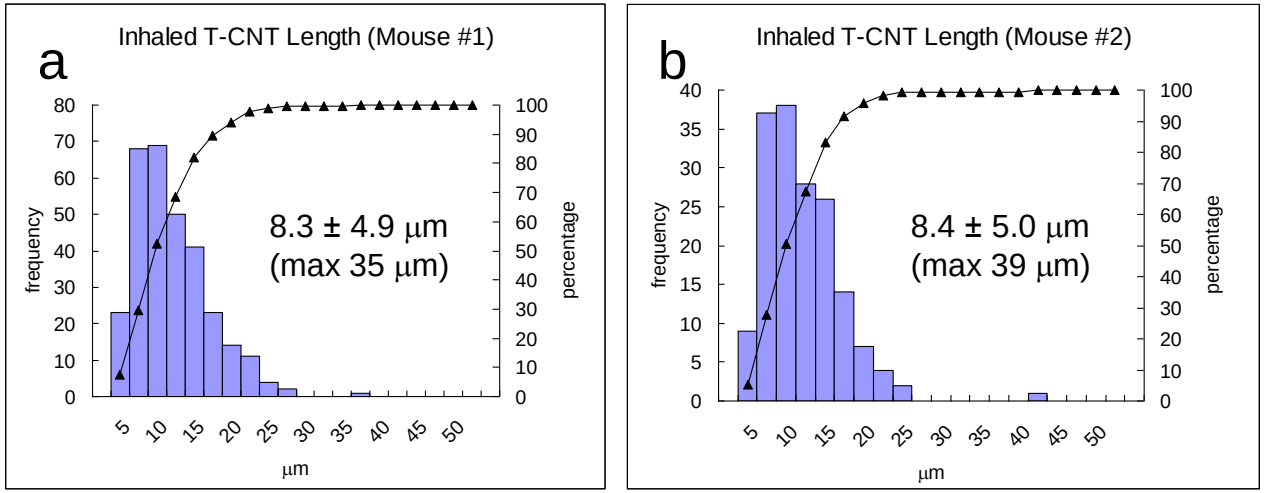
Taquahashi et al., JTS, 2013

Aerosol in exposure chamber has the same length and width



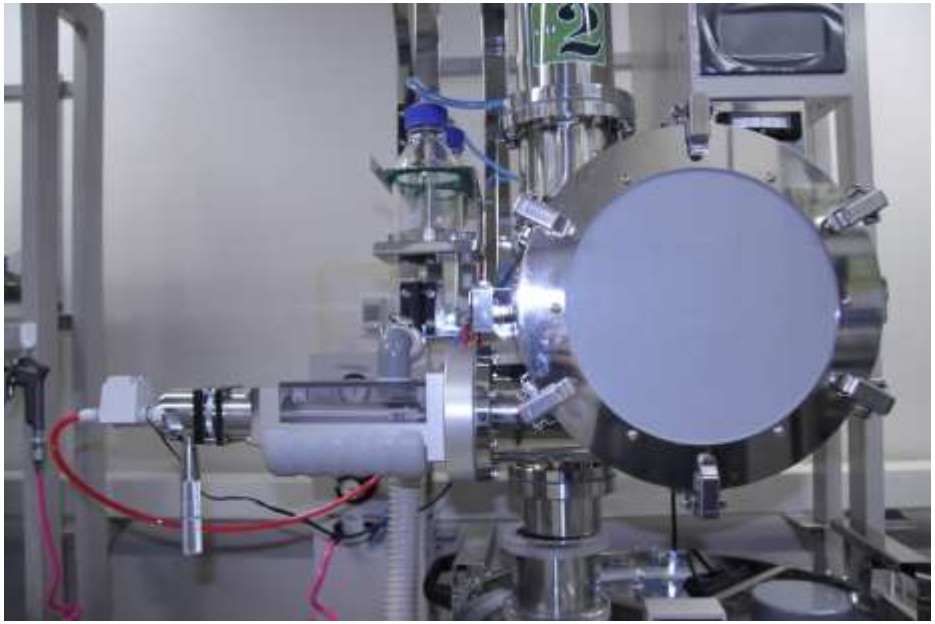
T-CNT counted on a filter by SEM (x2,500)（N=618)

CNT recovered from the lung shows same length and width



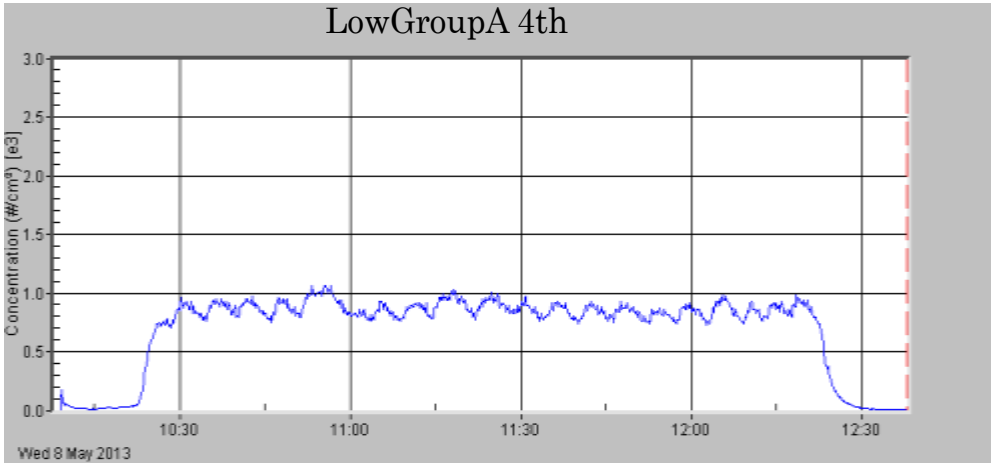
Taquahashi et al., JTS, 2013

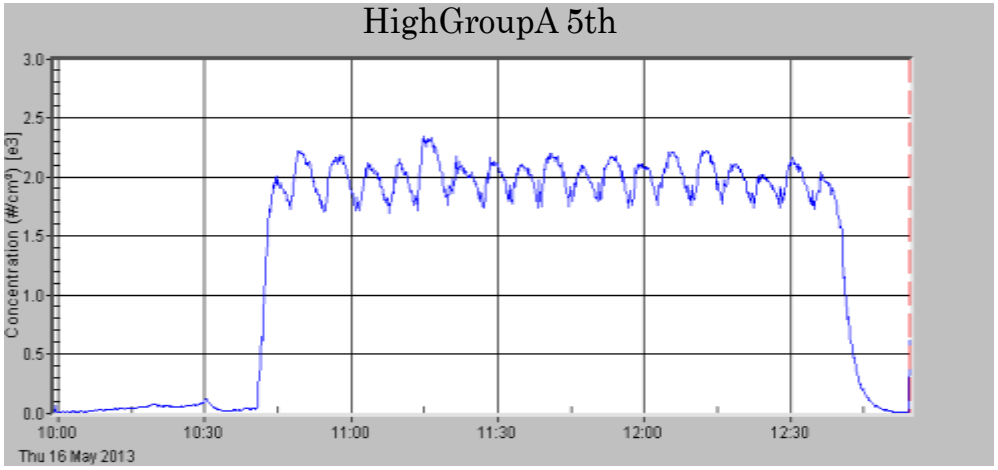
Version 2.5

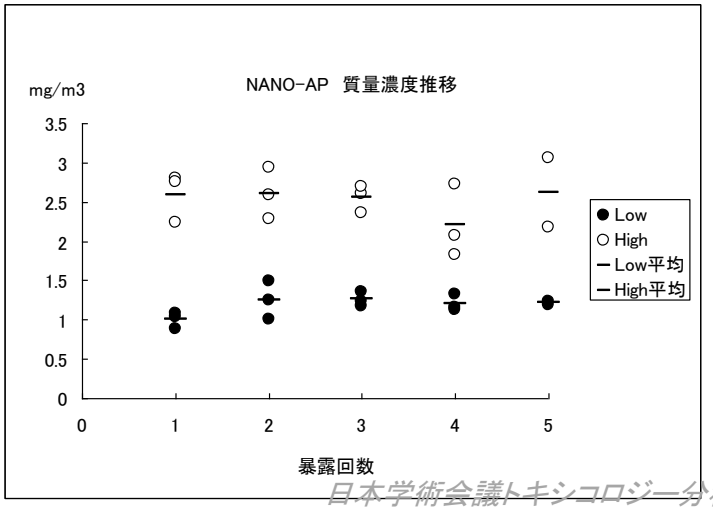


環境測定機器・科学機器の製造販売
SIBATA との共同開発

Concentration data of inhalation chamber







	低用量 mg/m^3	高用量 mg/m^3
1回目	1.00	2.59
2回目	1.25	2.60
3回目	1.26	2.55
4回目	1.20	2.20
5回目	1.21	2.62

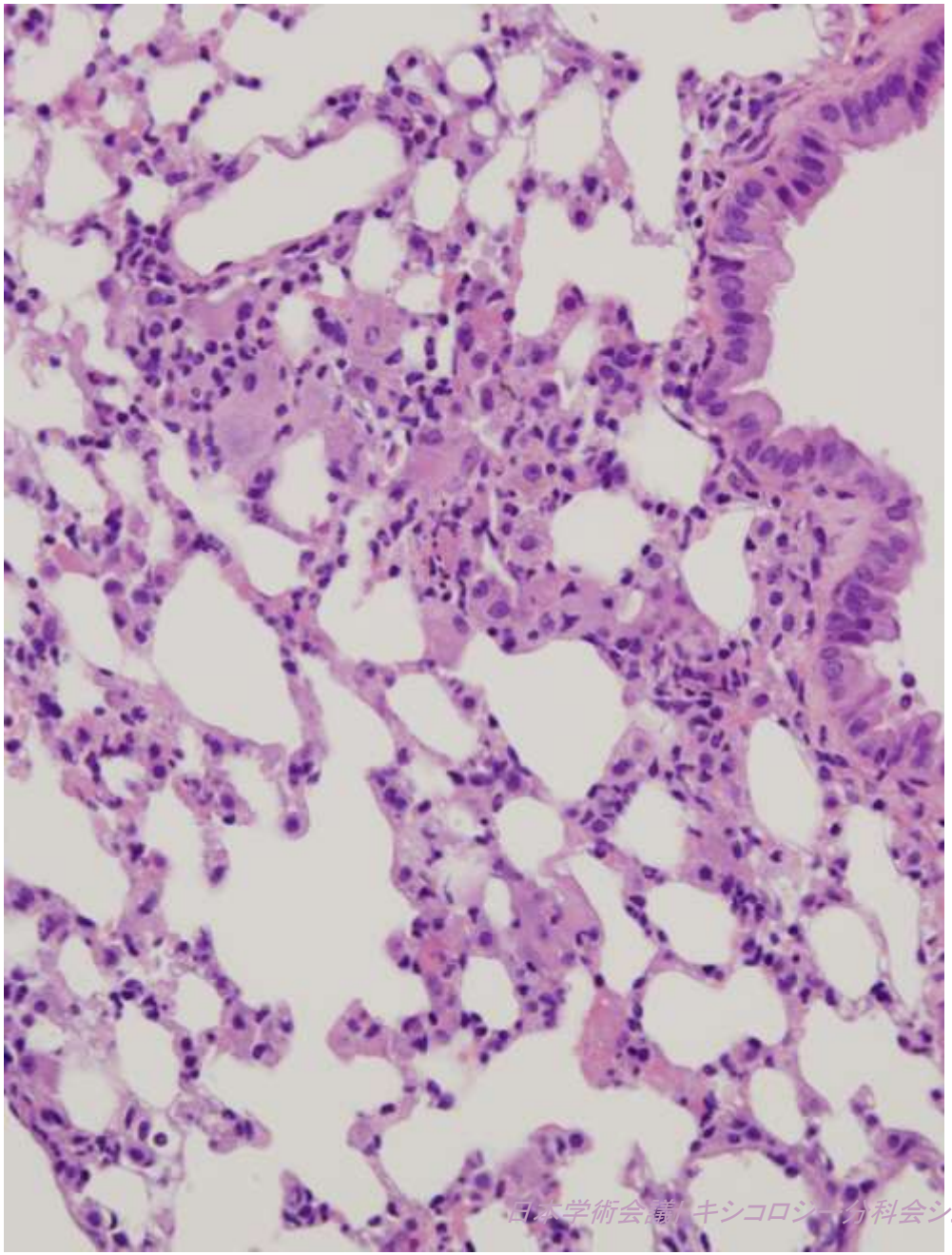
On-going study: Taquann-Direct Injection System whole body MWCNT inhalation study (C57BL/6 p53 +/- male)

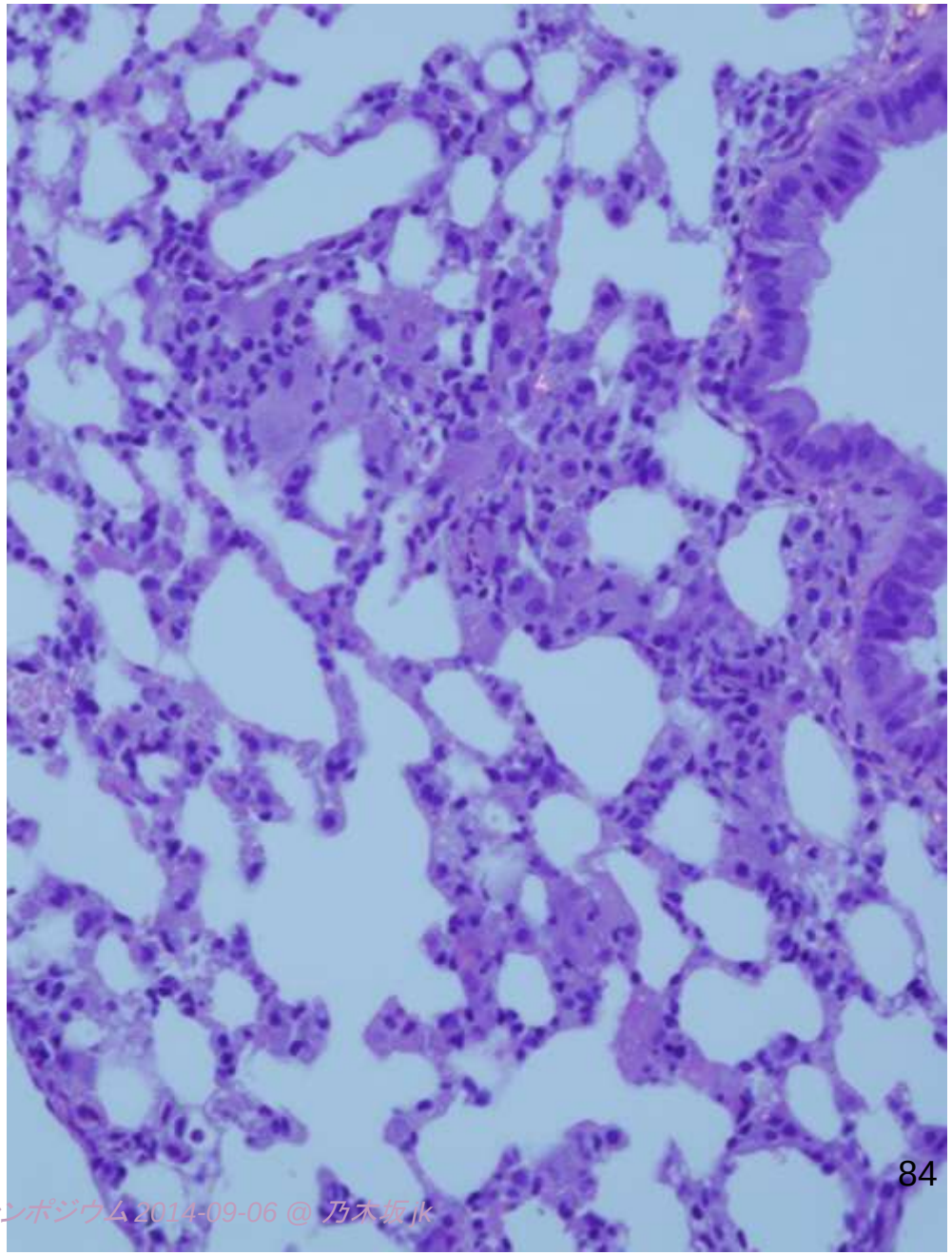
Group/ Exposure*	Conc.			Sampling				
	mg/m^3		Animal no.	0D	13W	26W	39W	52W
Control 0 μg/cartridge	0	Pathology	48	3	7	7	8	8
		Burden		3	3	3	3	3
Taquann L 250 μg/cartridge	1	Pathology	48	3	7	7	8	8
		Burden		3	3	3	3	3
Taquann H 500 μg/cartridge	2	Pathology	48	3	7	7	8	8
		Burden		3	3	3	3	3

*: 2hr exposure per week for 5 weeks (total 10 hr)

High 13W

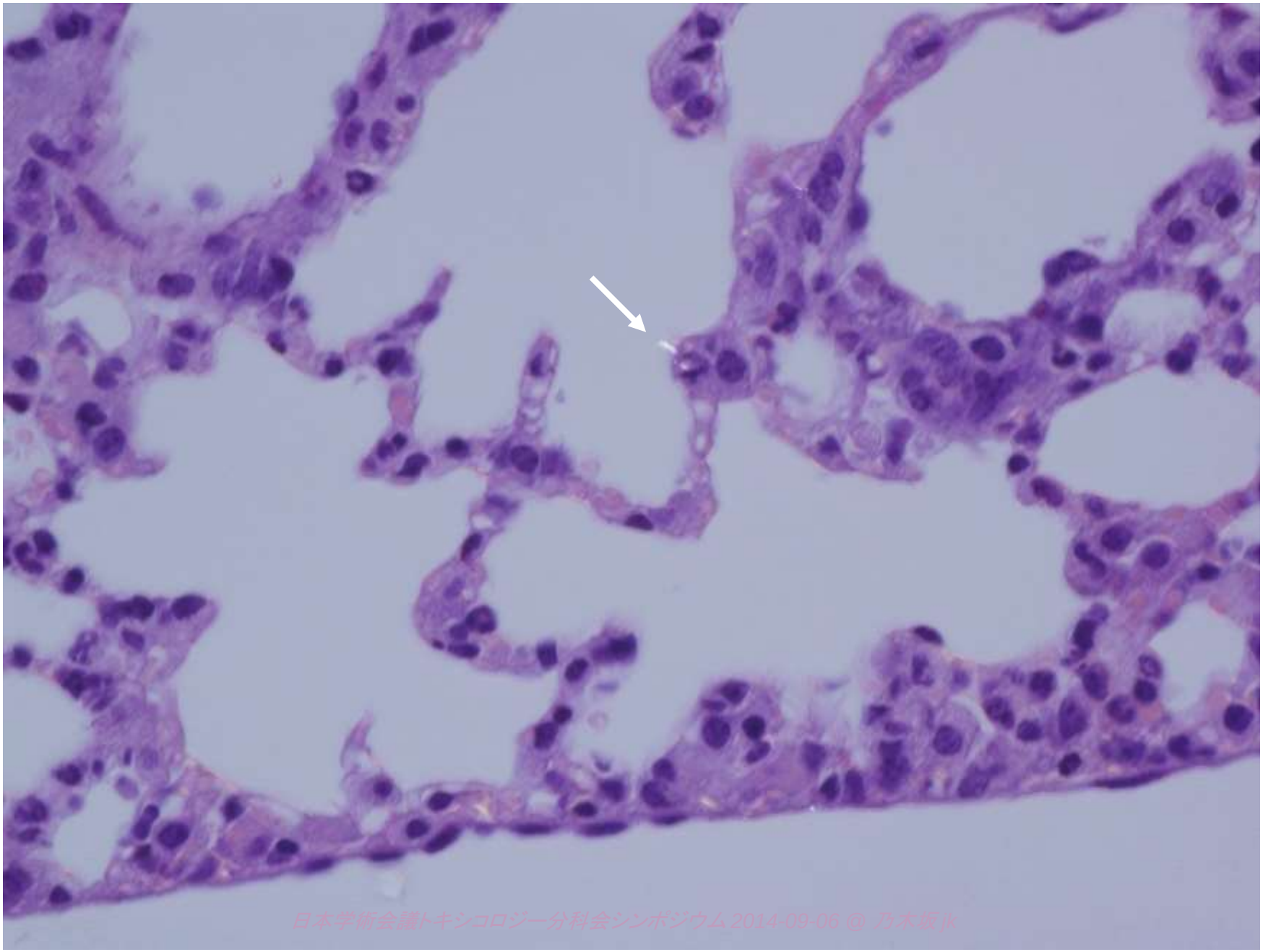
Inhalation study





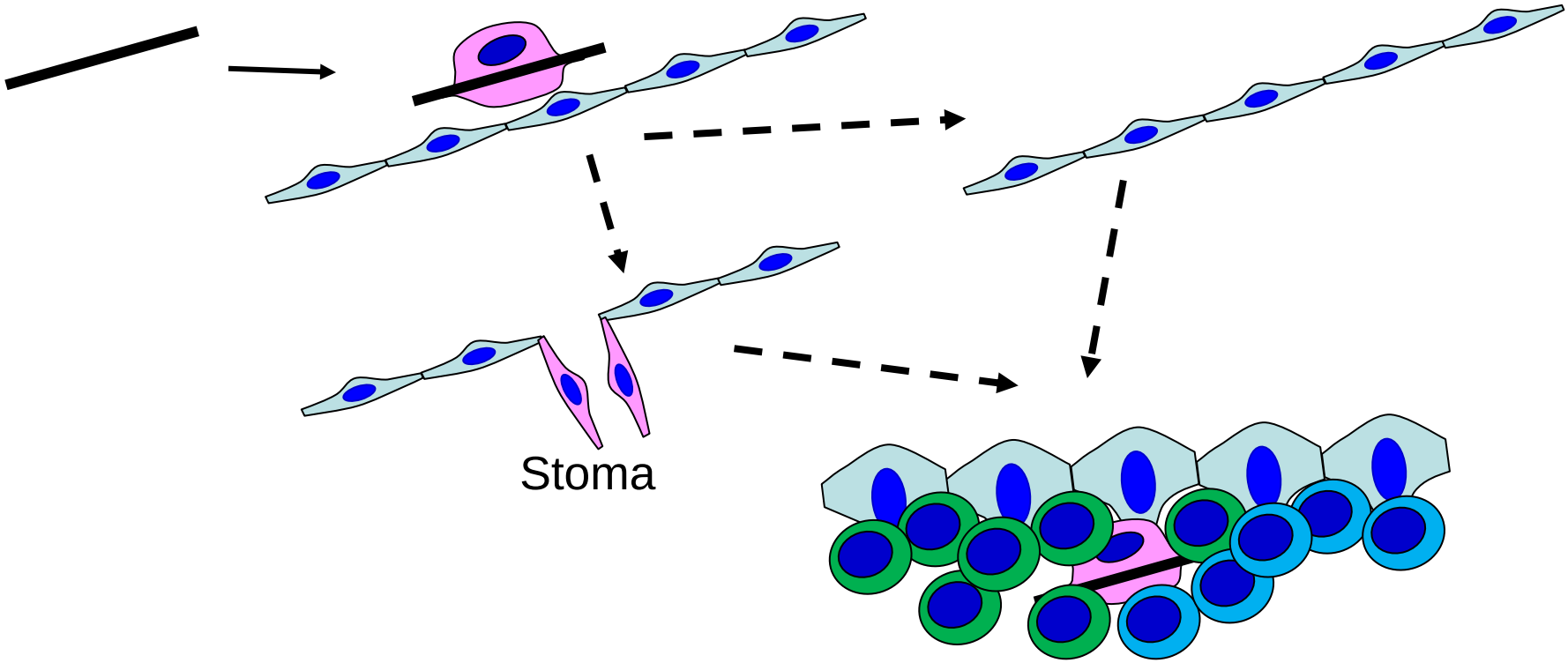
High 13W

Inhalation study

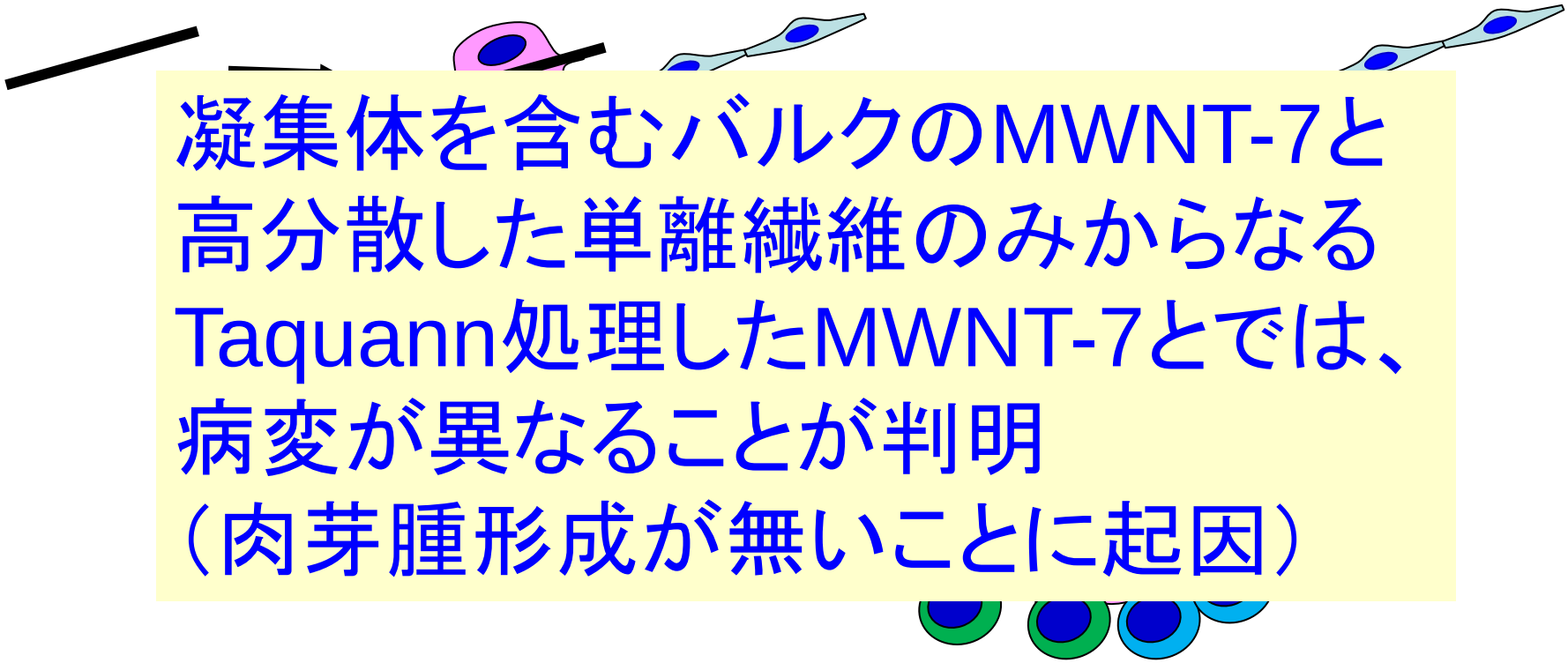


Inhalation study

Frustrated Phagocytosis (Mesotheliomagenesis)



Frustrated Phagocytosis (Mesotheliomagenesis)

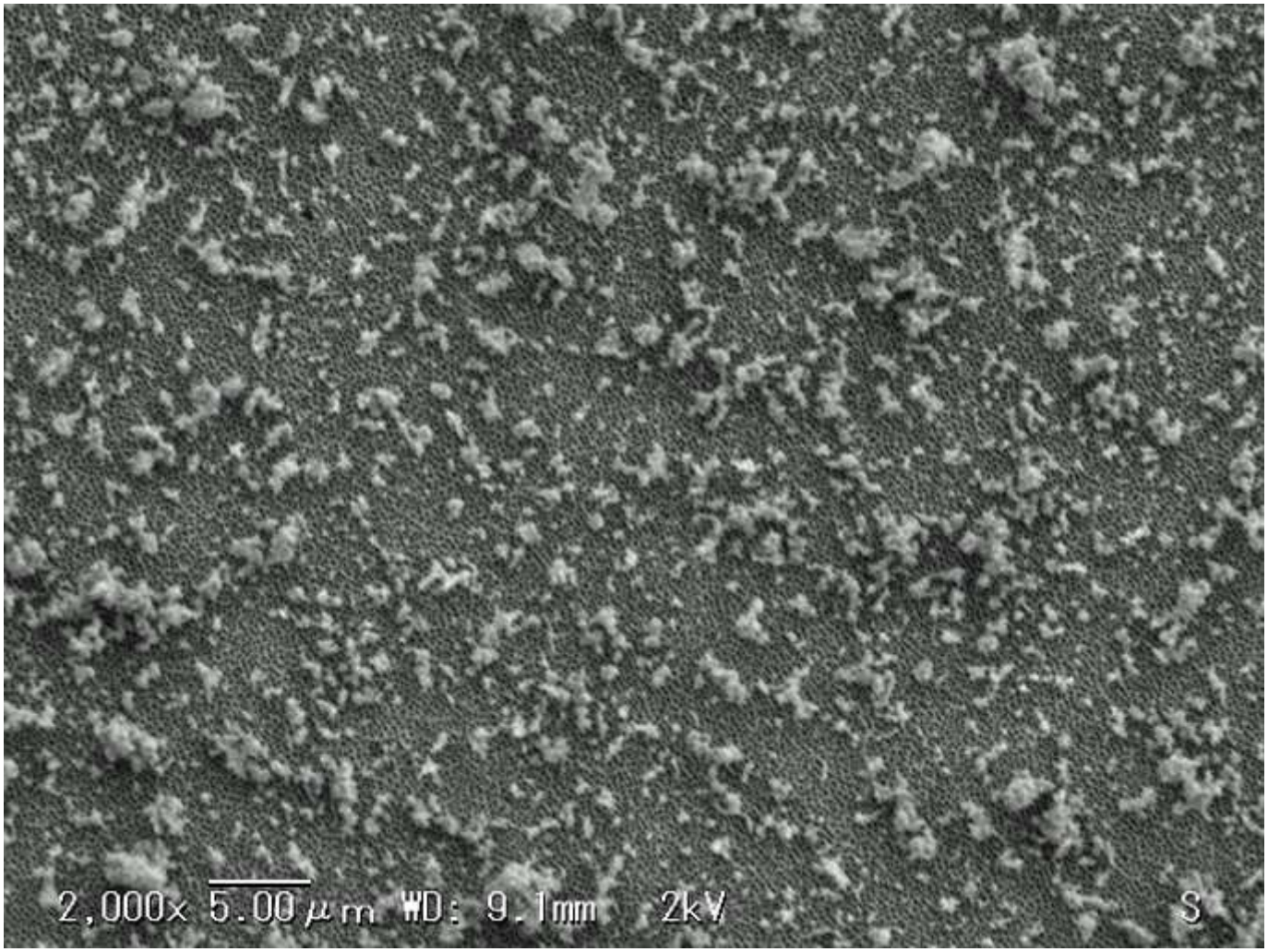


凝集体を含むバルクのMWNT-7と
高分散した単離繊維のみからなる
Taquann処理したMWNT-7とでは、
病変が異なることが判明
（肉芽腫形成が無いことに起因）

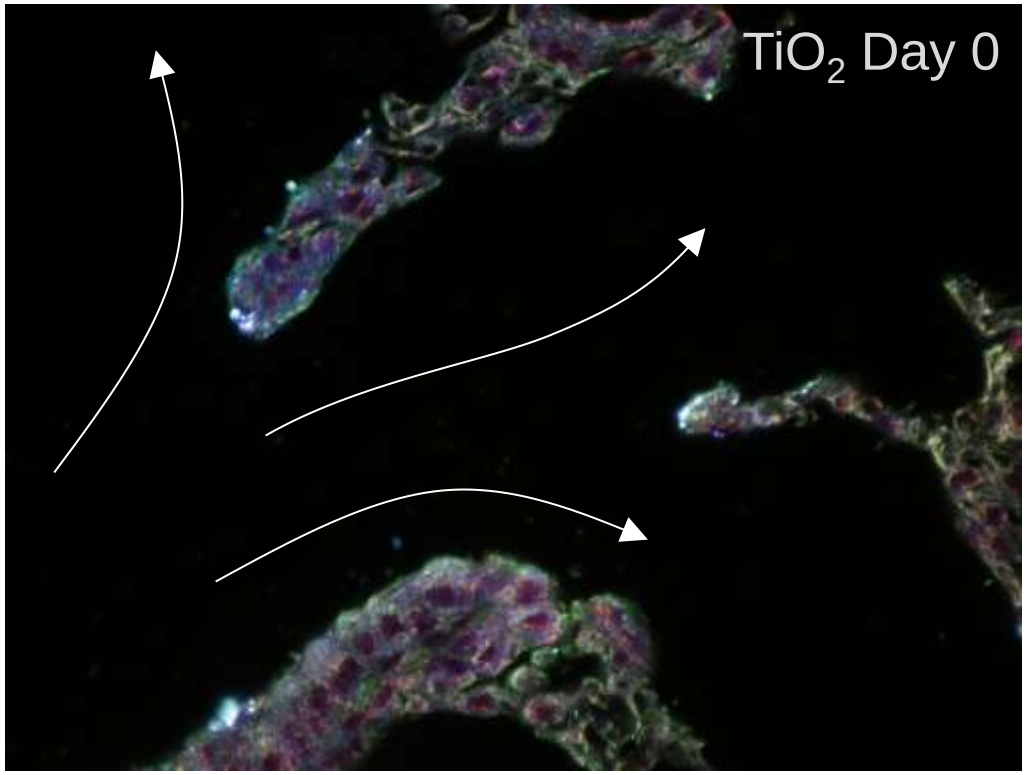
Contents of this presentation

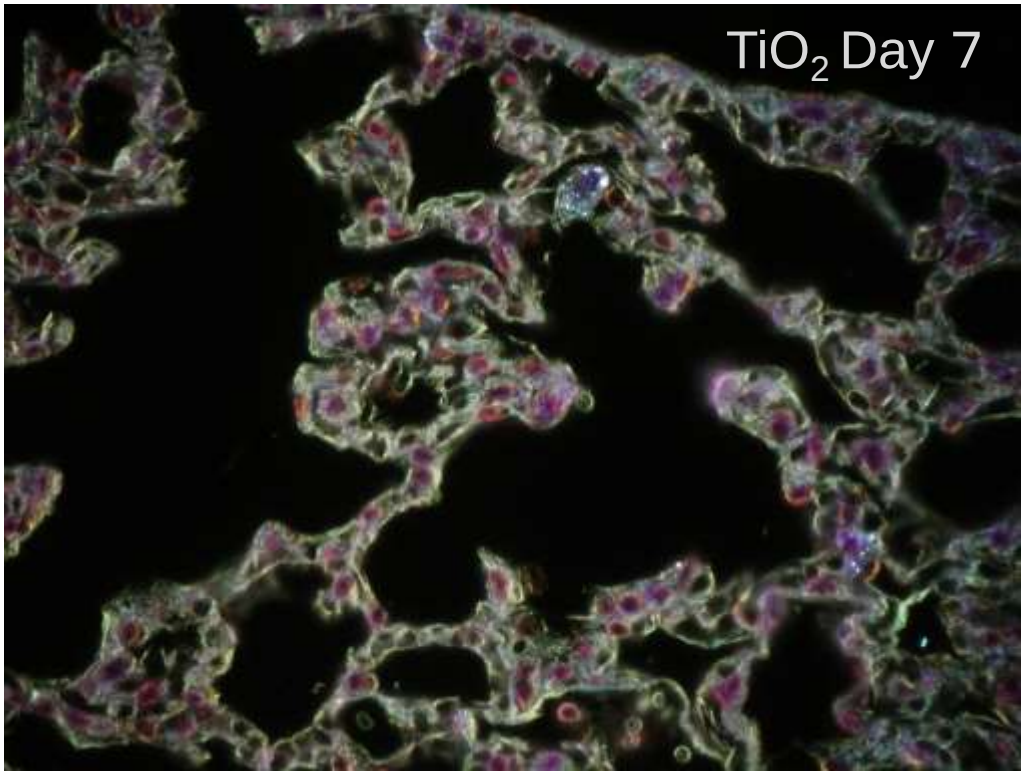
		Untreated MWCNT U-CNT	Taquann MWCNT T-CNT
intraperitonel injection	p53-/+	Mesothelioma	Mesothelioma
	wild	Not Planned	Mesothelioma & Fibrosis
whole body inhalation	p53-/+	Not Planned	Ongoing
	wild	Not Planned	Ongoing

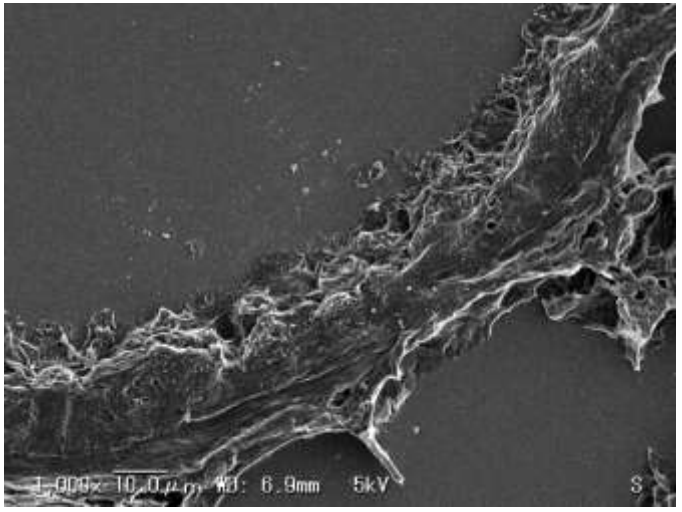
Taquann TiO_2

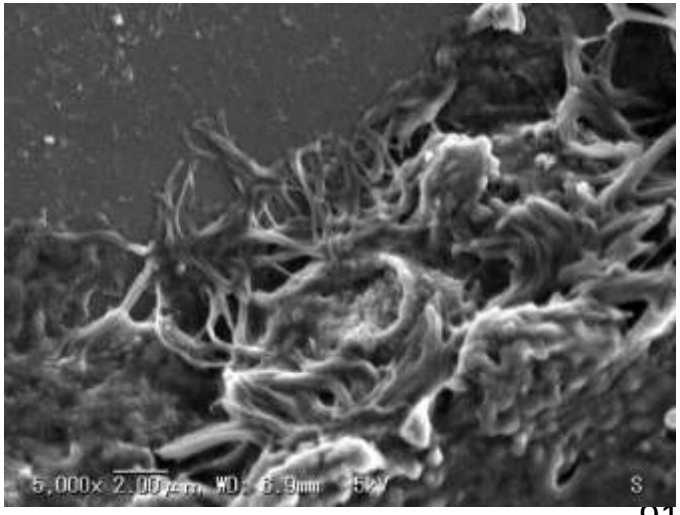


5L/min for 6 min on Φ 25mm Anodisc25 Inorganic aluminum oxide membrane filters, Whatman, pore size; 0.1μm


TiO_2 Day 0


TiO_2 Day 7


1,000x 10.0μm WD: 6.9mm 5kV
S


5,000x 2.00μm WD: 6.9mm 5kV
S

まとめ（1）

Taquann 法

- 凝集体を含まない高分散状態のMWCNTのエアロゾルを生成した
  - 分散した個々のMWCNT繊維の長さと太さに影響はない
- Taquann法 + カートリッジ直噴式　全身暴露吸入装置はうまく作動した
  - 二酸化チタンにもすぐに応用可能であることが示された

腹腔内投与試験からの所見

- 中皮腫発癌には、スタントン仮説が成り立ち、単離した繊維がその主要因である
- 大きな凝集体・凝固体は繊維発がんに寄与しない

まとめ (2)

全身暴露吸入試験

- 単離繊維が肺胞域まで到達し、その近位には肉芽腫形成を認めなかった。
- 境界不明瞭な間質性肺炎像をみとめ、MWCNT繊維はCD68陽性マクロファージ内に、あるいは単独で肺胞壁内に認められた。（肺負荷量　3μg/肺）
- 単離 MWCNT繊維が、壁側胸膜、ストーマ近傍に形成された、顕微鏡的限局性病変内のマクロファージと思われる細胞内に認められた。限局性病変は、マクロファージおよびリンパ球からなり、胸腔面は反応性中皮により覆われていた。
- この限局性病変は、腹腔内投与実験に於いて観察された微小病変（前駆病変と考えられる）に酷似していた。
- 胸腔内への単離繊維の移行量（translocation）は、経時的に増加する可能性が示唆された。

Taquann法　まとめ

- Taquann法処理検体は、凝集体・凝固体を含む原末とは異なる病理像を誘発する。（肉芽腫性病変を欠き、より均一広範囲は病変を誘発する）
- Taquann直噴全身暴露吸入システムは、種々のナノマテリアル検体に容易に適用可能であることが示唆された。
- 本システムは、全身暴露吸入の普及に役立つことが期待される。
  - Taquann法はごく簡単で、設備投資がほとんど不要である
  - 直噴吸入装置は、比較的安価で、運転が容易である
  - 検体を濾過した後は、液相～ほぼ閉鎖系であり、検体のロスがない。
    - 施設の汚染管理が容易である
    - 微量の検体を全身吸入できる

↓

Taquann法　まとめ

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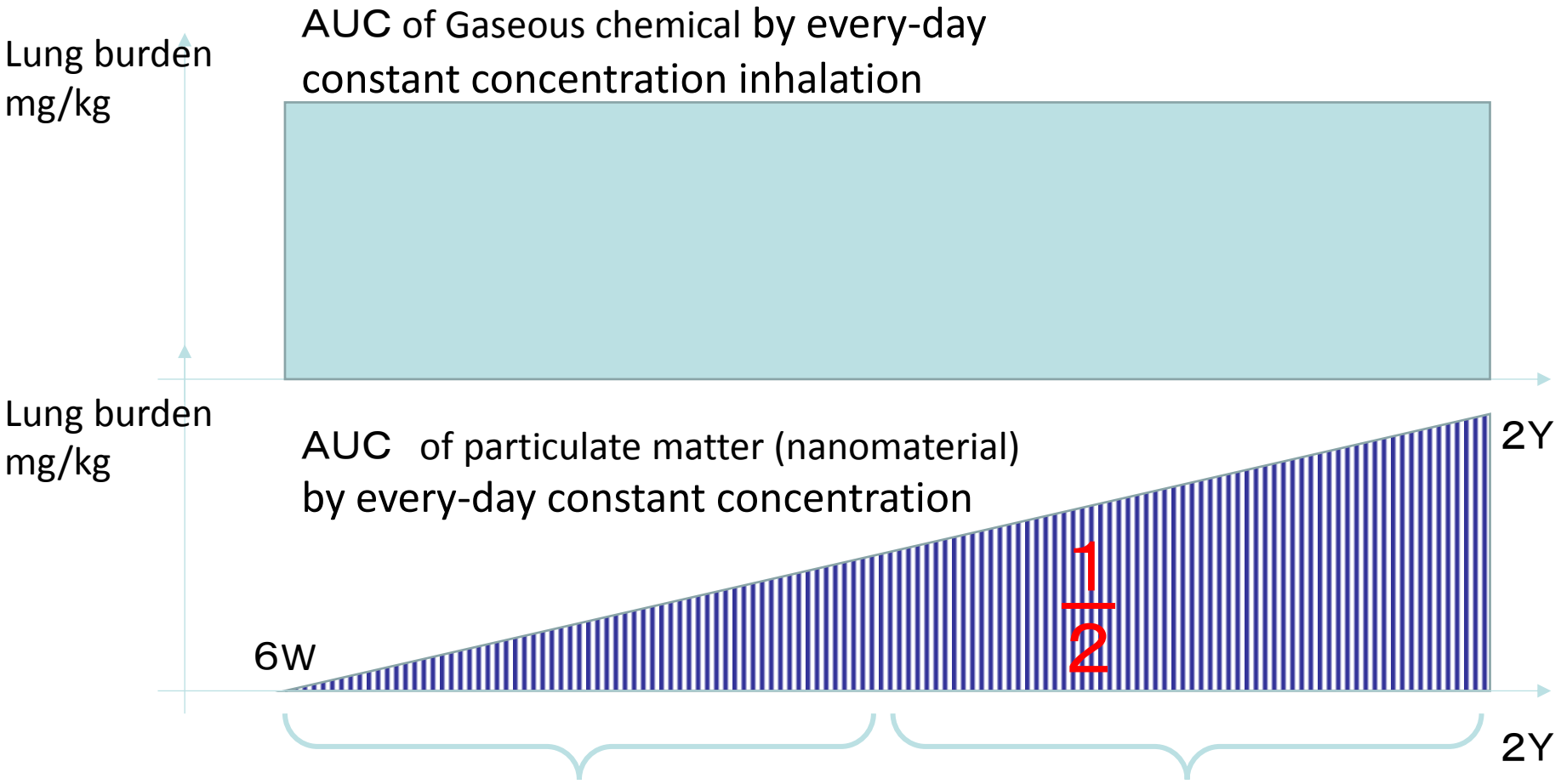
    - 施設の汚染管理が容易である
    - 微量の検体を全身吸入できる

- **少量新規ナノマテリアルに適用可能！？**

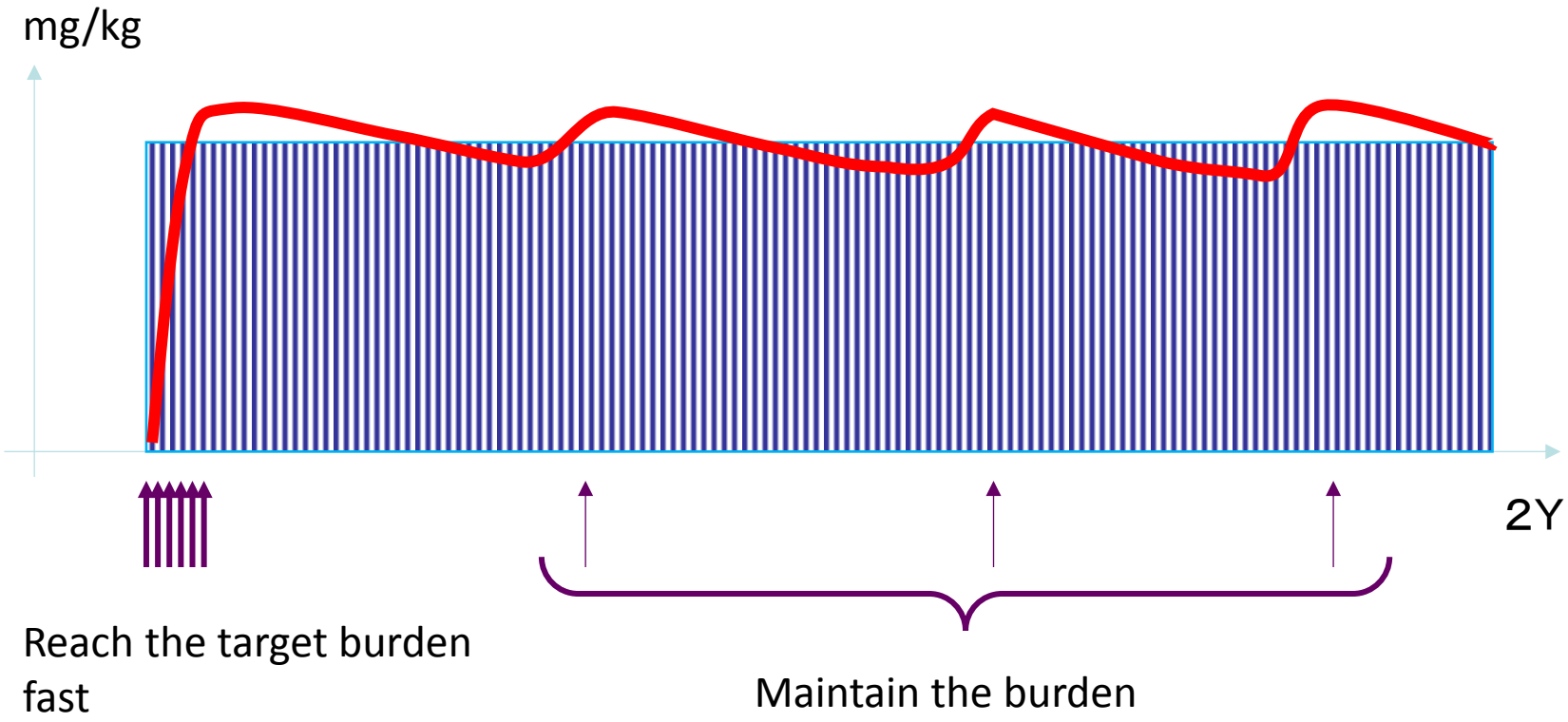
Area Under the Curve (AUC) = burden x time



Low exposure during sensitive period

Overload toxicity during cancer development

Proposed protocol for nanomaterial inhalation



まとめ

- ナノマテリアル、特にカーボン系は、安定性が高いものが多いので、
  - 毒性を判断する際には、慢性影響に注意する必要がある。
  - アスベストや代替繊維の毒性知識が適応されるナノチューブがある。Stanton仮説は、今や仮説ではないと考えるべき。
    - 単体には、中皮腫発癌性があり、閾値が設定できないと考えて、生産活動・商品開発を行う必要がある。
    - 肺がん、肺の線維症など、中皮腫以外の毒性も誘発することを念頭に、生産活動・商品開発を行う必要がある。
- ほとんどのナノマテリアルの毒性は、未知である。

終わり