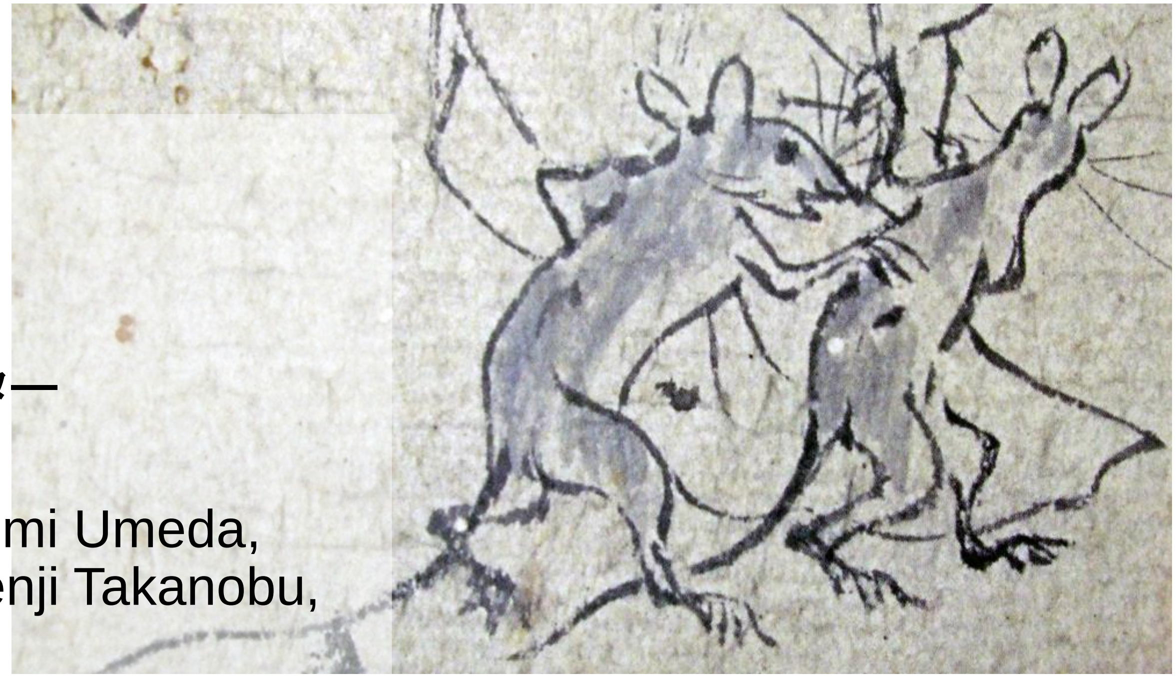
ナノマテリアルを含む種々の化学物質の吸入が引き起こす呼吸器の毒性の現状と展望



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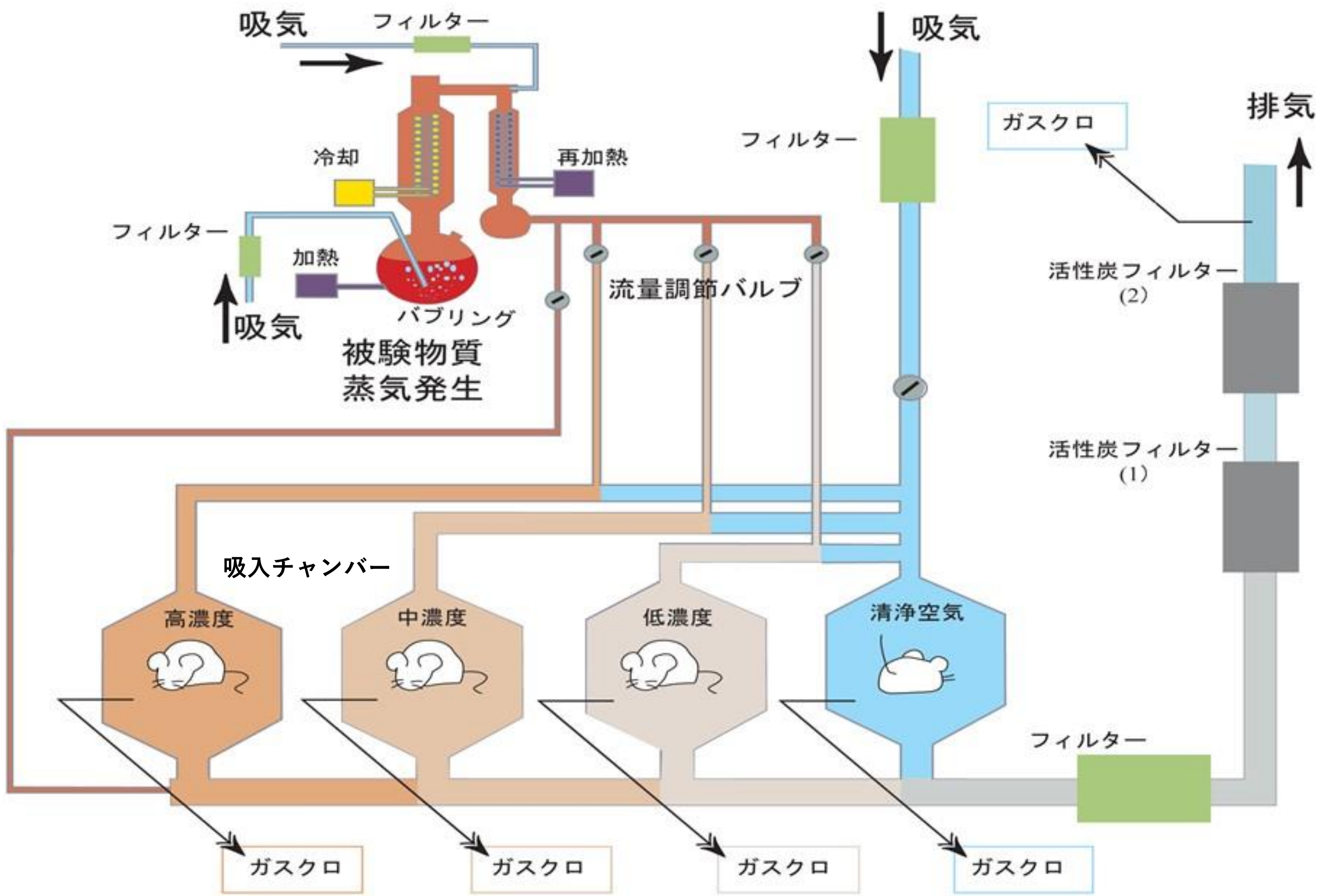
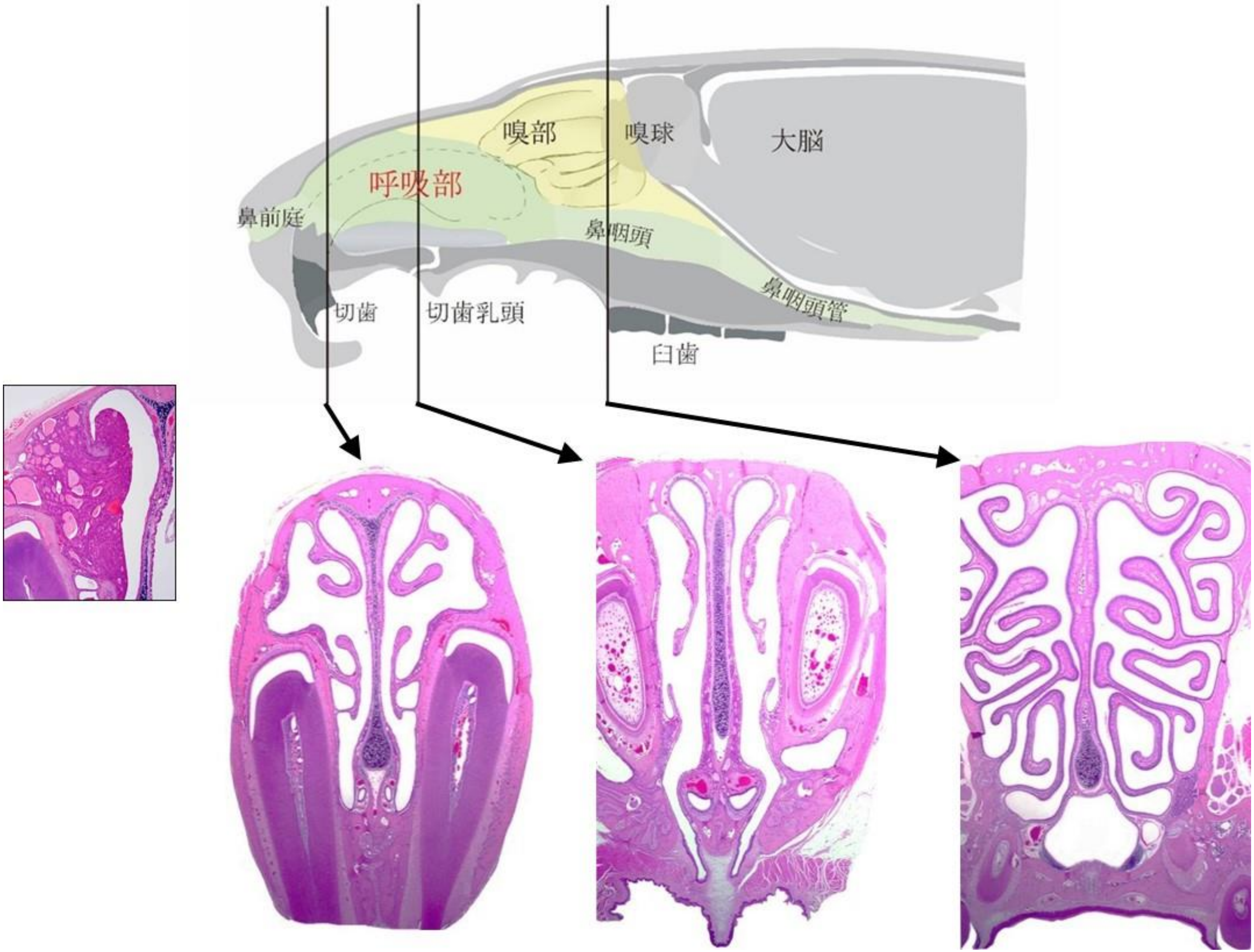
全身曝露吸入チャンバー（2年間がん原性試験用）

吸入曝露装置(全身曝露用)





嗅部
嗅球
大脳
呼吸部
鼻前庭
鼻咽頭
切歯
切歯乳頭
鼻咽頭管
臼歯

過去5年間の吸入癌原性試験

物質名称	ラット(F344)	マウス(BDF_1)
1,2-ジクロロプロパン	鼻腔(♂♀)	ハーダー腺(♂) 肺(♀)
N,N-ジメチルアセトアミド	肝(♂)	肝(♂♀)
エチレングリコールモノエチルエーテルアセテート	(ー)	(ー)
メタクリル酸	鼻腔、腹膜中皮、皮膚、皮下(♂) 鼻腔、乳腺、子宮(♀)	鼻腔、前胃(♂) 鼻腔、肺、子宮(♀)
多層カーボンナノチューブ(MWNT-7)	肺(♂♀)	(実施せず)
アクロレイン	鼻腔(♂♀)	鼻腔(♀)

- 粒子状物質による人身事故例

（１）アスベスト発がん（繊維発がんfiber carcinogenesis）

- 悪性中皮腫　frustrated phagocytosis
- 肺腺癌 : メカニズム?　　中皮腫より多いと言われる
- **★閾値が設定できない (WHO: threshold is not known to exist)**
- アスベストの全身分布による有害影響（他臓器発がん・免疫異常）

（２）トロトラスト　） 大戦中に用いられたレントゲン造影剤

- 細網内皮系（肝、脾、リンパ節など）に補足される　()

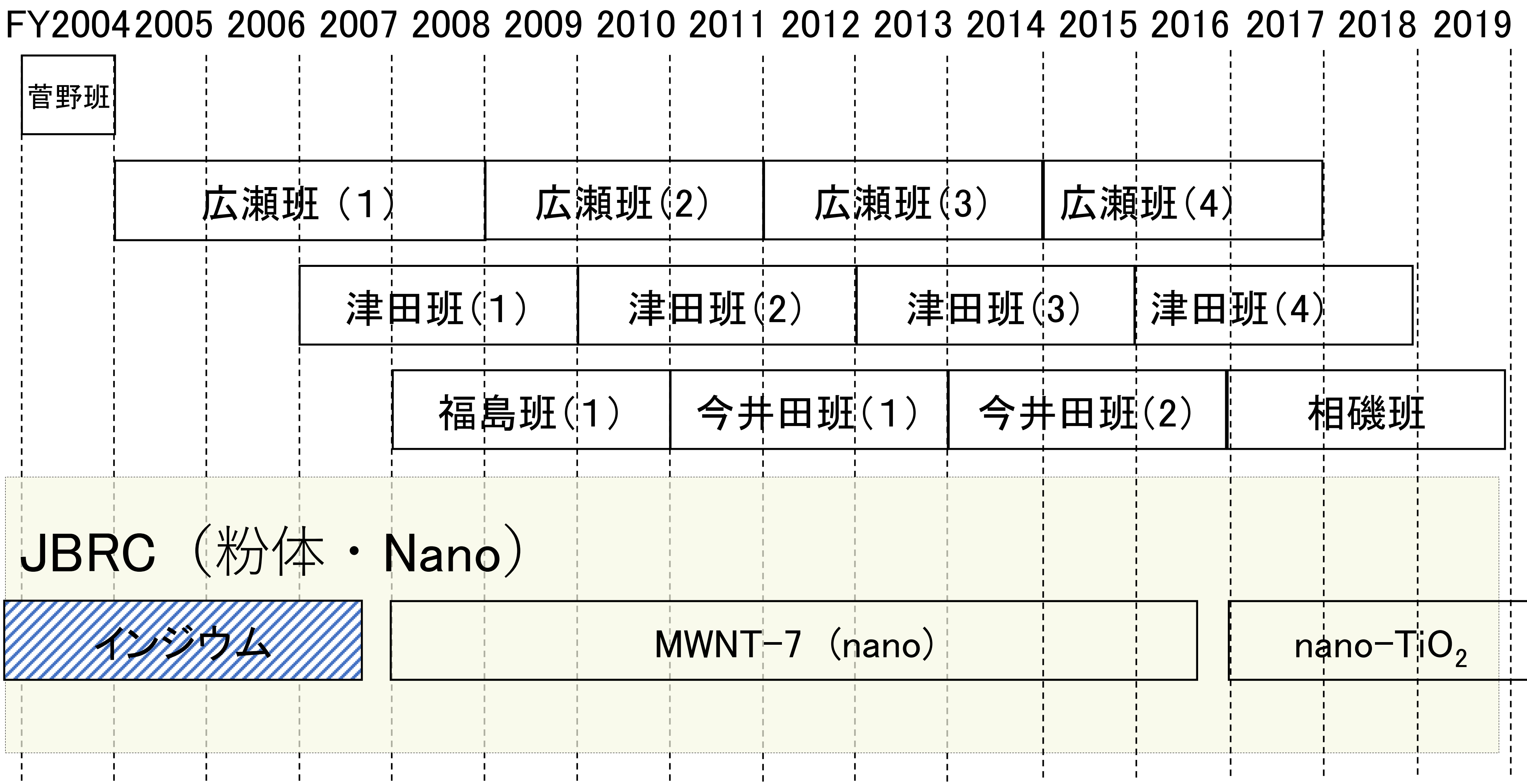
  ★人体半減期 = 22～400 年

- 3～10 nm の粒子である　3~10 nm emulsion**

（３）溶接フューム（循環器）

*　reticuloendothelial system
** thanks to Dr. Hakan Wallin for the size info

ナノ物質のヒト健康影響に関する研究
厚生労働科学研究費補助金【化学物質リスク研究事業】研究班



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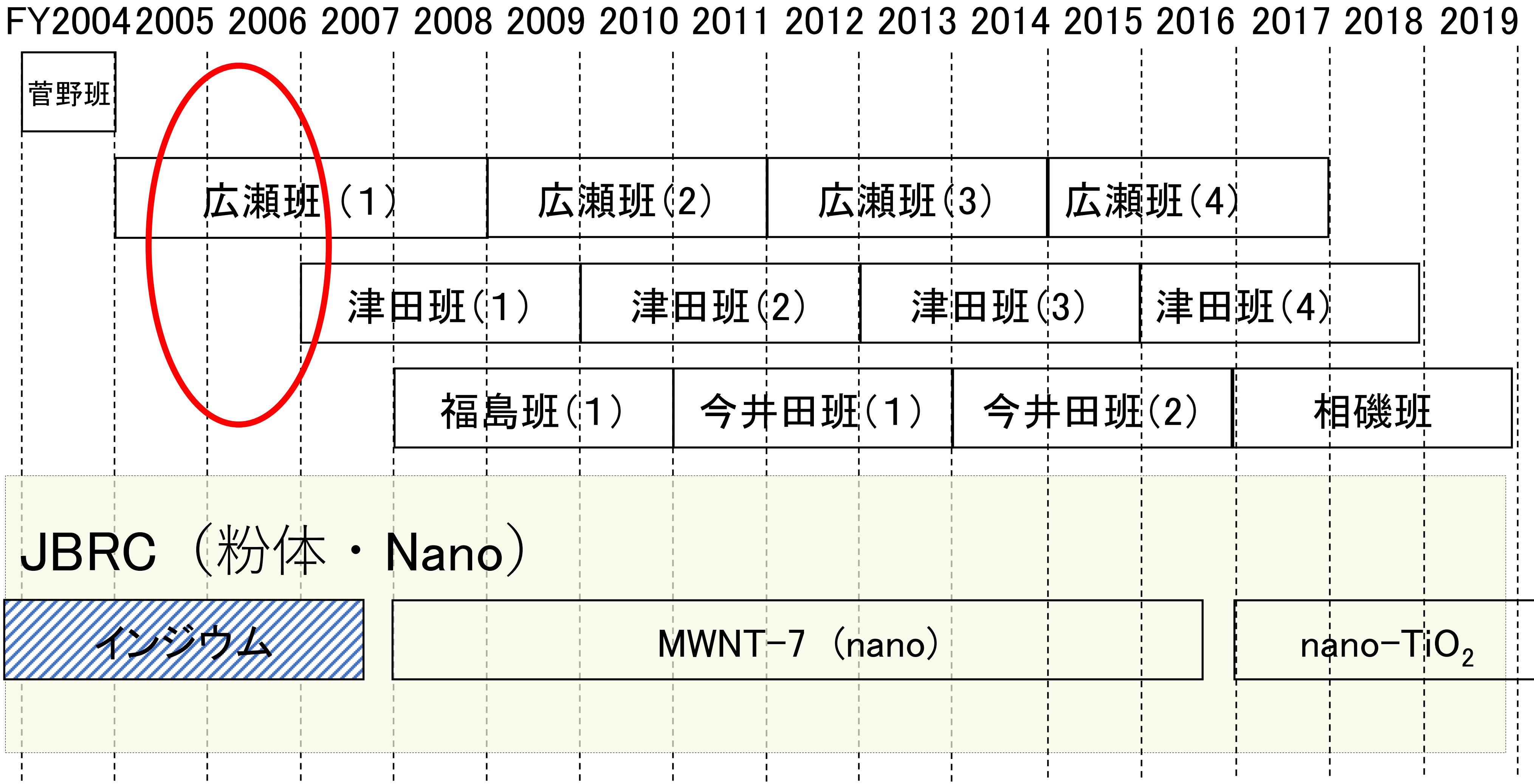
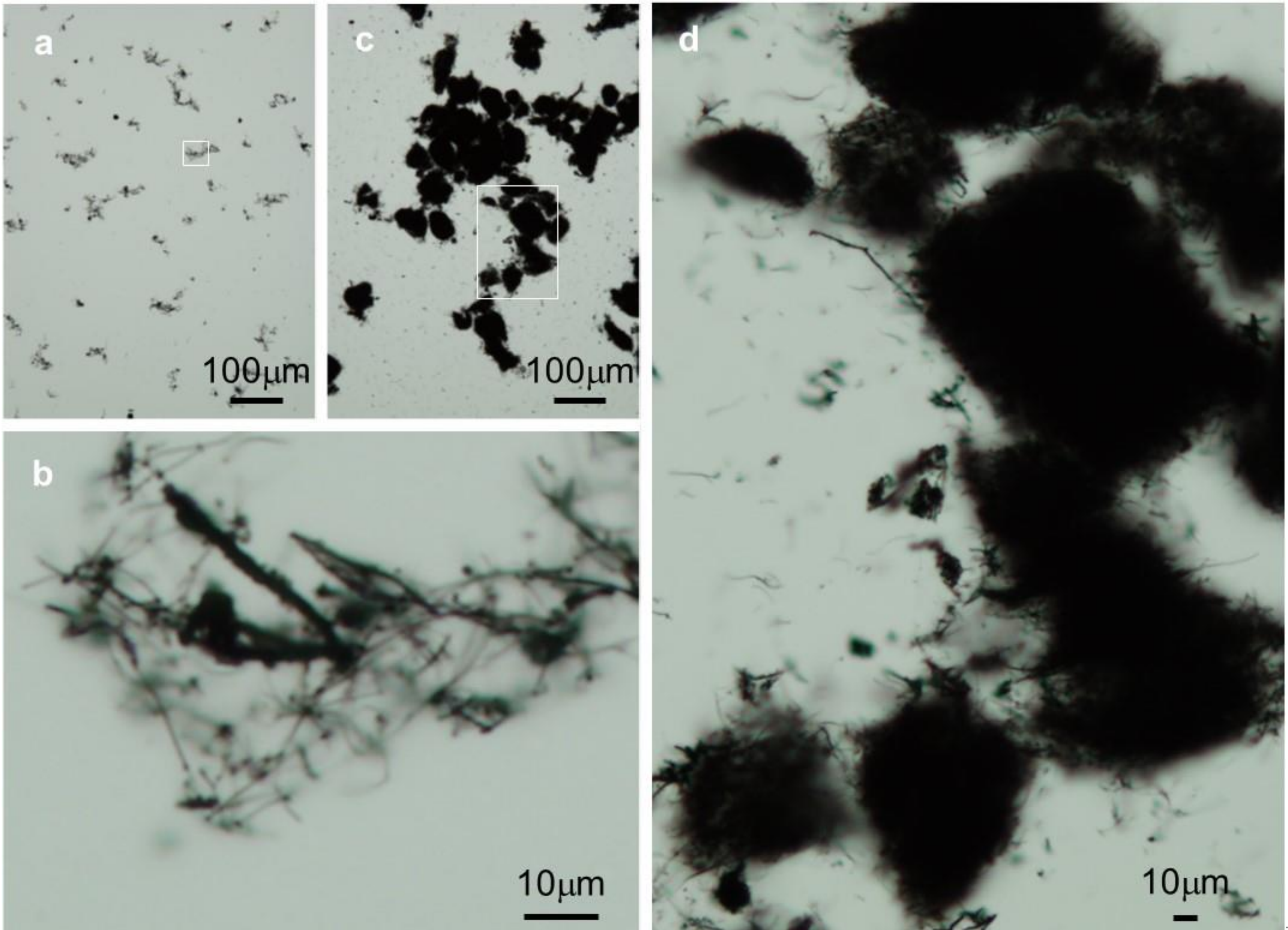


MWCNT (Mitsui MWNT-7)



MWCNT (Mitsui MWNT-7)

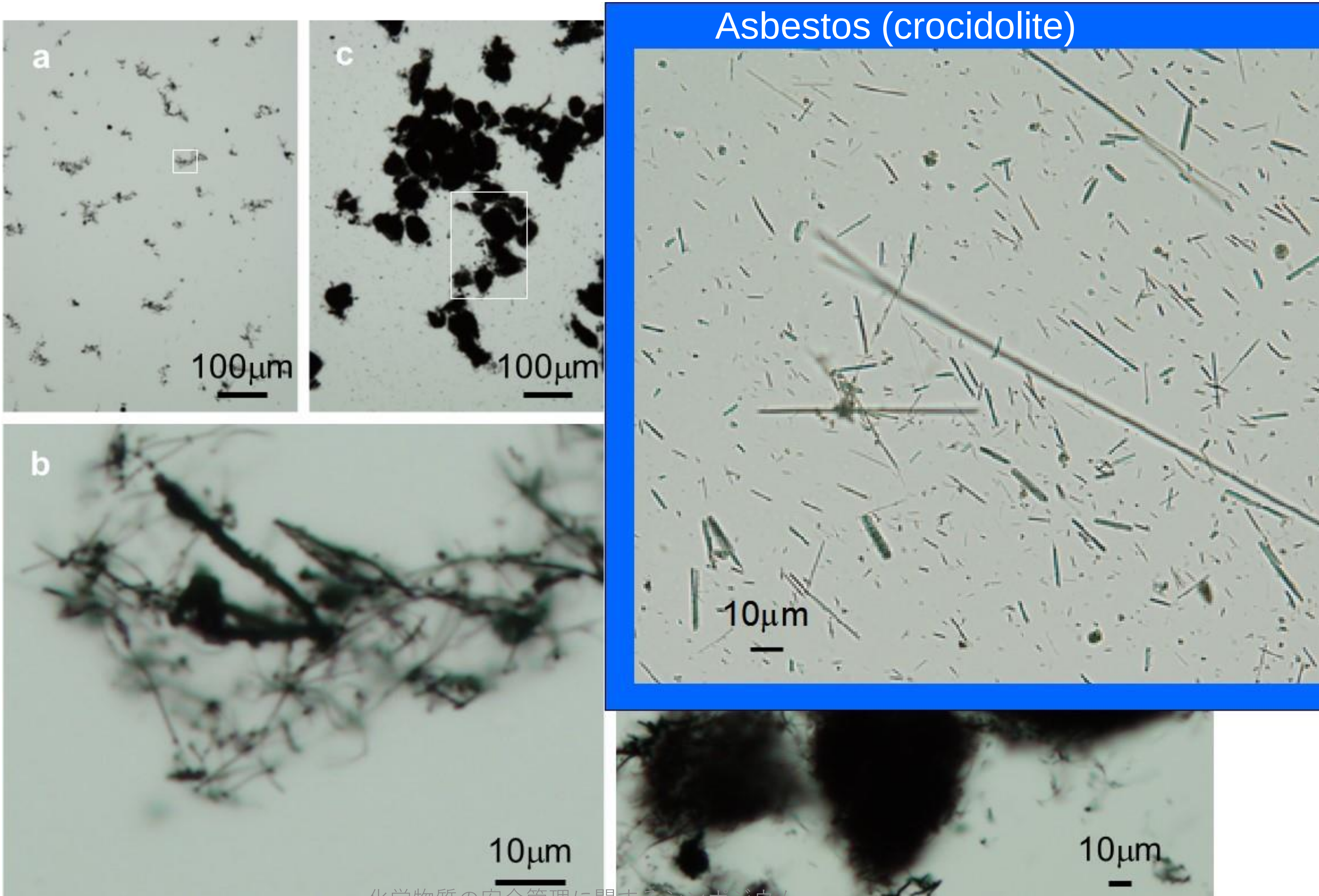


Figure 4-3

MALIGNANT MESOTHELIOMA

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

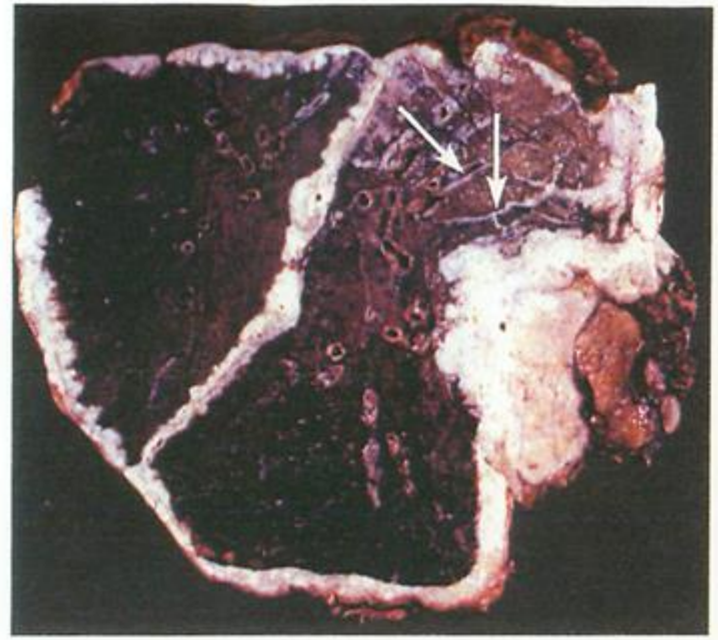


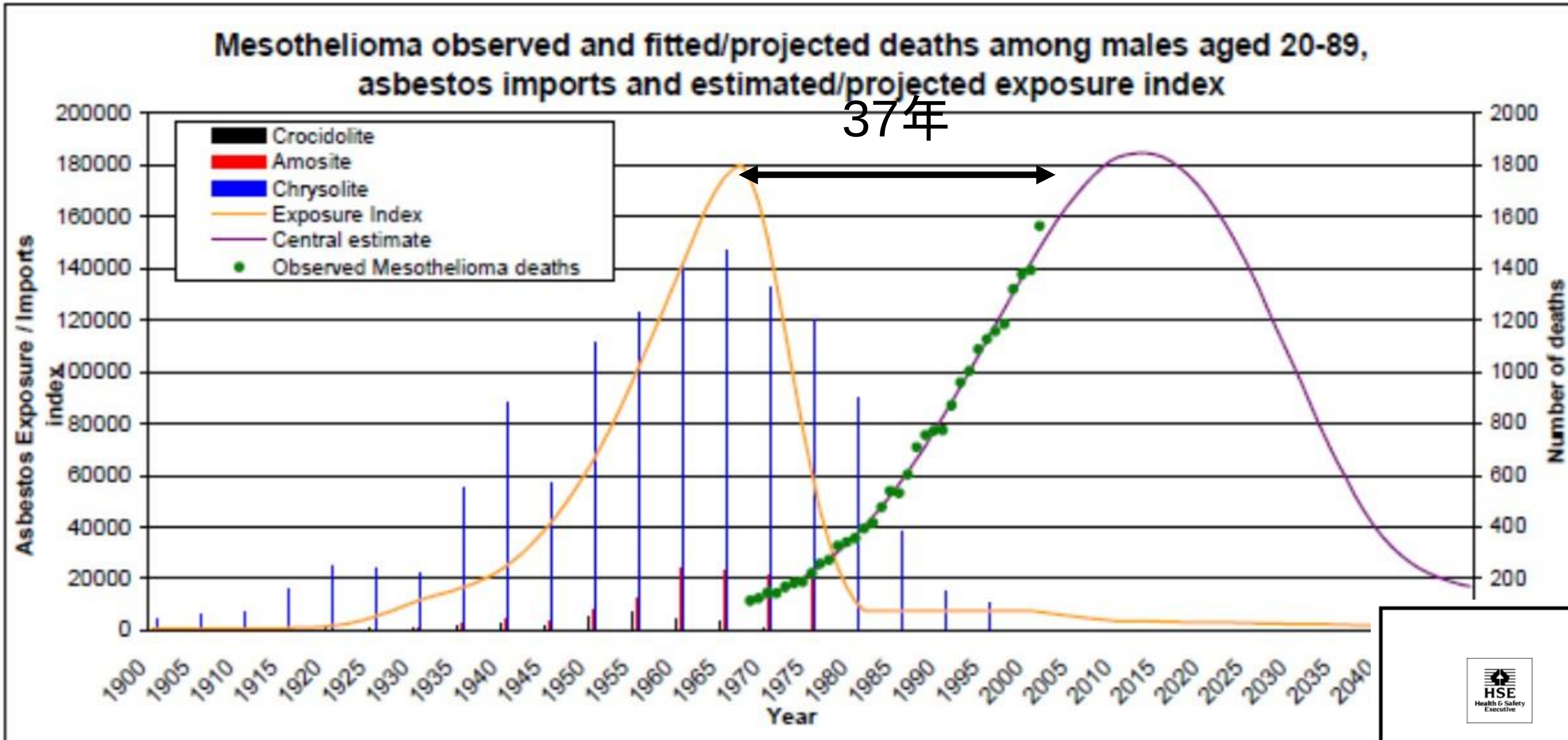
Figure 4-4

MALIGNANT MESOTHELIOMA

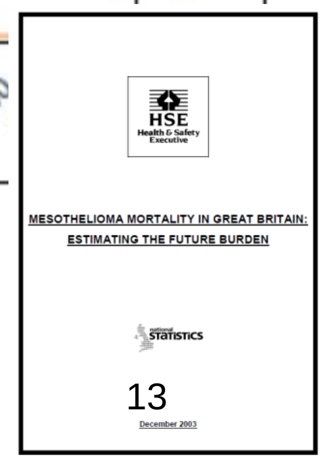
The tumor almost completely encases the lung and extends along the major fissure. Tumor also grows into the lung along the interlobular septa, surrounding small vessels and airways (arrows).

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 early mesotheliomas that are only apparent mi-

Figure 3



4. Discussion



繊維発癌の基礎　スタントン－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

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3	Si carbide	17/26	100	5.15	39	Glass
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5	Tremolite 1	22/28	100	3.14	41	Glass
6	Tremolite 2	21/28	100	2.84	42	Glass
7	Dawson 1	20/25	95±4.8	4.66	43	Alumi
8	Crocid 1	18/27	94±6.0	5.21	44	Dawso
9	Crocid 2	17/24	93±6.5	4.30	45	Dawso
10	Crocid 3	15/23	93±6.9	5.01	46	Wolla
11	Amosite	14/25	93±7.1	3.53	47	Crocic
12	Crocid 4	15/24	86±9.0	5.13	48	Attapı
13	Glass 1	9/17	85±13.2	5.16	49	Glass
14	Crocid 5	14/29	78±10.8	3.29	50	Glass

Diameter (μm) × Length (μm)

(1) Titanate 1 95%

Diameter	>.01-1	>1-4	>4-8	>8-64	>64
>8.0					
>4.0-8.0					
>2.5-4.0					
>1.5-2.5					
>.50-1.5			3.75	4.11	
>.25-.50	3.57	4.41	4.79	4.87	
>.10-.25	3.87	5.08	5.34	5.17	
>.05-.10	3.27	5.02	5.02	4.44	
>.01-.05					

(2) Titanate 2 100%

Diameter	>.01-1	>1-4	>4-8	>8-64	>64
>8.0					
>4.0-8.0					
>2.5-4.0					
>1.5-2.5					
>.50-1.5			3.70	3.40	
>.25-.50	3.70	4.18	4.52	4.18	
>.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	>.01-1	>1-4	>4-8	>8-64	>64
>8.0					
>4.0-8.0			1.82	1.35	
>2.5-4.0			1.82	1.65	1.35
>1.5-2.5		2.25	2.04	1.95	
>.50-1.5	2.92	3.08	3.03	3.24	1.35
>.25-.50	3.29	3.89	4.20	4.40	
>.10-.25	0.81	4.01	4.19	4.56	
>.05-.10		4.21	4.41	4.74	
>.01-.05	3.76	4.48	4.54	4.70	

(4) Dawson 5 100%

Diameter	>.01-1	>1-4	>4-8	>8-64	>64
>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	>.01-1	>1-4	>4-8	>8-64	>64
>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	>.01-1	>1-4	>4-8	>8-64	>64
>8.0					
>4.0-8.0					
>2.5-4.0			2.54	3.01	
>1.5-2.5		3.14	2.84	2.54	
>.50-1.5		4.05	3.68	3.77	
>.25-.50	3.44	3.86	3.38	3.31	
>.10-.25	4.09	4.04	3.38	2.84	
>.05-.10	3.14	2.84			
>.01-.05					

(7) Dawson 1 95%

Diameter	>.01-1	>1-4	>4-8	>8-64	>64
>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	>.01-1	>1-4	>4-8	>8-64	>64
>8.0					
>4.0-8.0					
>2.5-4.0					
>1.5-2.5					
>.50-1.5			4.07		
>.25-.50		4.07		4.56	
>.10-.25	5.75	5.69	4.67	5.15	
>.05-.10	6.52	5.62	4.67	4.37	
>.01-.05	5.87	4.67			

(9) Crocid. 2 93%

Diameter	>.01-1	>1-4	>4-8	>8-64	>64
>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	>.01-1	>1-4	>4-8	>8-64	>64
>8.0					
>4.0-8.0					
>2.5-4.0					
>1.5-2.5					
>.50-1.5			4.10	4.10	
>.25-.50			4.10	4.40	
>.10-.25	6.12	5.71	4.95	5.01	
>.05-.10	6.52	5.84	4.10		
>.10-.05	5.62	4.58	4.10		

(11) Amosite 93%

Diameter	>.01-1	>1-4	>4-8	>8-64	>64
>8.0					
>4.0-8.0					
>2.5-4.0				2.13	
>1.5-2.5				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	>.01-1	>1-4	>4-8	>8-64	>64
>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	>.01-1	>1-4	>4-8	>8-64	>64
>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	>.01-1	>1-4	>4-8	>8-64	>64
>8.0					
>4.0-8.0			2.81		
>2.5-4.0			2.81		
>1.5-2.5		2.81	3.29	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	>.01-1	>1-4	>4-8	>8-64	>64
>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	>.01-1	>1-4	>4-8	>8-64	>64
>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	2.56	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	

(17) Glass 4 (M6L) 71%

Diameter	>.01-1	>1-4	>4-8	>8-64	>64
>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	

(18) Alumin. 1 70%

Diameter	>.01-1	>1-4	>4-8	>8-64	>64
>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	

Length

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

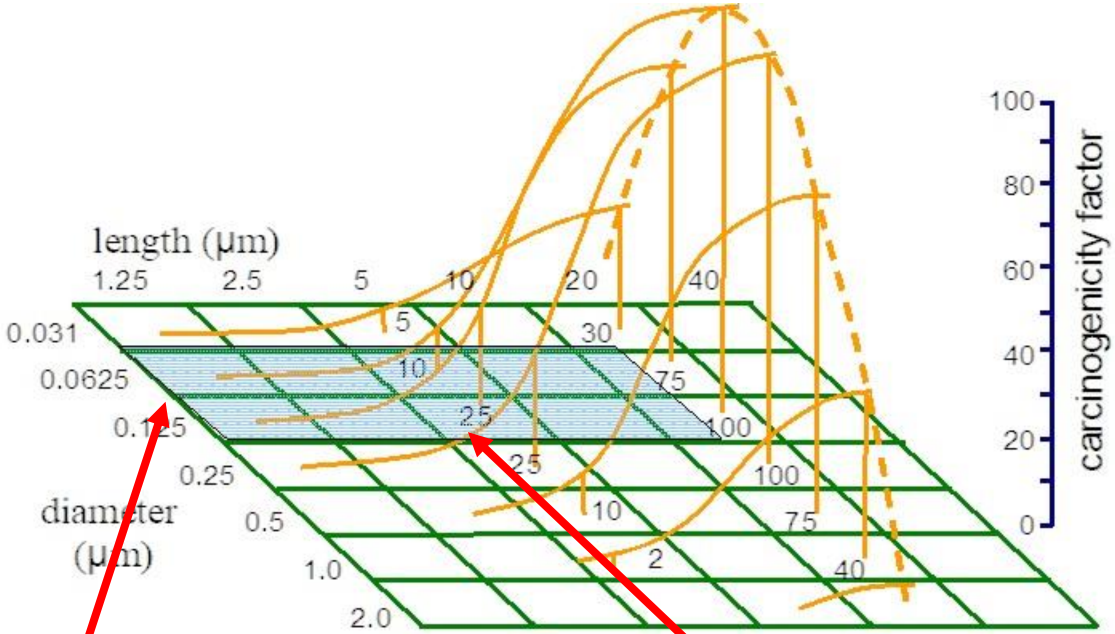
Diameter

(10) Crocid. 3 93%

(13) Glass 1 (M0L) 85%

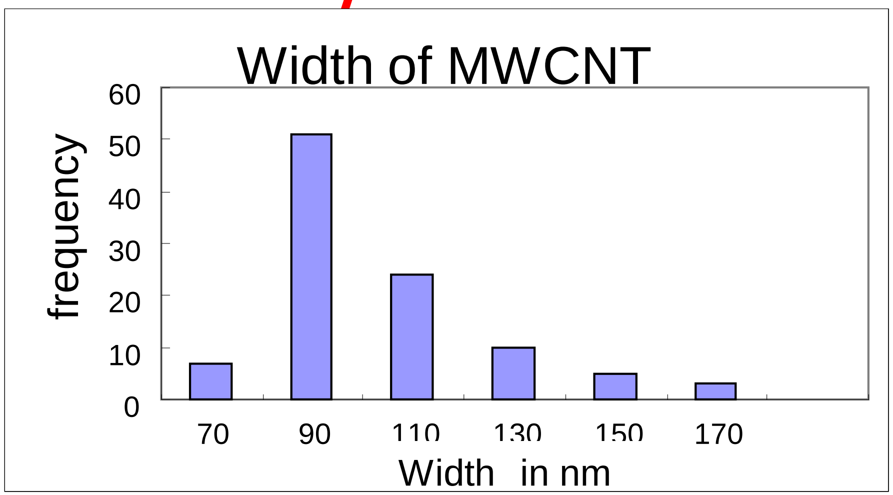
(16) Glass 3 (KL) 74%

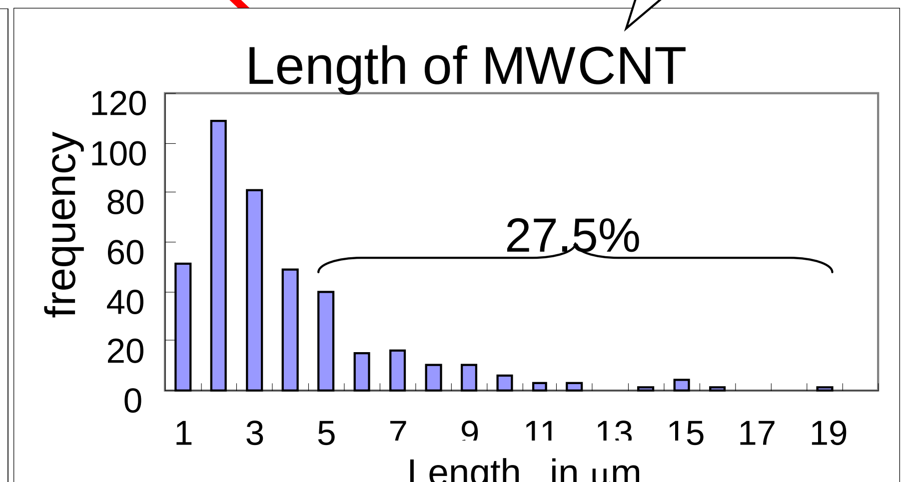
TEXT-FIGURE 1.—Fiber distribution by common log of th



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)

ip p53 +/- mouse

The Journal of Toxicological Sciences (J. Toxicol. Sci.)
Vol.33, No.1, 105-116, 2008

Original Article

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

Atsuya Takagi[1], Akihiko Hirose[2], Tetsuji Nishimura[3], Nobutaka Fukumori[4], Akio Ogata[4], Norio Ohashi[4], Satoshi Kitajima[1] and Jun Kanno[1]

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(Received November 20, 2007; Accepted December 9, 2007)

ip p53 +/- mouse

Cancer Science
The official journal of the Japanese Cancer Association

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

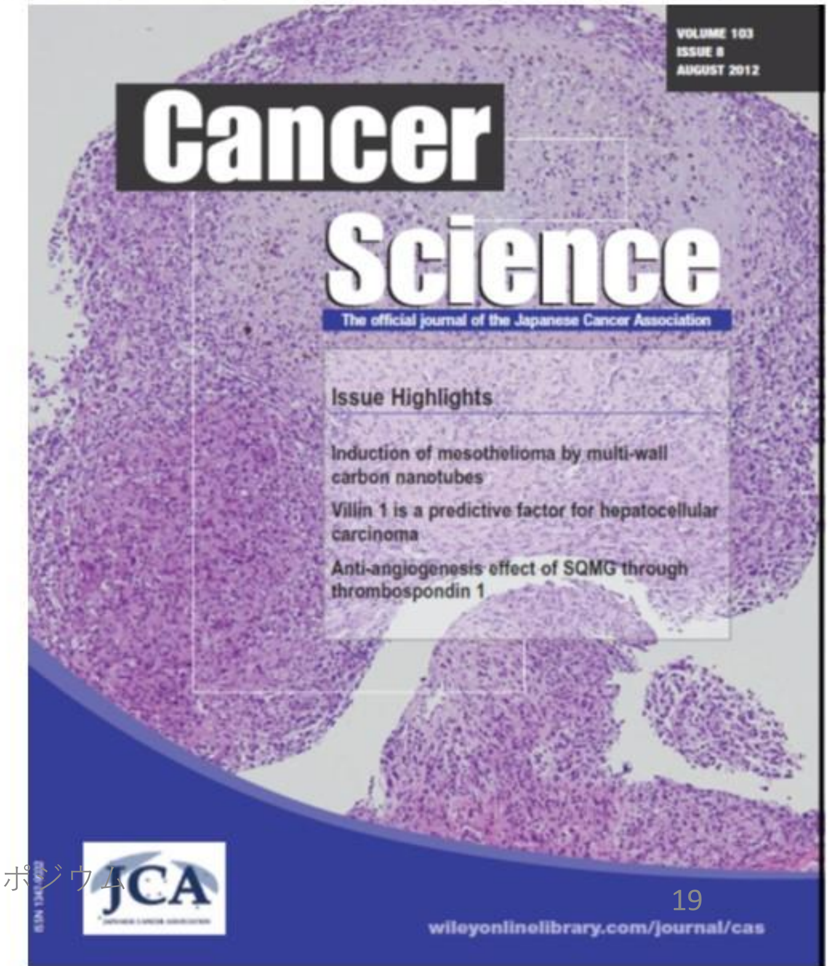
Atsuya Takagi,[1] Akihiko Hirose,[2] Mitsuru Futakuchi,[3] Hiroyuki Tsuda[4] and Jun Kanno[1,5]

[1]Division of Cellular and Molecular Toxicology, [2]Division of Risk Assessment, Biological Safety Research Center, National Institute of Health Sciences, Tokyo; [3]Department of Molecular Toxicology, Nagoya City University Graduate School of Medical Sciences; [4]Nanomaterial Toxicology Project Laboratory, Nagoya City University, Nagoya, Japan

(Received February 21, 2012/Revised March 26, 2012/Accepted April 22, 2012/Accepted manuscript online April 27, 2012/Article first published online June 21, 2012)

Three doses

300 μg/animal = 1×10^8 fiber /animal
30 μg/animal = 1×10^7 fiber /animal
3 μg/animal = 1×10^6 fiber /animal



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?

Agnes B. Kane and Robert H. Hurt

are at Brown University, Providence, Rhode Island 02912, USA.

e-mail: Agnes_Kane@brown.edu; Robert_Hurt@brown.edu

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.

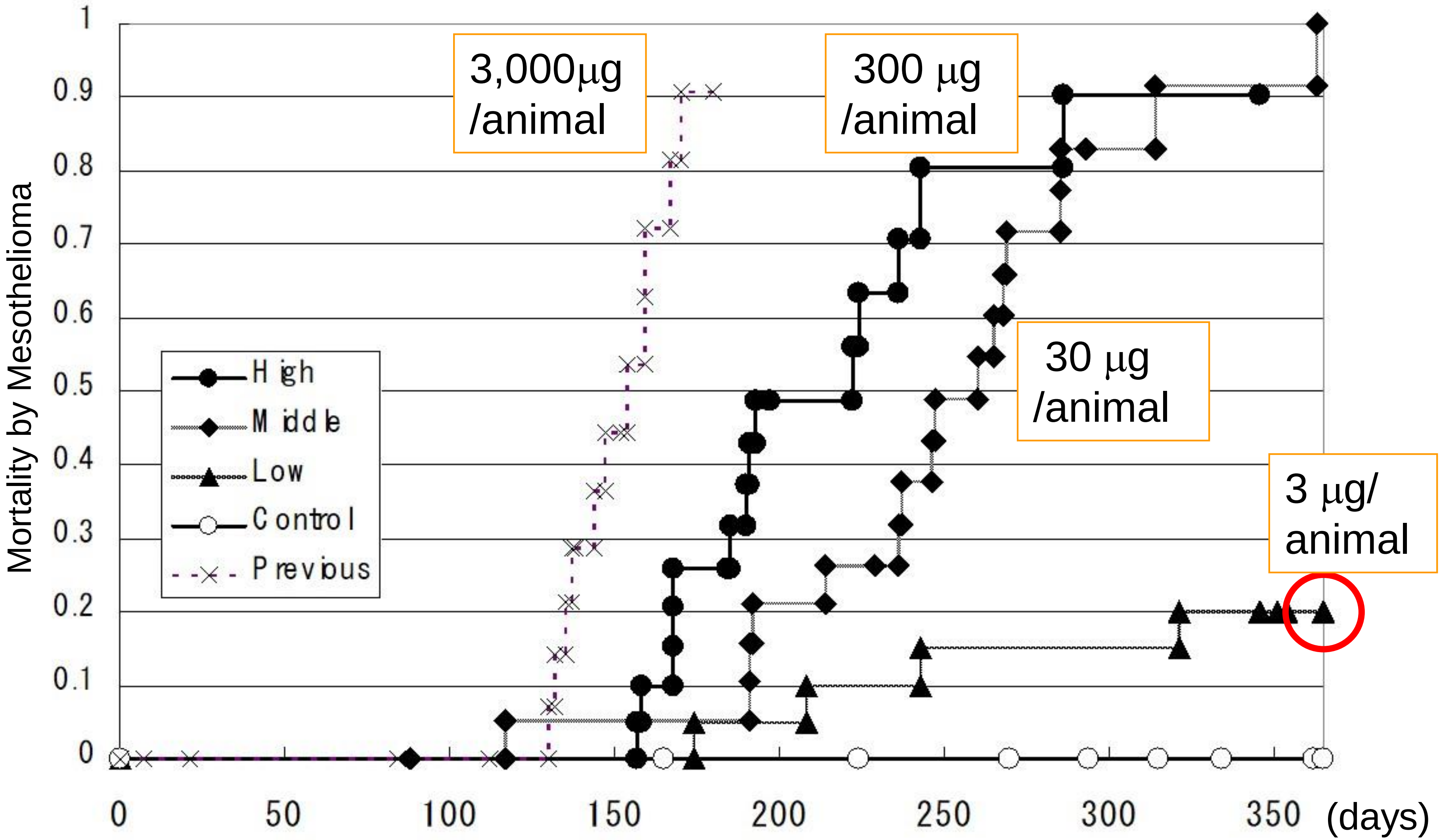
On page 423 of this issue[2], Ken Donaldson of the MRC/University of Edinburgh and co-workers in the UK and US report that long multiwalled carbon nanotubes (MWNTs) injected directly into the abdominal cavity of mice induce inflammation, formation of nodular lesions called granulomas and early fibrosis 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.

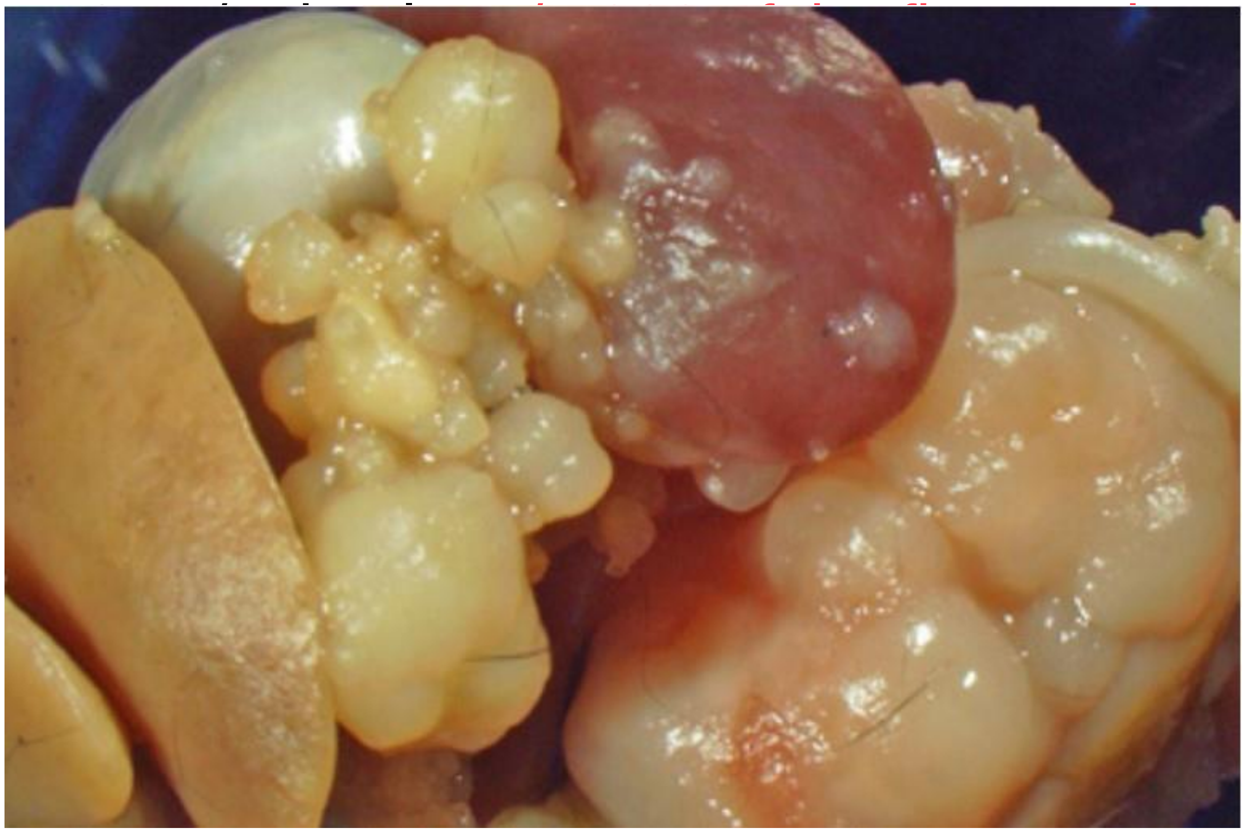
Both of these reports identify key physical properties of carbon nanotubes that may be relevant for potential toxicity

ip p53 +/- mouse



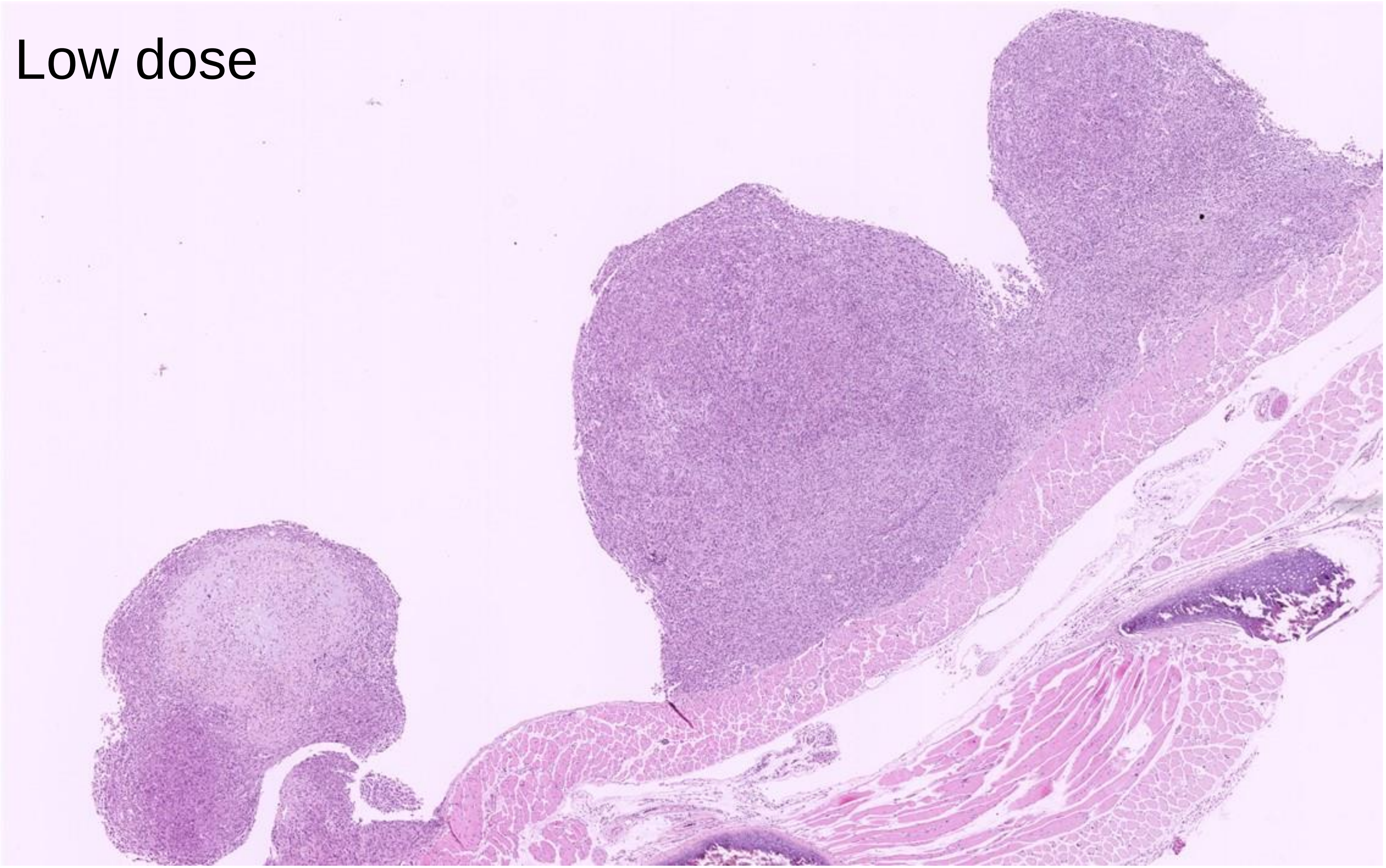
Takagi et al. Cancer Science, 2012

Low dose group #19



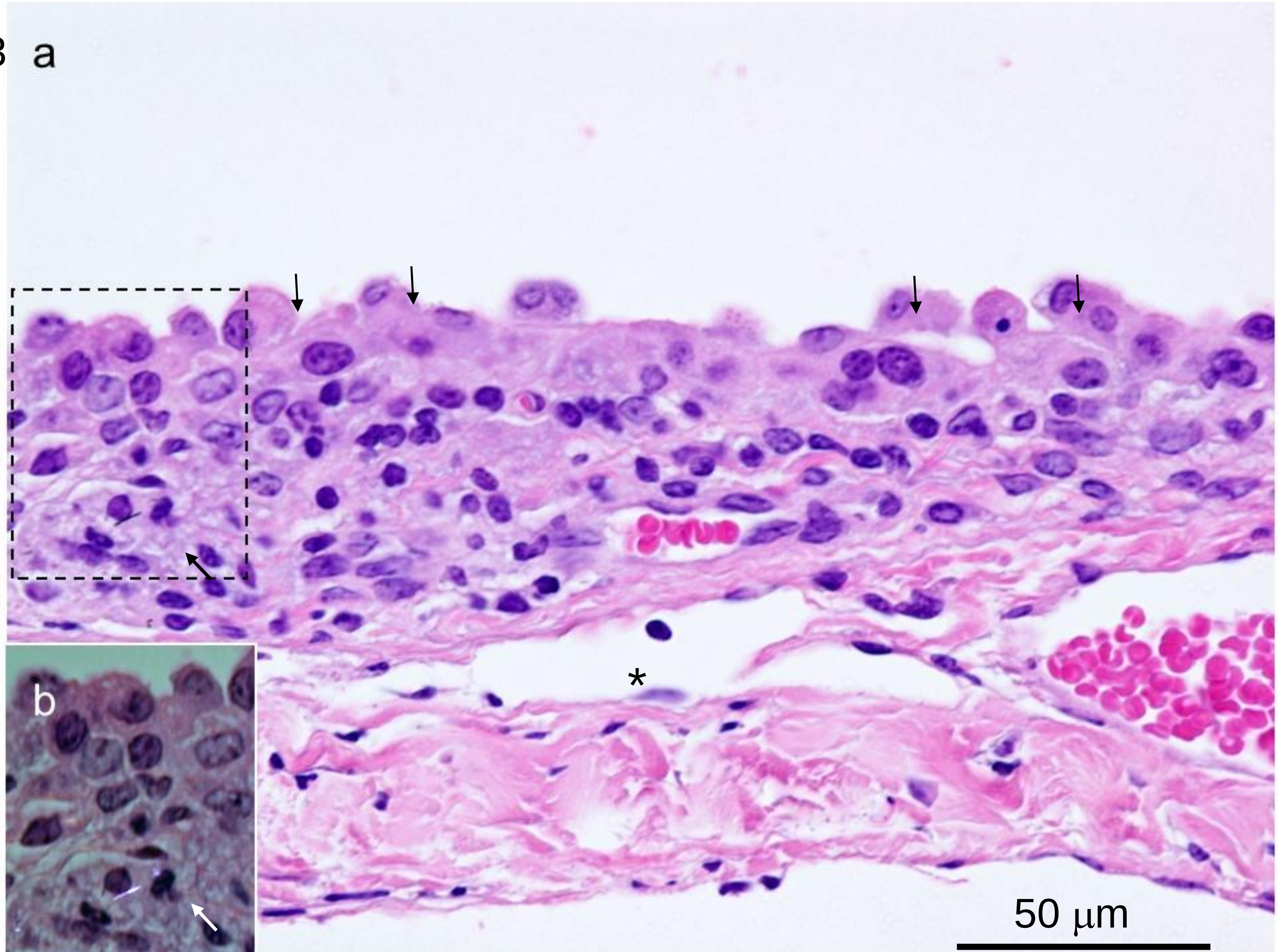
Takagi et al. Cancer Science, 2012

ip p53 +/- mouse

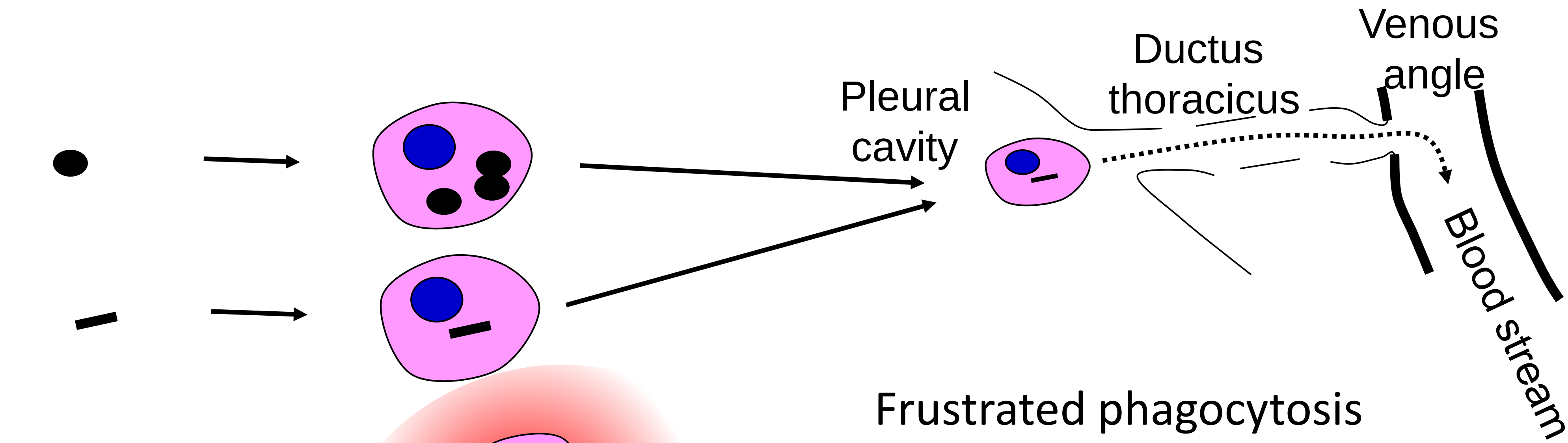


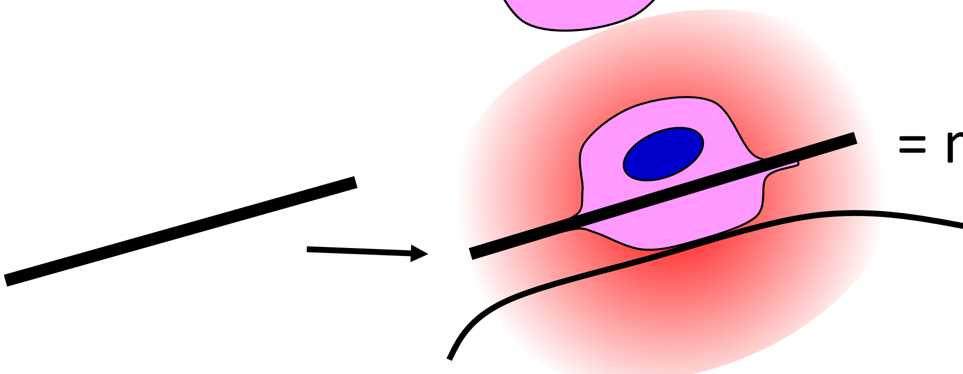
ip p53 +/- mouse

Figure 3

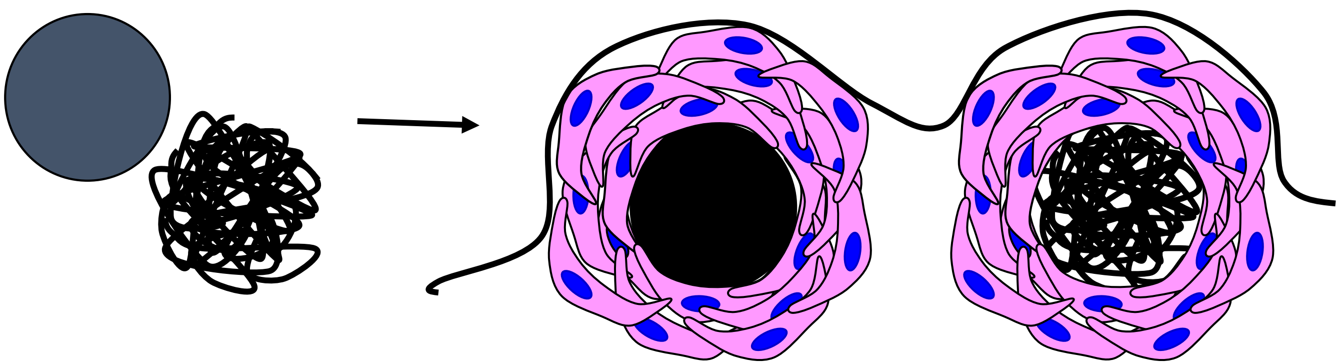


Cancer Science



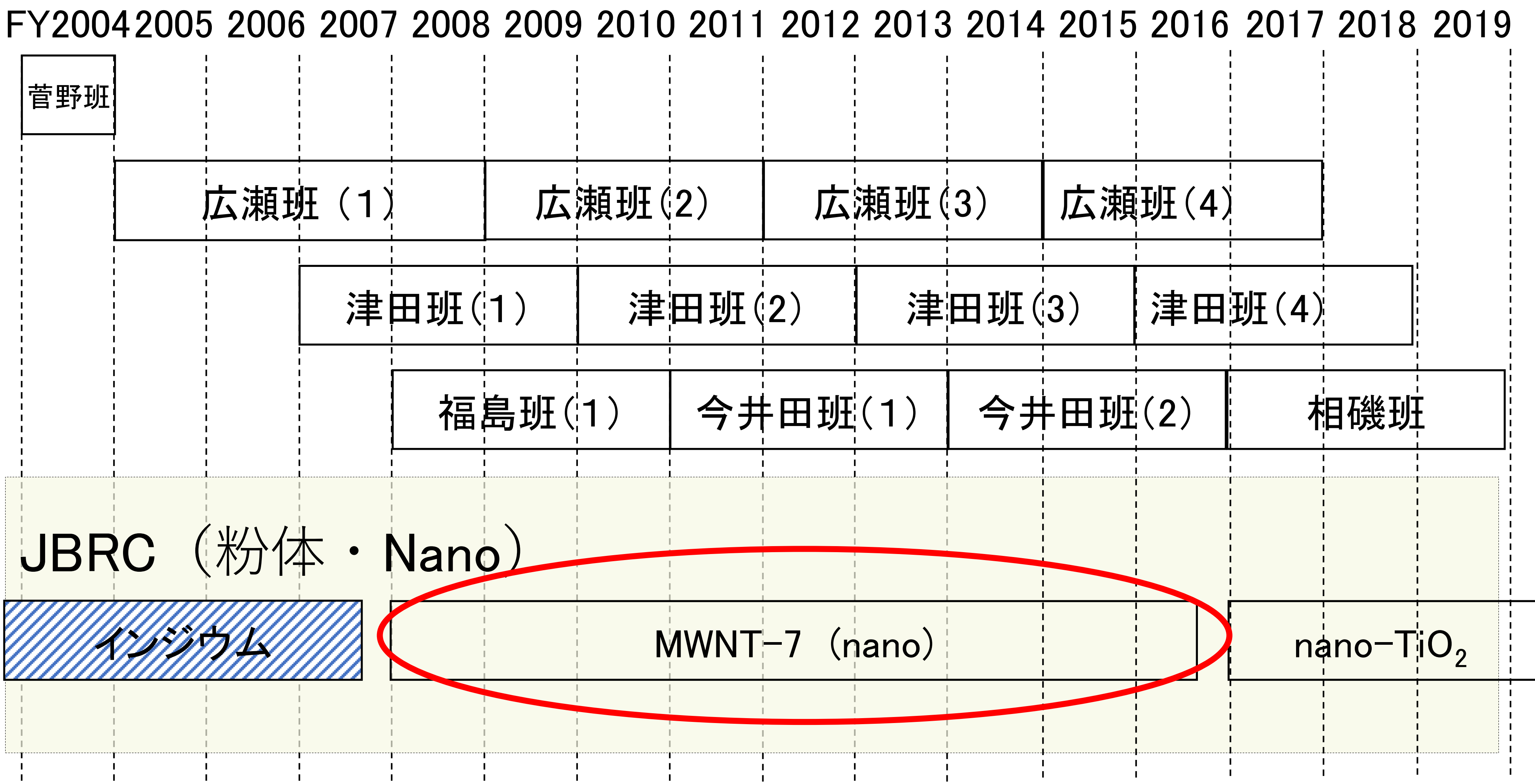


Frustrated phagocytosis
= macrophages eject lysosomal contents
outside the cell.
→ Mesothelioma



Segregation
(less tumor from this
lesion)

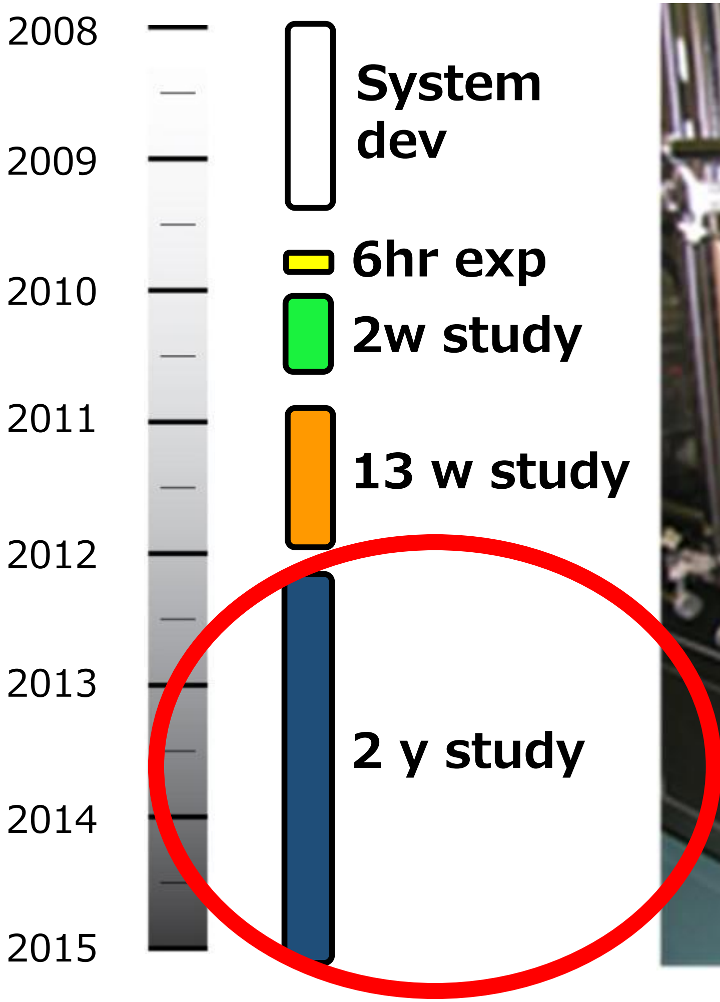
ナノ物質のヒト健康影響に関する研究
厚生労働科学研究費補助金【化学物質リスク研究事業】研究班

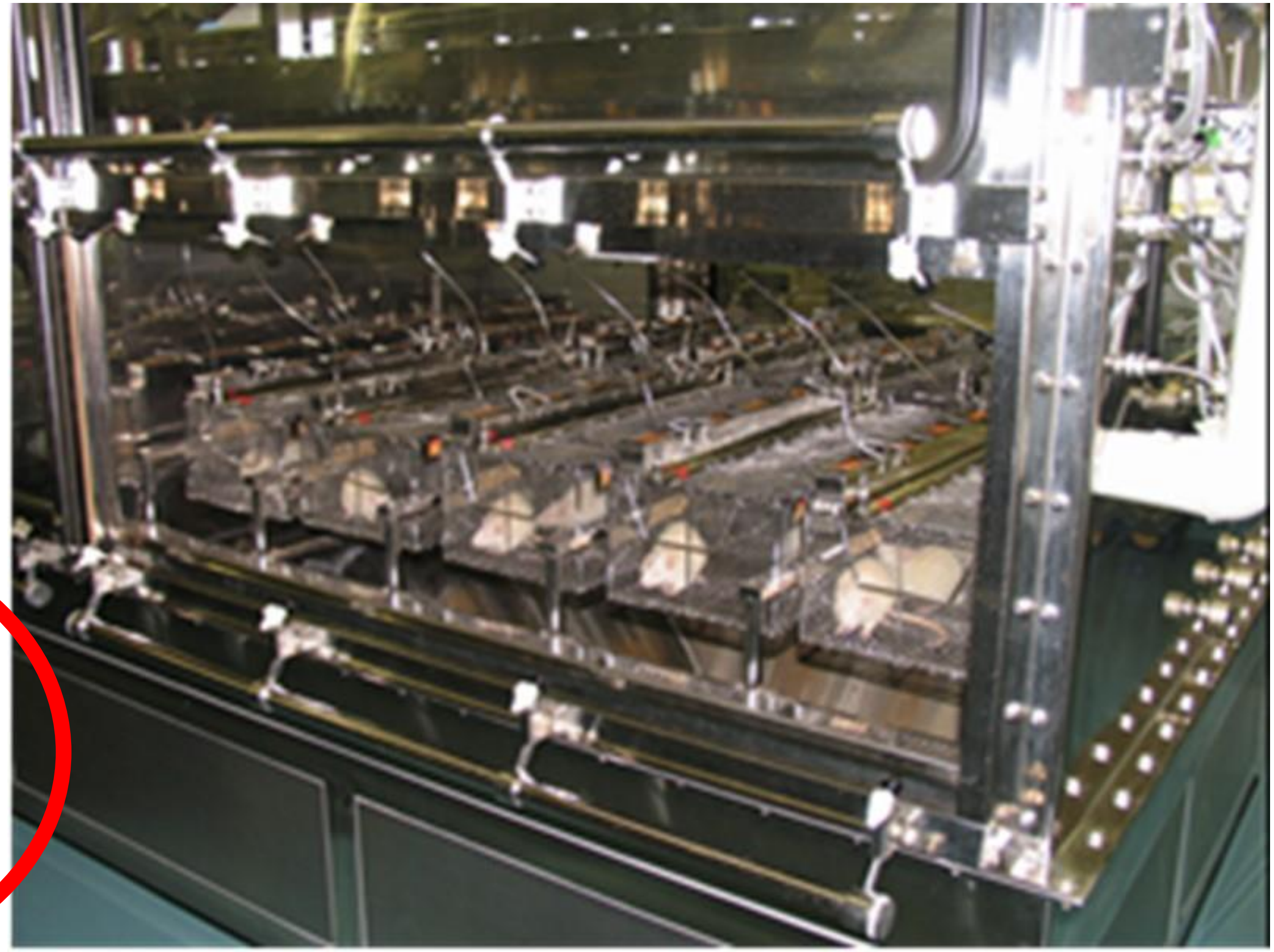


Japan Bioassay Research Center (JBRC)

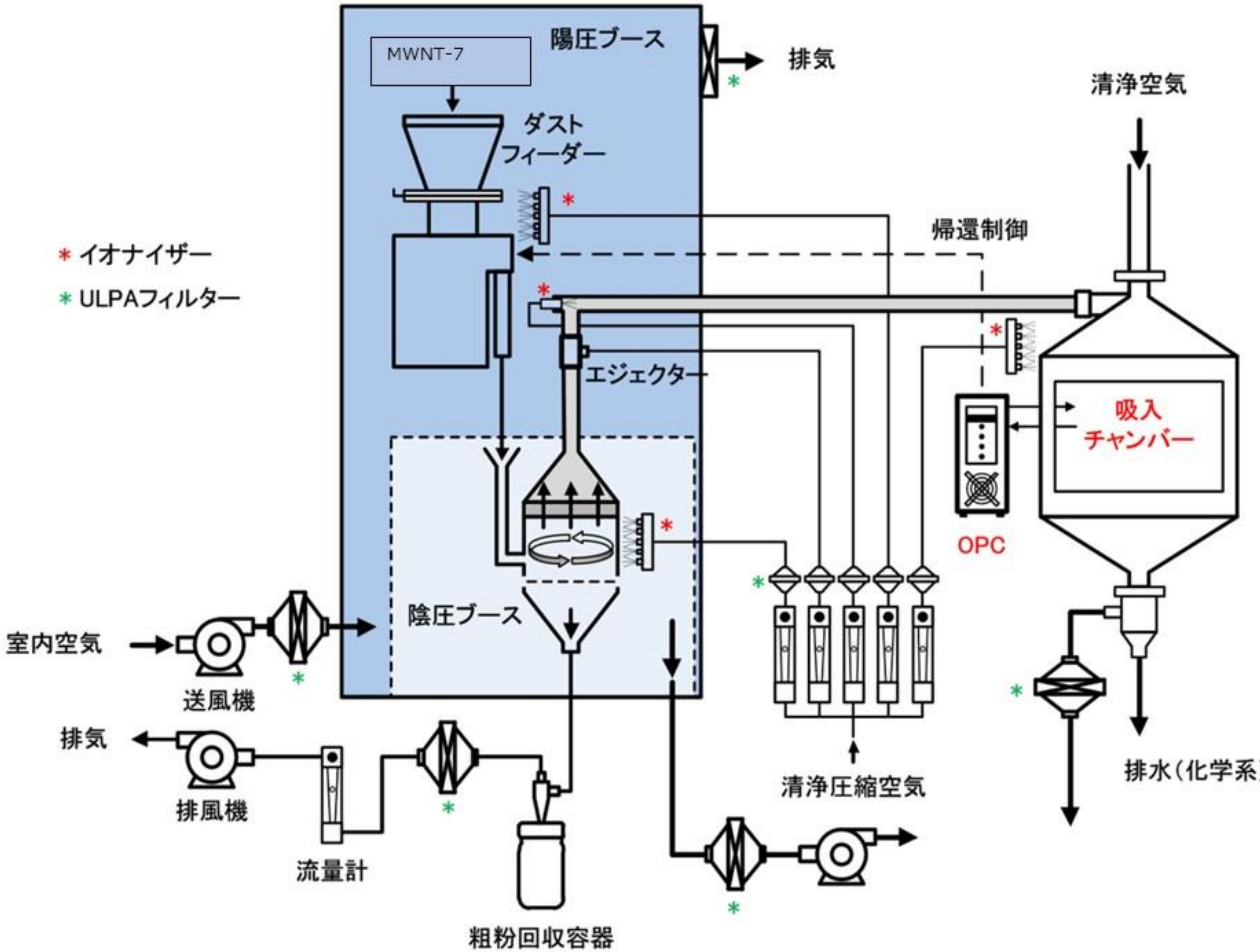
Japan Organization of Occupational Health and Safety
2445, Hirasawa, Hadano, kanagawa, Japan 257-0015

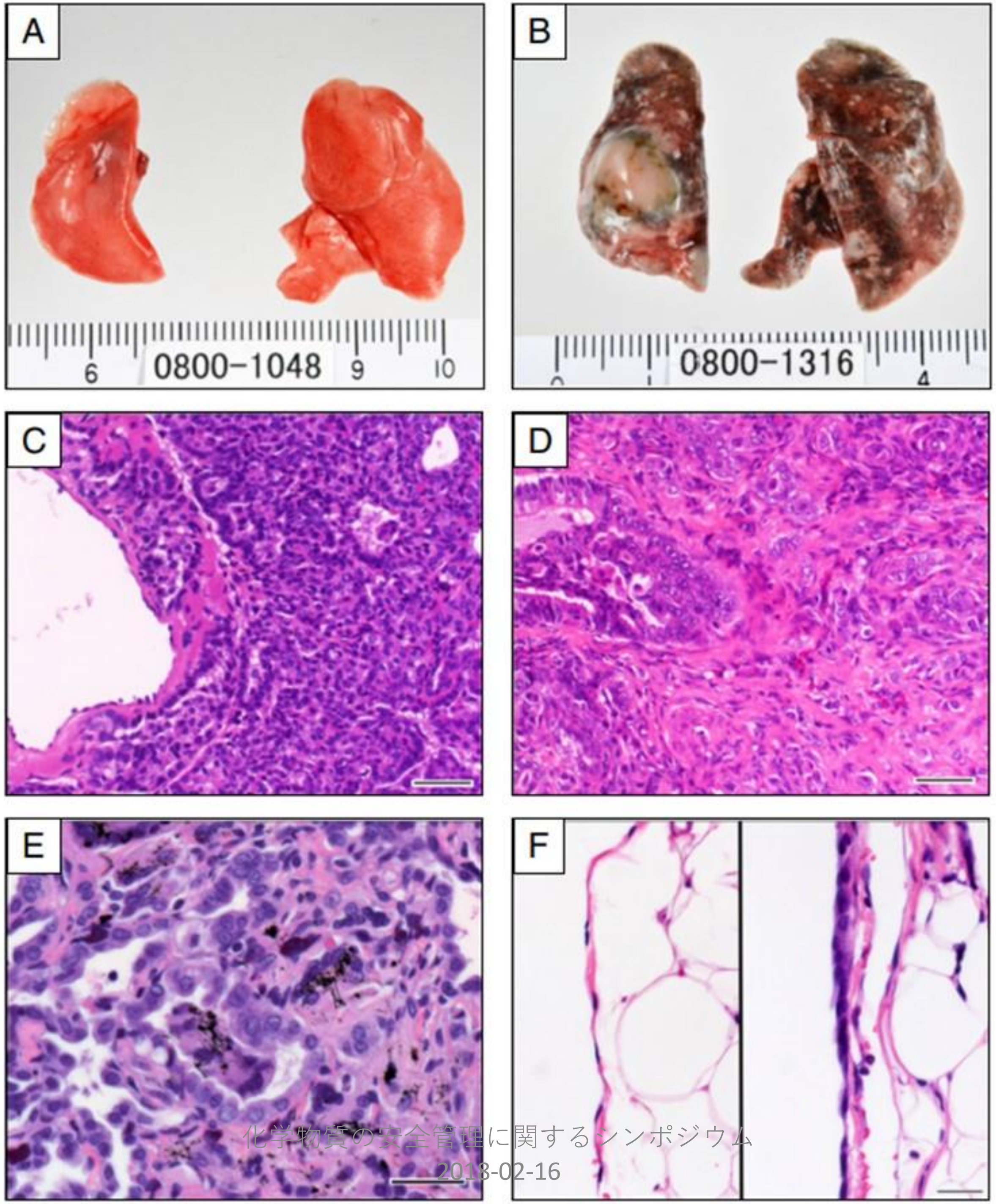
MWNT-7 rat 2 year whole body inhalation Carcinogenesis study (GLP)



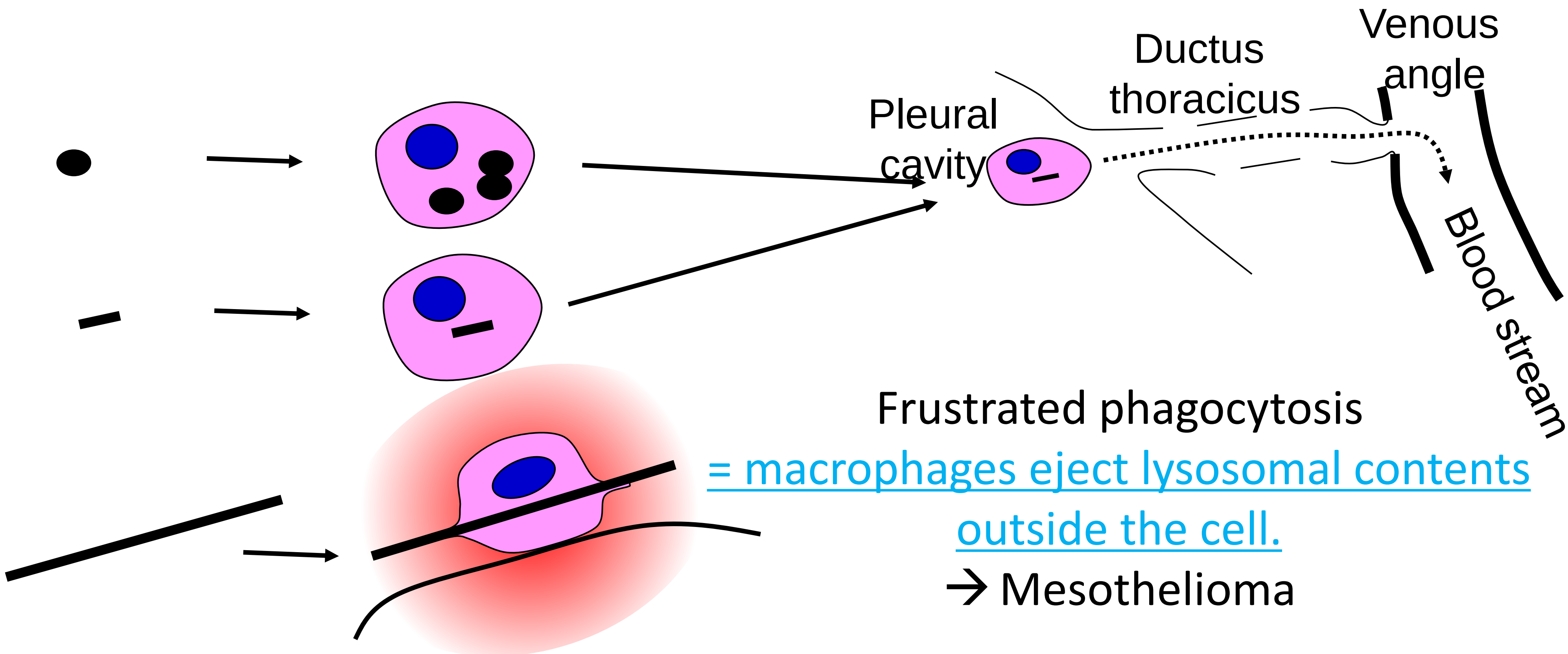


Aerosol generator





Kasai *et al. Particle and Fibre Toxicology* (2016) 13:53



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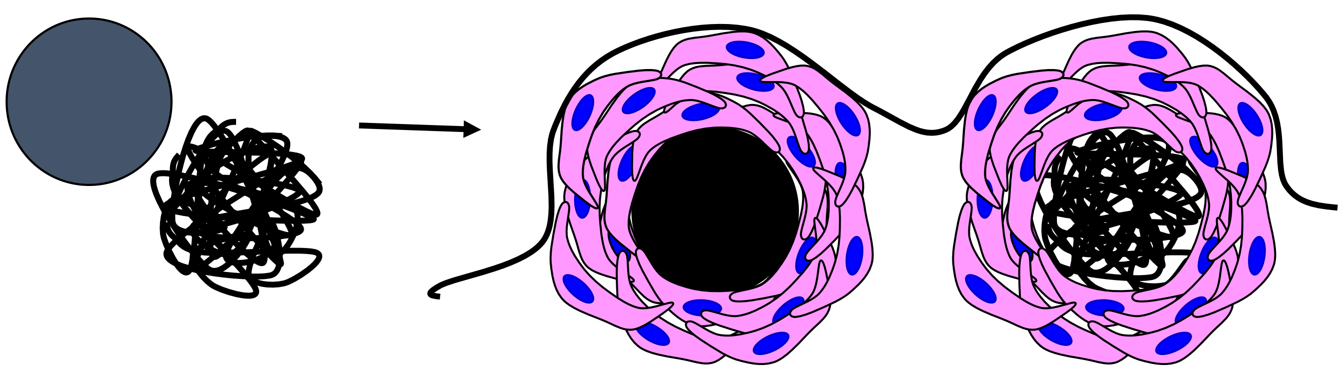
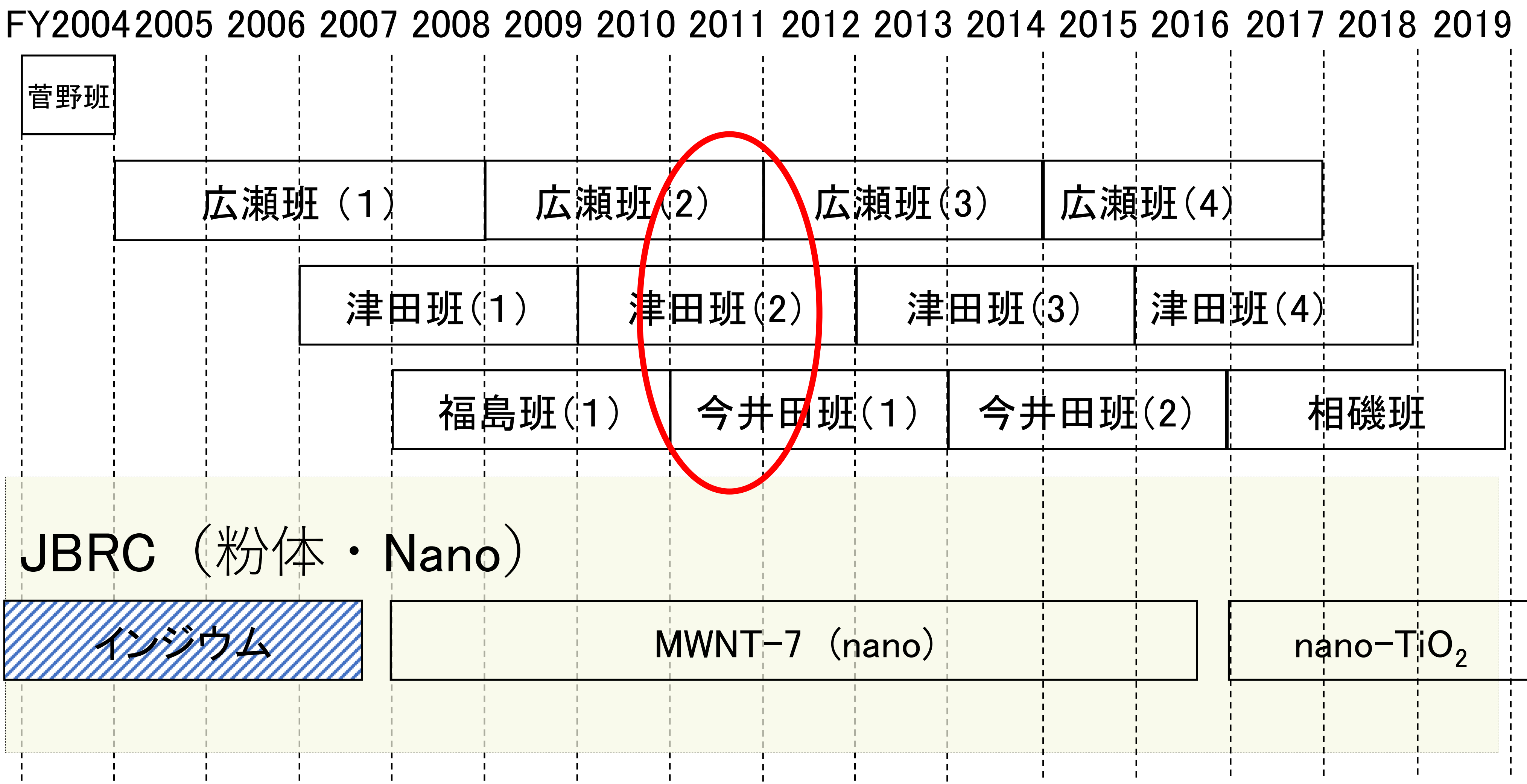


Segregation
(less tumor from this lesion)

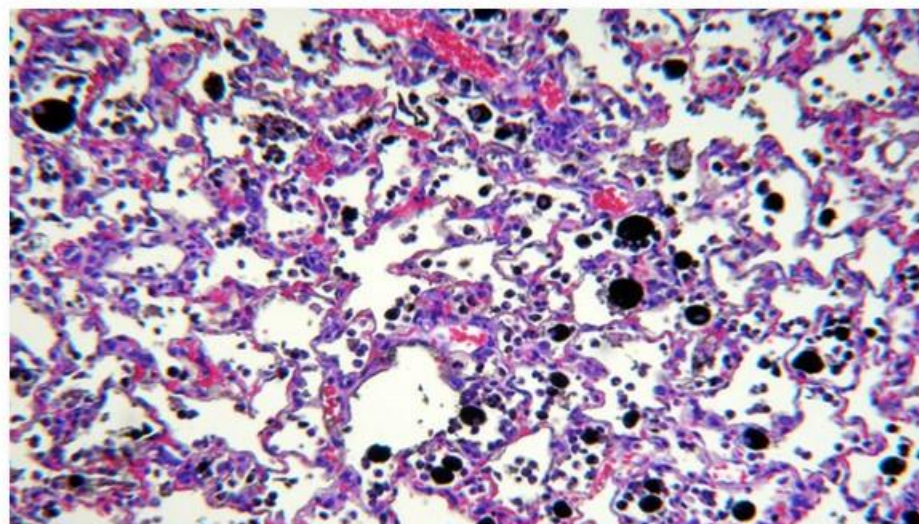
ナノ物質のヒト健康影響に関する研究
厚生労働科学研究費補助金【化学物質リスク研究事業】研究班



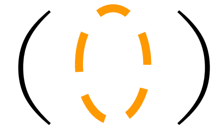
より簡便な方法の模索

- 気管内投与法
  - 気管内噴霧
  - 気管内投与
  - 自然吸引
- 全身曝露吸入法の改良
  - NOISH方式
  - Taquann分散法
  - Taquann直噴式

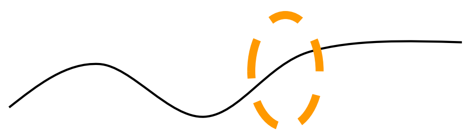
気管内投与法（気管内噴霧法）写真提供：名古屋市立大・津田洋幸先生

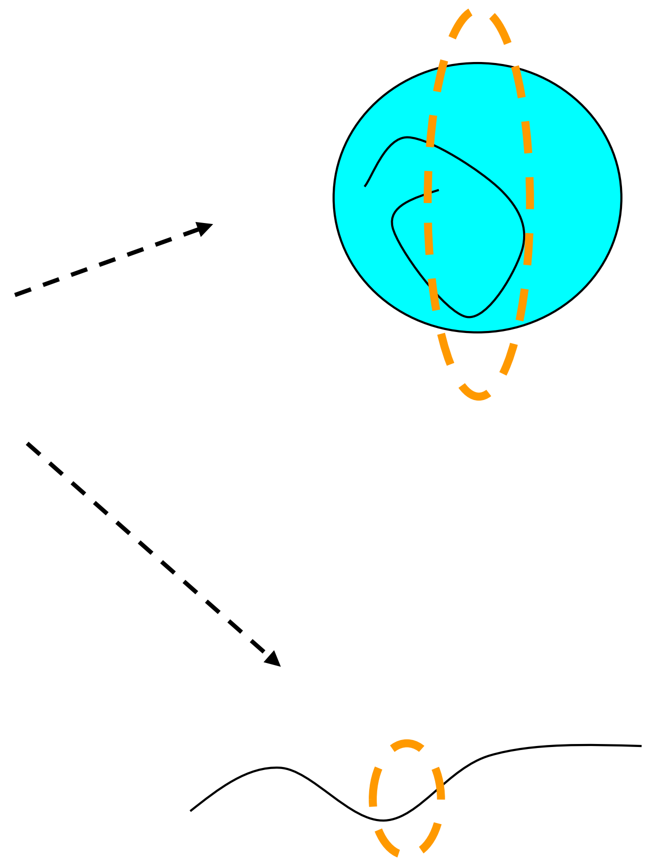


Indian ink

Aerodynamic diameter 

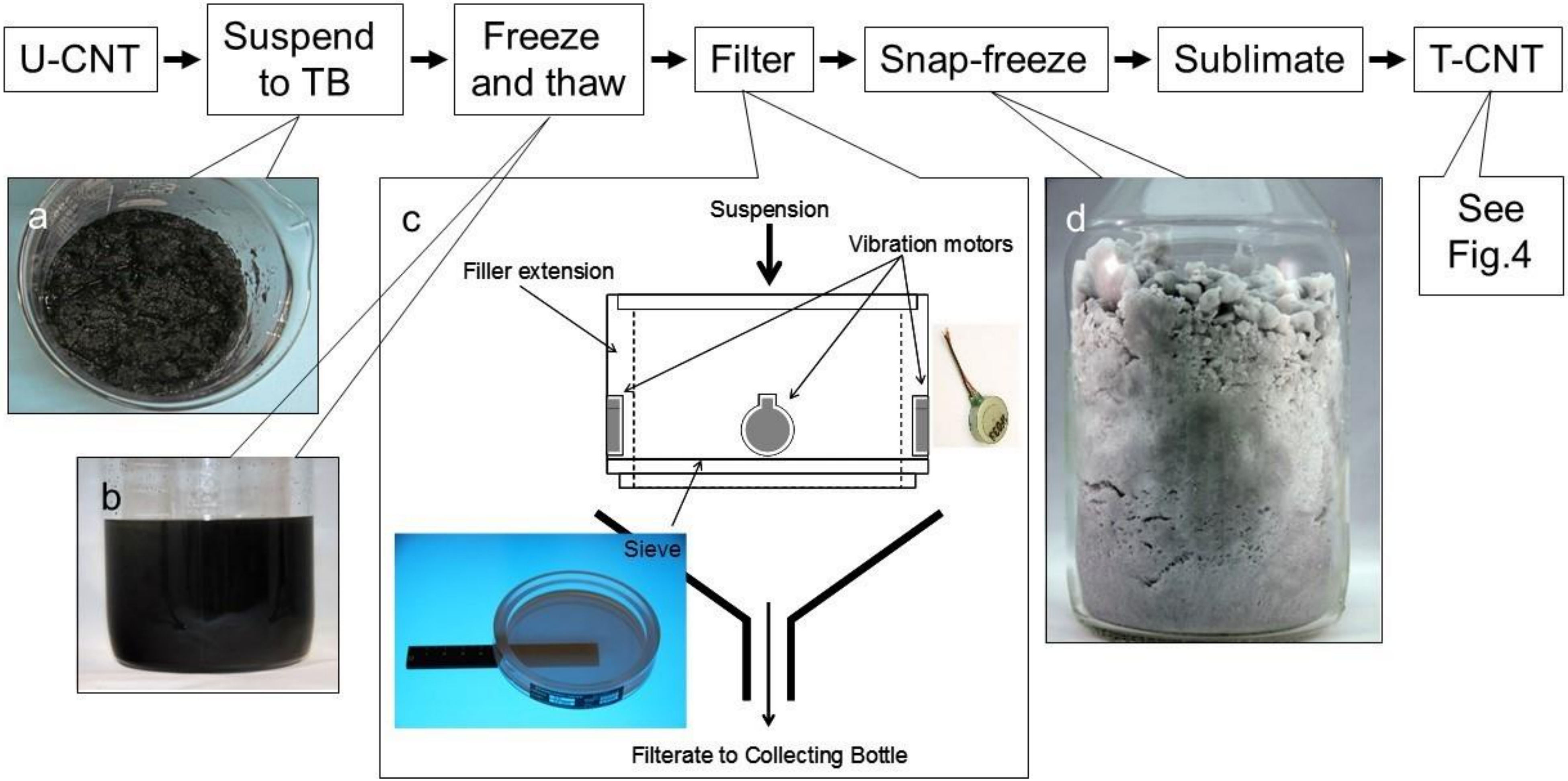
- やわらかい繊維状粒子
- エアロゾル：水滴中の状態
  - 表面張力による球体化





- 気相中：
  - 自然な繊維状を維持

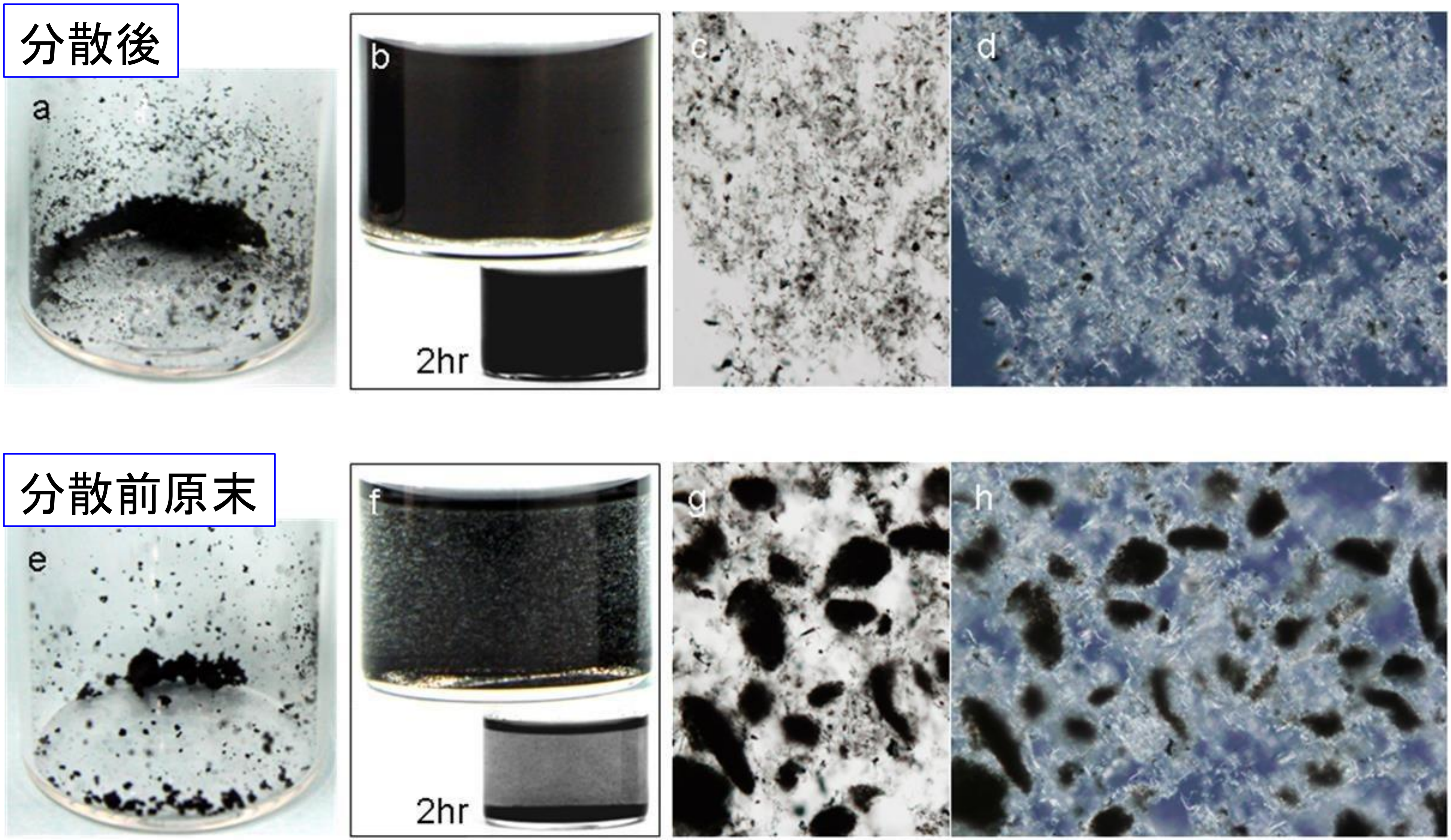
Taquann分散法 ＝ 液相分散ろ過 ＋ 臨界点乾燥



TB: Tertiary butyl alcohol (f.p. 25.69 ℃)

Taquahashi et al., J Tox Sci , 2013

MWNT-7 Taquann法による分散



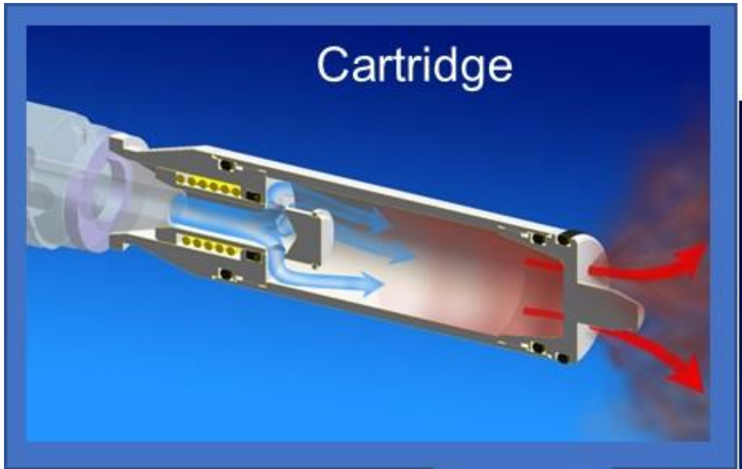
Taquahashi et al., JTS, 2013

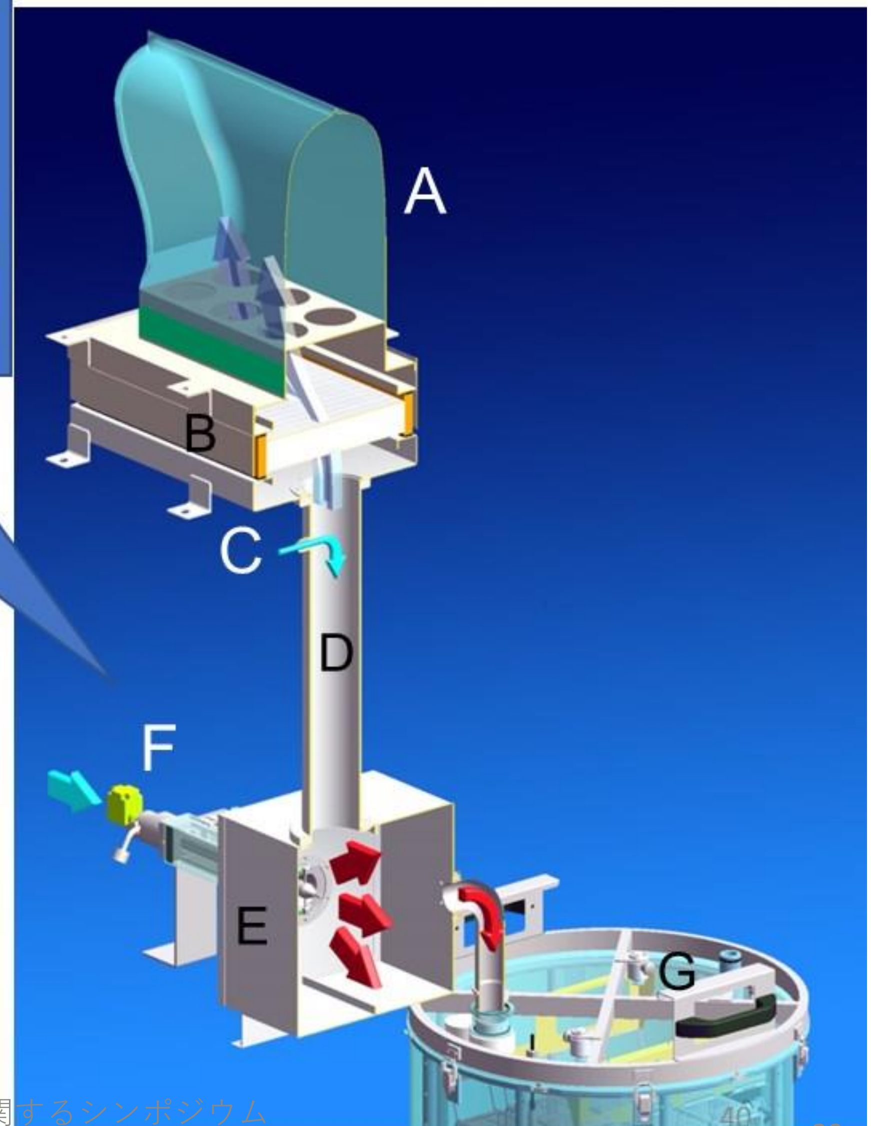
＠国立衛研･毒性部（NANO-AS）

Mitsui MWNT-7
野生型C57BL/6マウス
全身暴露吸入実験
2時間/日 × 5回
2mg/m^3

その後、無処置観察 13週、26週

Taquann Direct-Injection Whole Body Inhalation System　Version 2.0





A+B+D: Air Pressure Relief Dumper

A: Flexible Plastic Film for Insulation

B: ULPA Filter Unit

C: Main Flow Inlet (cut off during injection)

D: Air Pressure Dumper Duct

E: Subchamber

F: Cartridge Loader/Injector

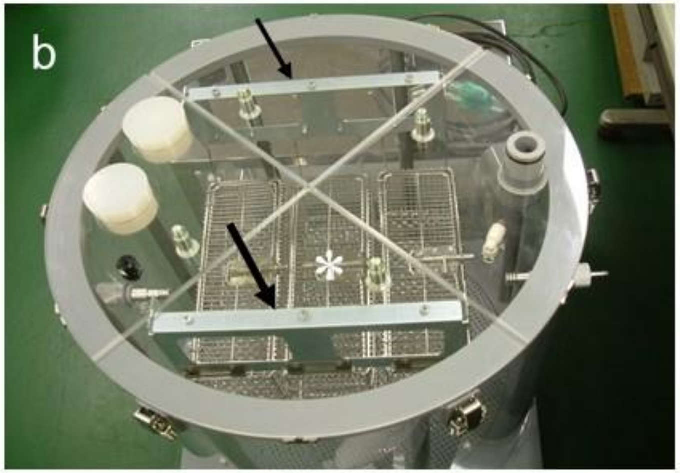
G: Inhalation Chamber (with animal cages)

特許出願:「吸入曝露試験装置」
特願2012-148848

Inhalation chamber

Disposable inner (capacity = 16 mice)

・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



・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

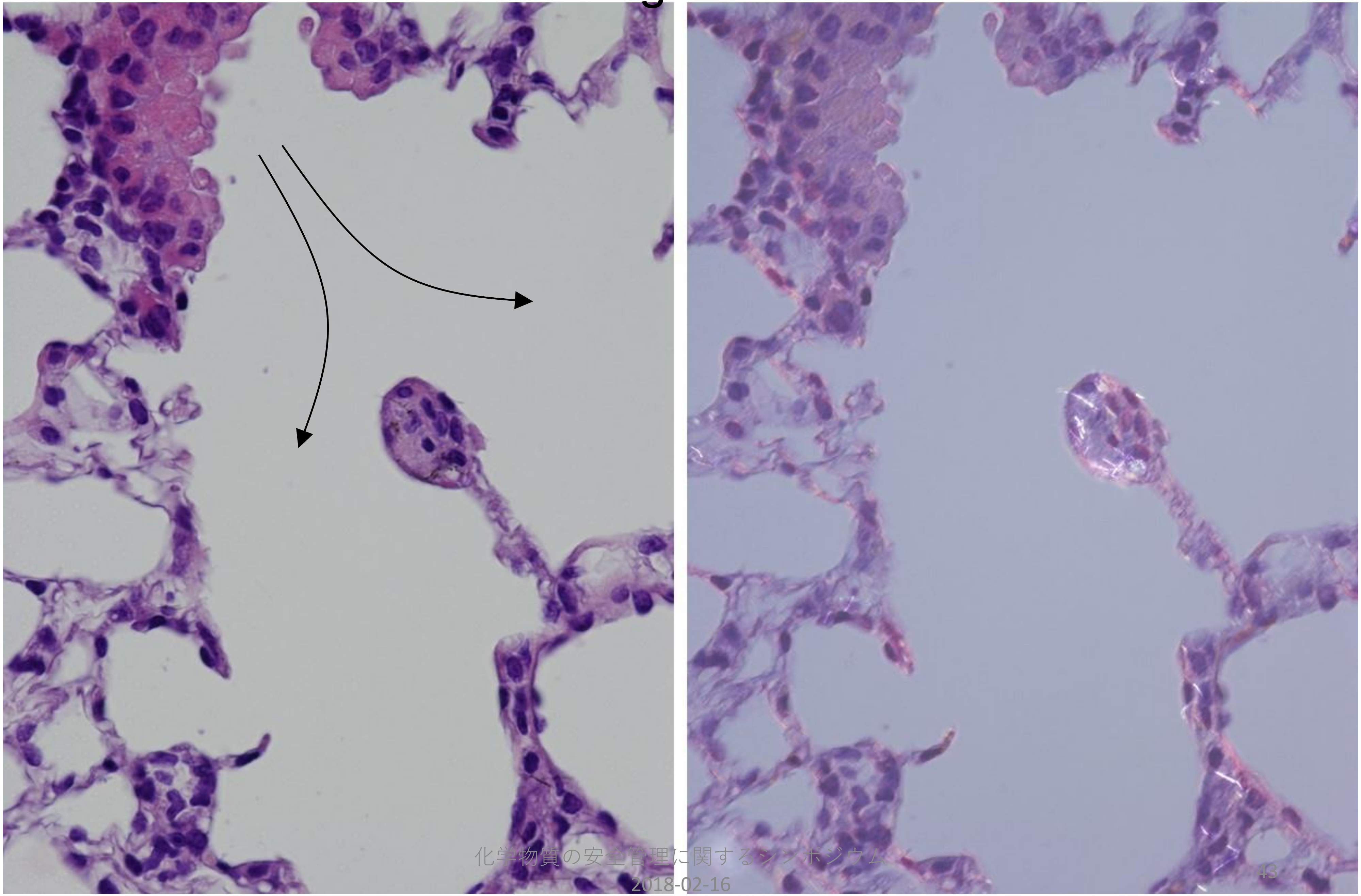
Version 2.5


Collaboration with
SIBATA SCIENTIFIC TECHNOLOGY LTD.
SIBATA

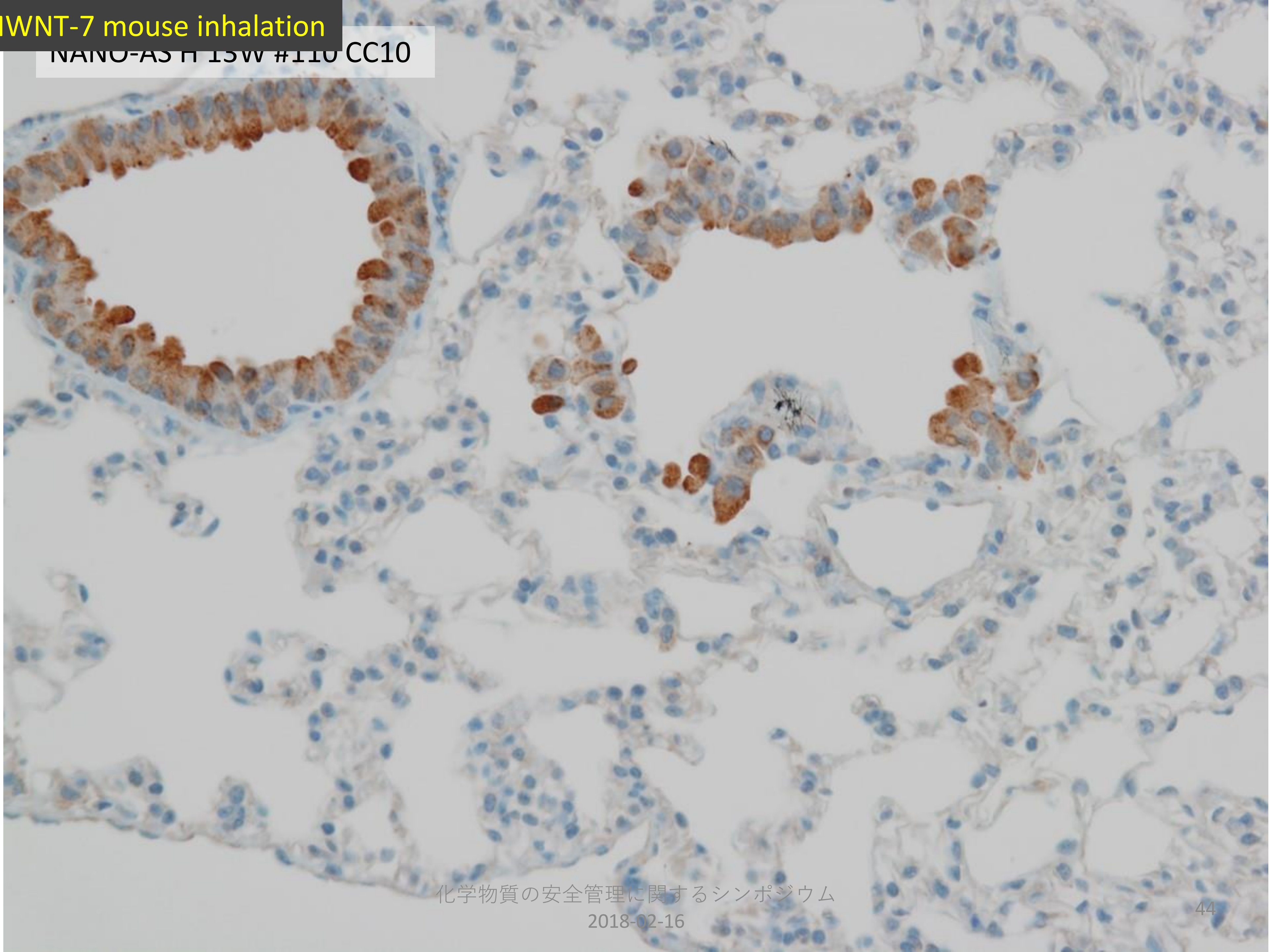
Taquann 直噴式全身曝露吸入装置 ver 3 (NIHS川崎納入例）

MWNT-7 mouse inhalation _513

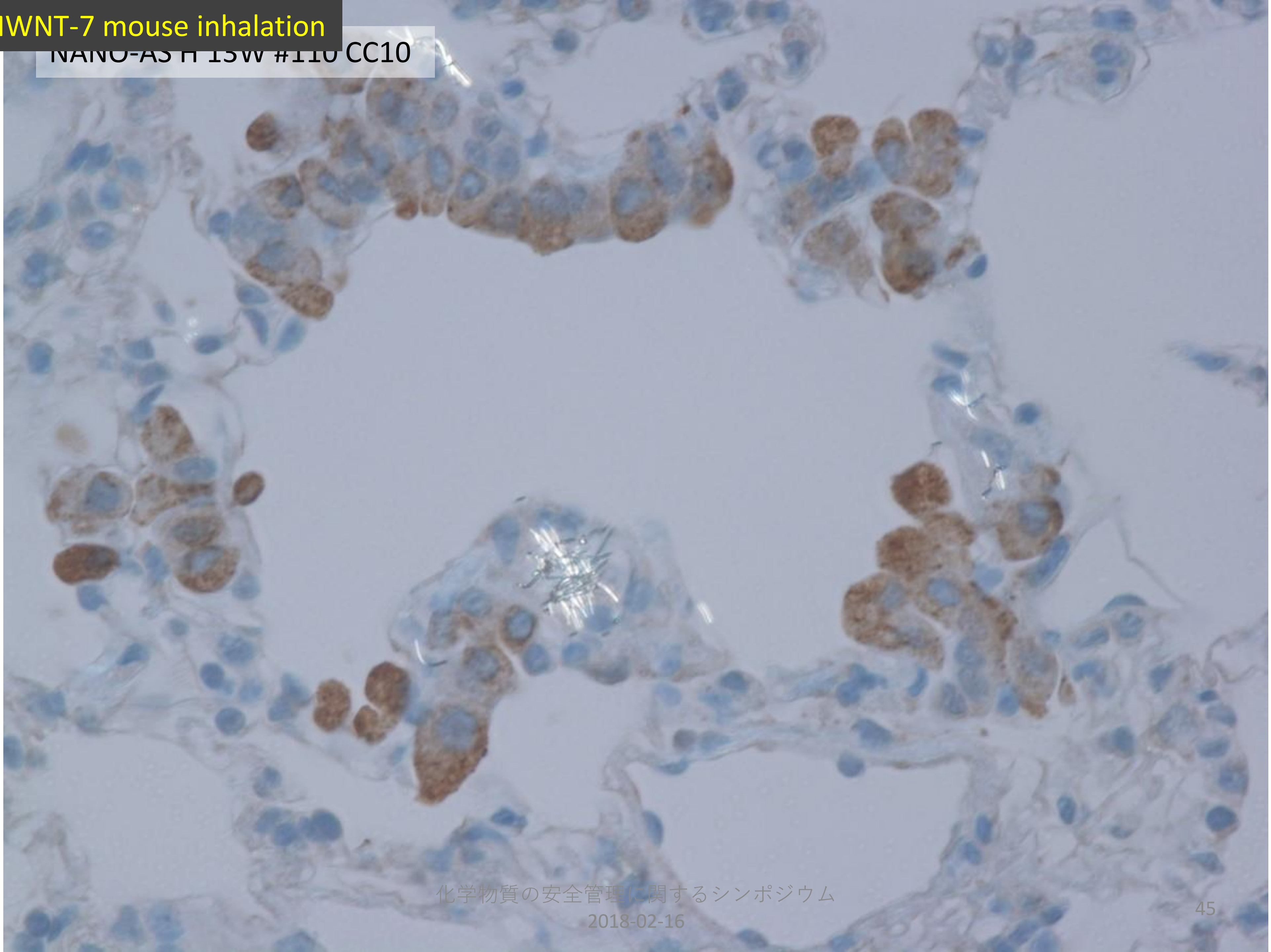
High 13W



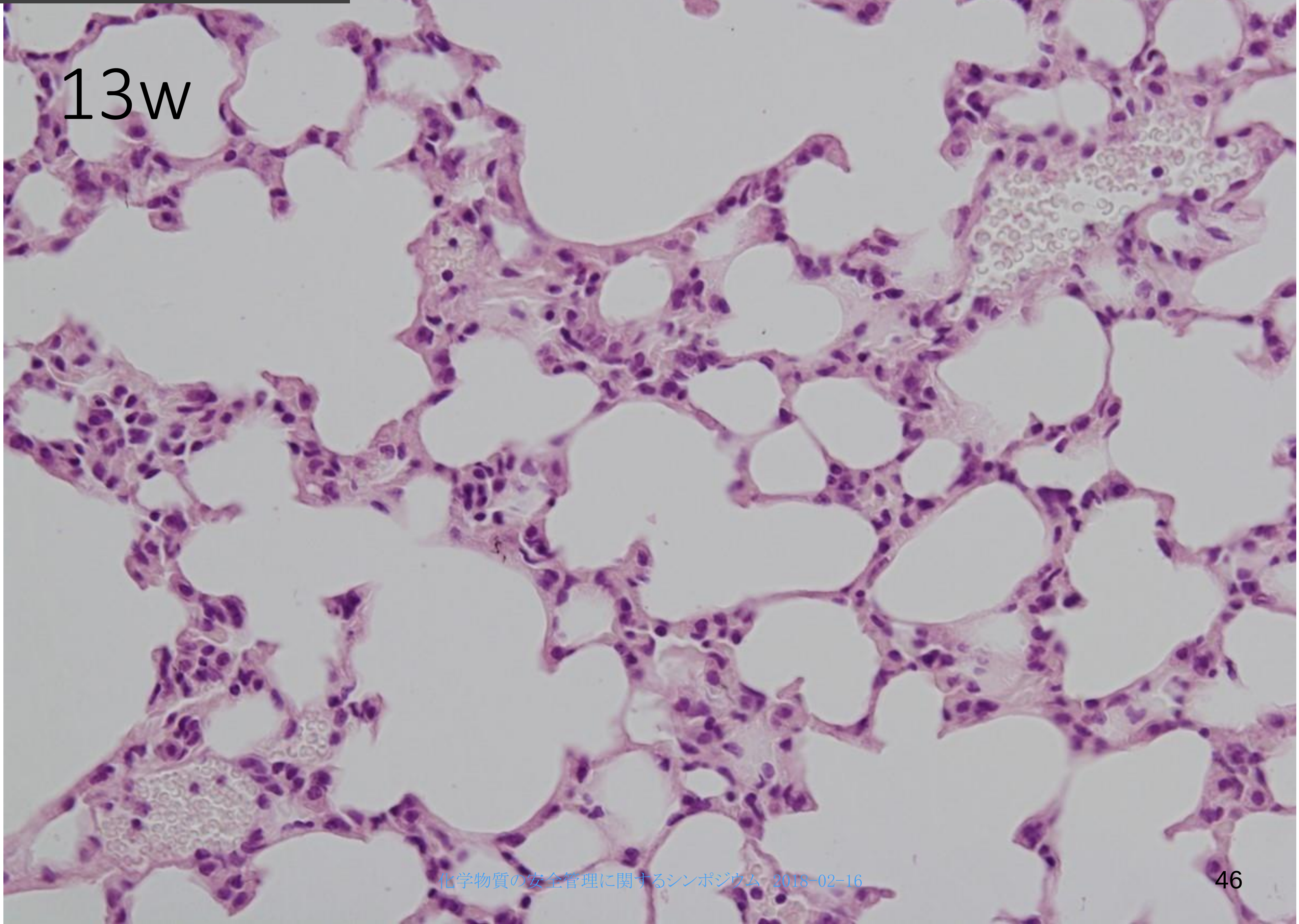
MWNT-7 mouse inhalation



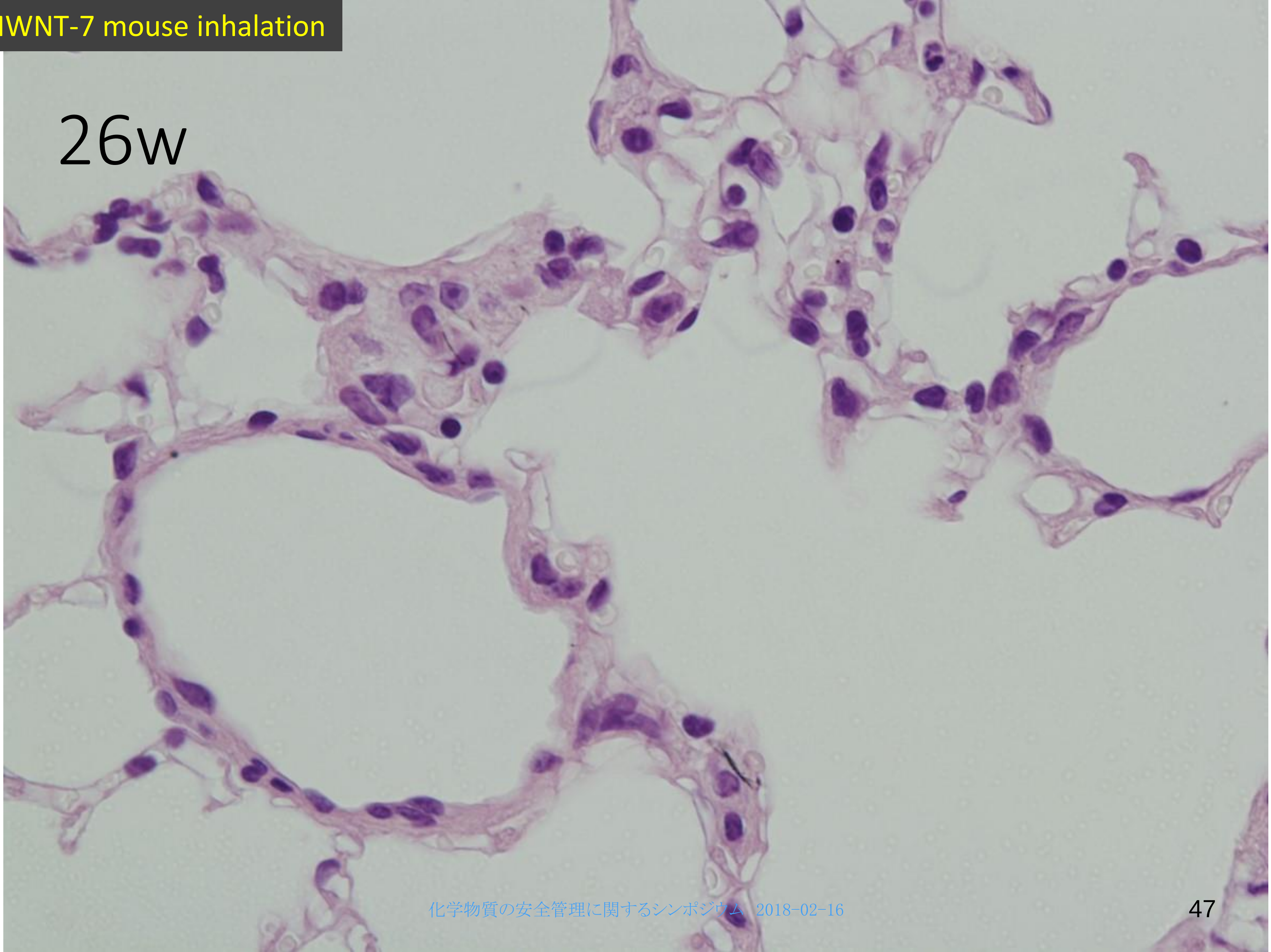
MWNT-7 mouse inhalation



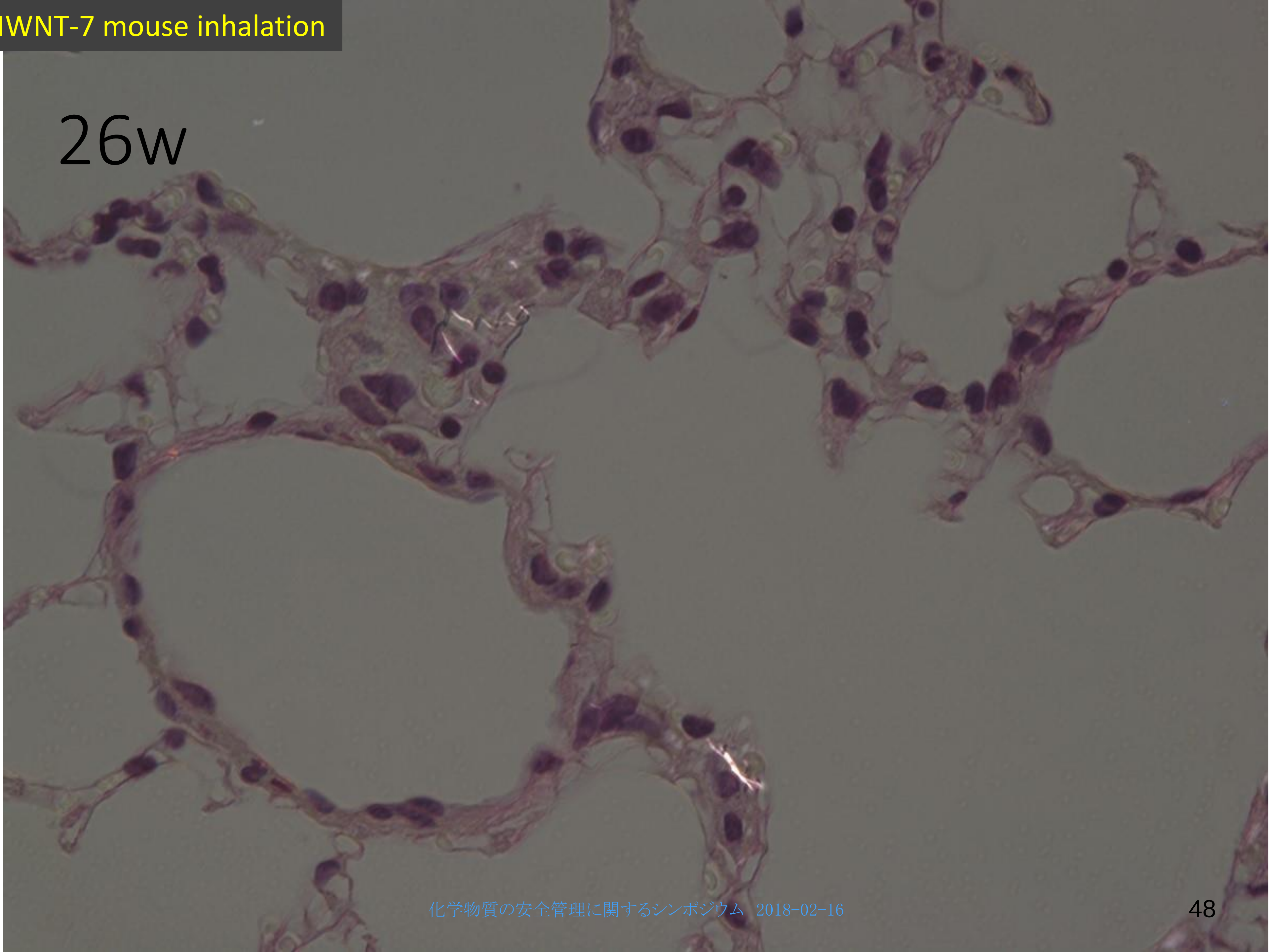
MWNT-7 mouse inhalation



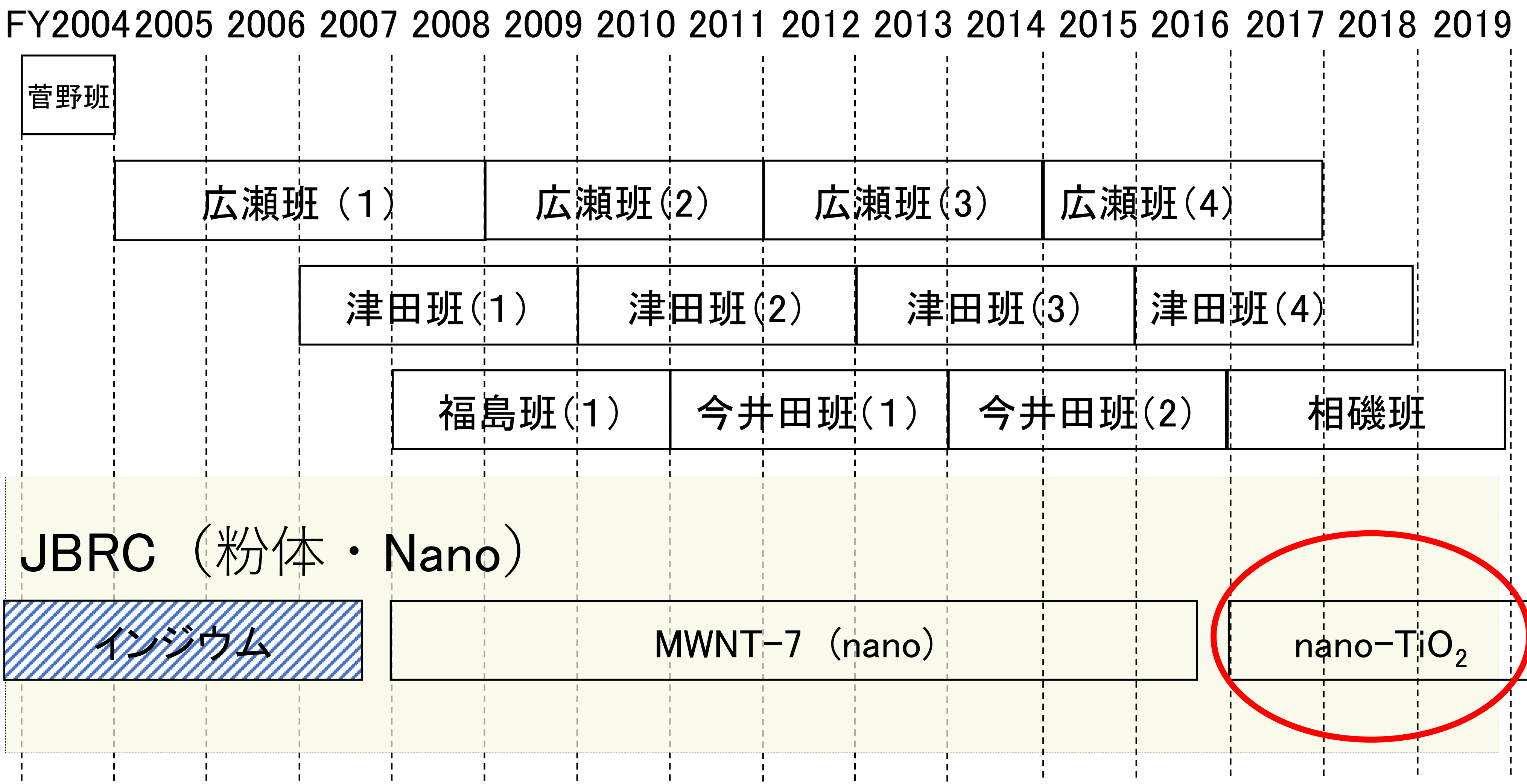
MWNT-7 mouse inhalation

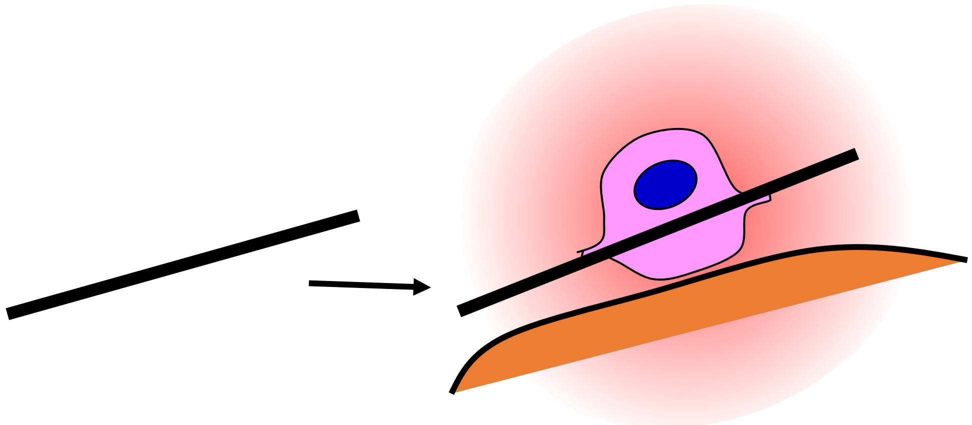


MWNT-7 mouse inhalation



ナノ物質のヒト健康影響に関する研究
厚生労働科学研究費補助金【化学物質リスク研究事業】研究班

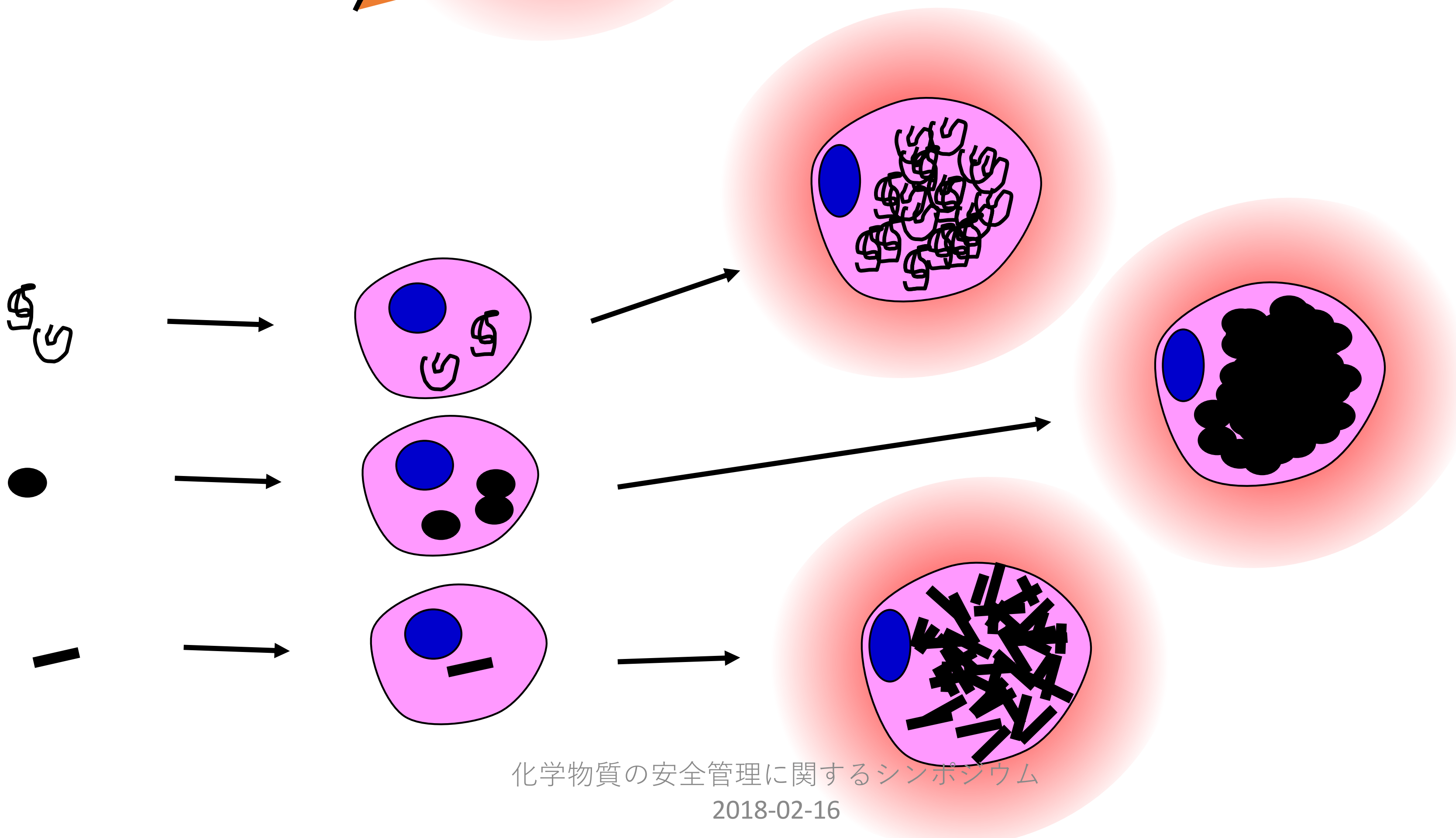




Non-Granulomatous Frustrated phagocytosis

→ Mesothelioma, Carcinoma？

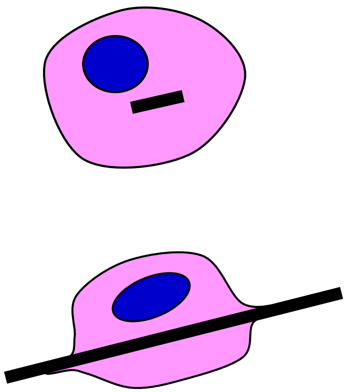
→ fibrosis？

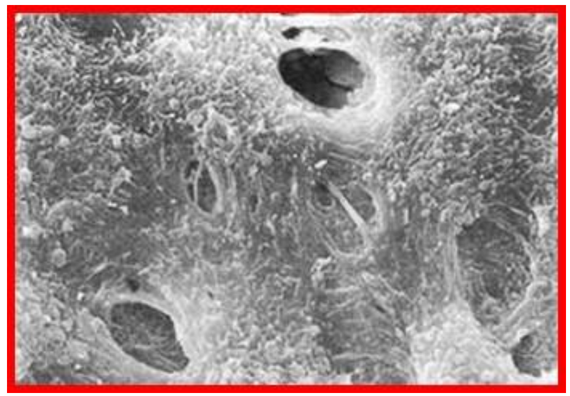


① マクロファージの大きさとの関係:貪食できるサイズを超えているか
size of particle versus size of macrophage

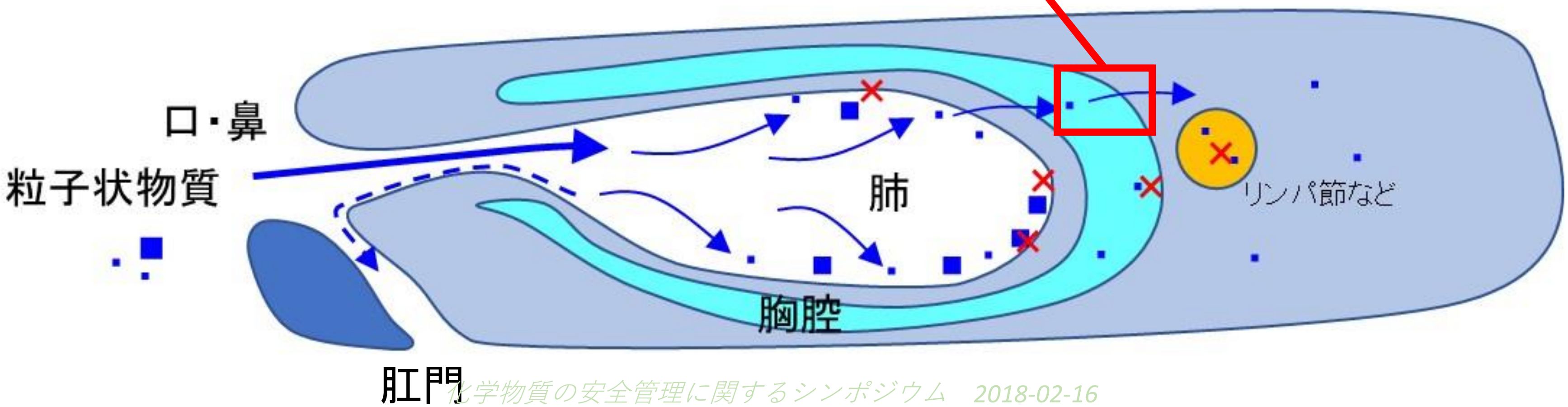
② 粒子の形
shape of particle

③ 胸膜面の排水口の直径よりも長いか(Pleural Stomata)
size of particle versus diameter of pleural stomata





From:
Anatomy of the Pleura, Thomas W. Shields. Chapter 54,
General Thoracic Surgery, 6th Edition,
Eds: Shields, Thomas W.; LoCicero, Joseph; Ponn, Ronald B.; Rusch, Valerie W. 2005
Lippincott Williams & Wilkins.



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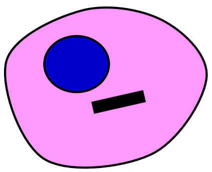
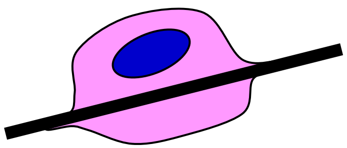
size of particle versus size of macrophage

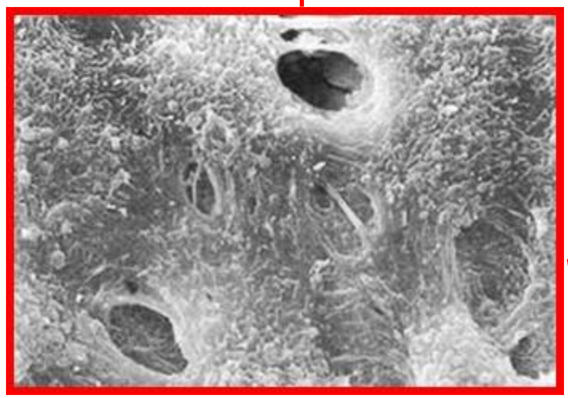
② 粒子の形
shape of particle

③ 胸膜面の排水口の直径よりも長いか(Pleural Stomata)
size of particle versus diameter of pleural stomata

④ 肉芽腫形成（類上皮細胞化）するかしないか。
granuloma formation/ epithelioid cell formation or not







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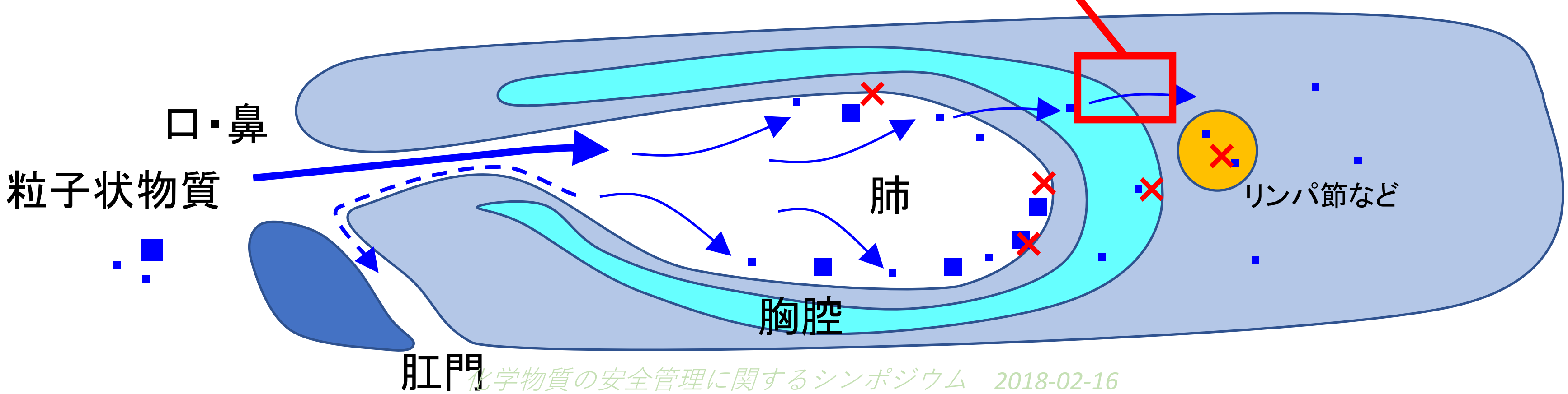

まとめ

- 粉体毒性学は、難易度が高く、未解明の点が多い。
- アスベストは、第１に肺癌、第２に中皮腫。
- 繊維発がん機構の研究が、「アスベスト労災認定」後、途絶えた。
  - 中皮腫発がんには　Frustrated Phagocytosis説がある。
  - 肺癌にも適用されるのか否か。

問題点多数

- 繊維発がんの範疇（WHO fiber）から外れる繊維状物質、および粒子状物質の肺発がん性の機構が不詳である。
- 短くて柔らかい繊維は発がん性が無いと言えないであろう、、
  - 中皮腫は誘発されなさそうであるが、肺癌は誘発される？白石綿！

新手の粉体毒性

厚生労働省
Ministry of Health, Labour and Welfare

平成29年4月28日
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報道関係者各位

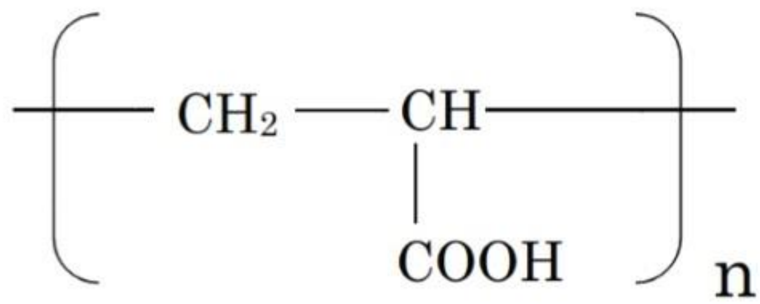
有機粉じんによる肺疾患の防止について関係労働局に指示しました

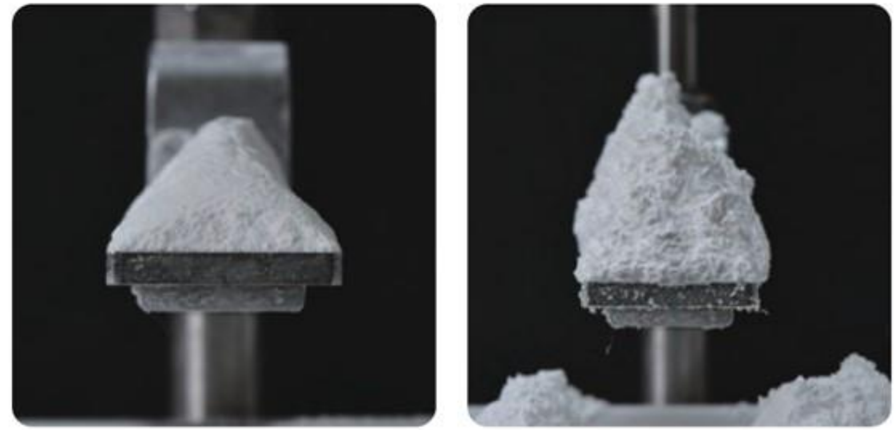
厚生労働省は、有機粉じんの一種である「架橋型アクリル酸系水溶性高分子化合物を主成分とする吸入性粉じん」※の製造事業場に対し、肺疾患などの予防的観点から、粉じんばく露防止を指導するよう関係労働局に指示しました。さらに、本日、当該製品および類似製品のメーカー等計4社に対し、流通先企業における、(1)粉じん吸入防止の徹底、(2)健康診断で肺に所見があった場合の精密検査の実施などを要請しました（別添2のとおり）。

併せて、化学物質の種類を問わず、高濃度の粉じんなどを吸入することは肺疾患などの健康障害を生じるおそれがあることから、中央労働災害防止協会など計3団体に対して、吸入性粉じんのばく露防止について注意喚起しました（別添3のとおり）。

○　外観は、白い粉末状。

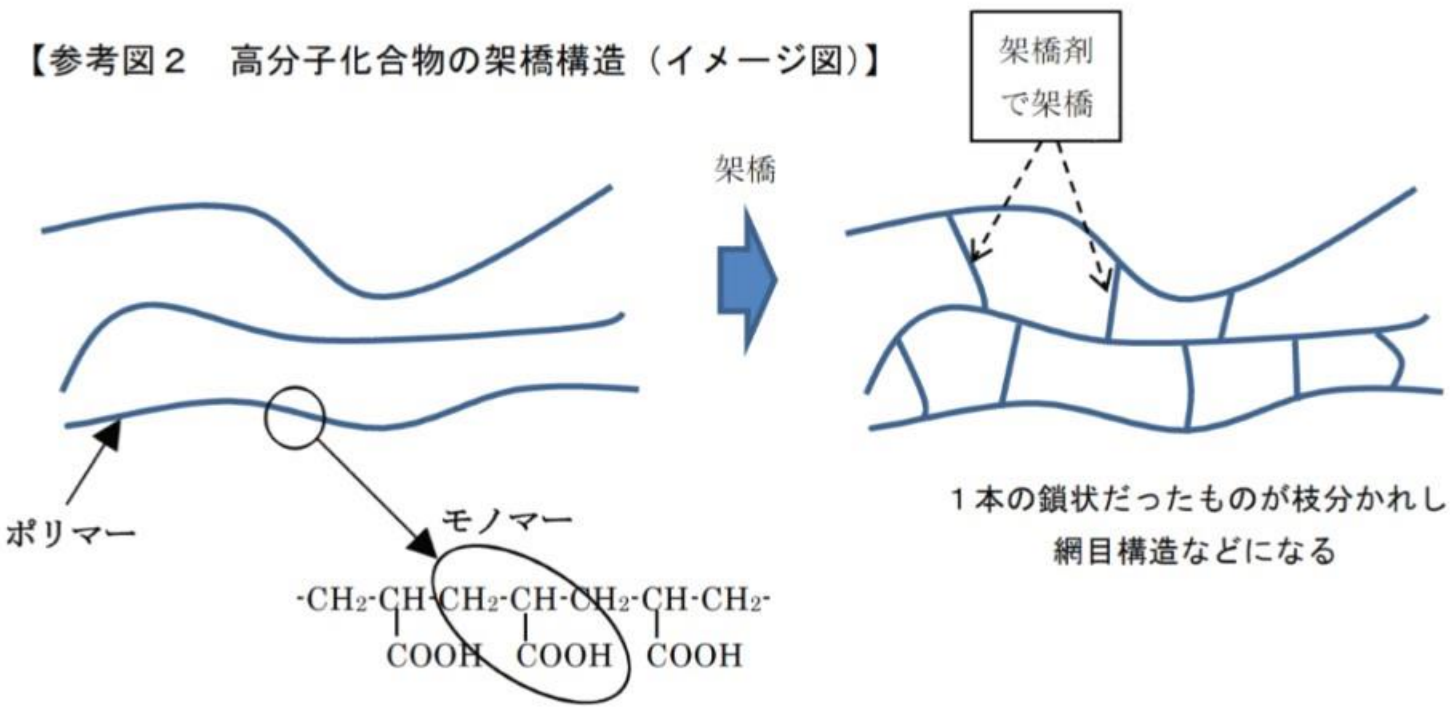
【参考図１　アクリル酸高分子化合物の基本構造】

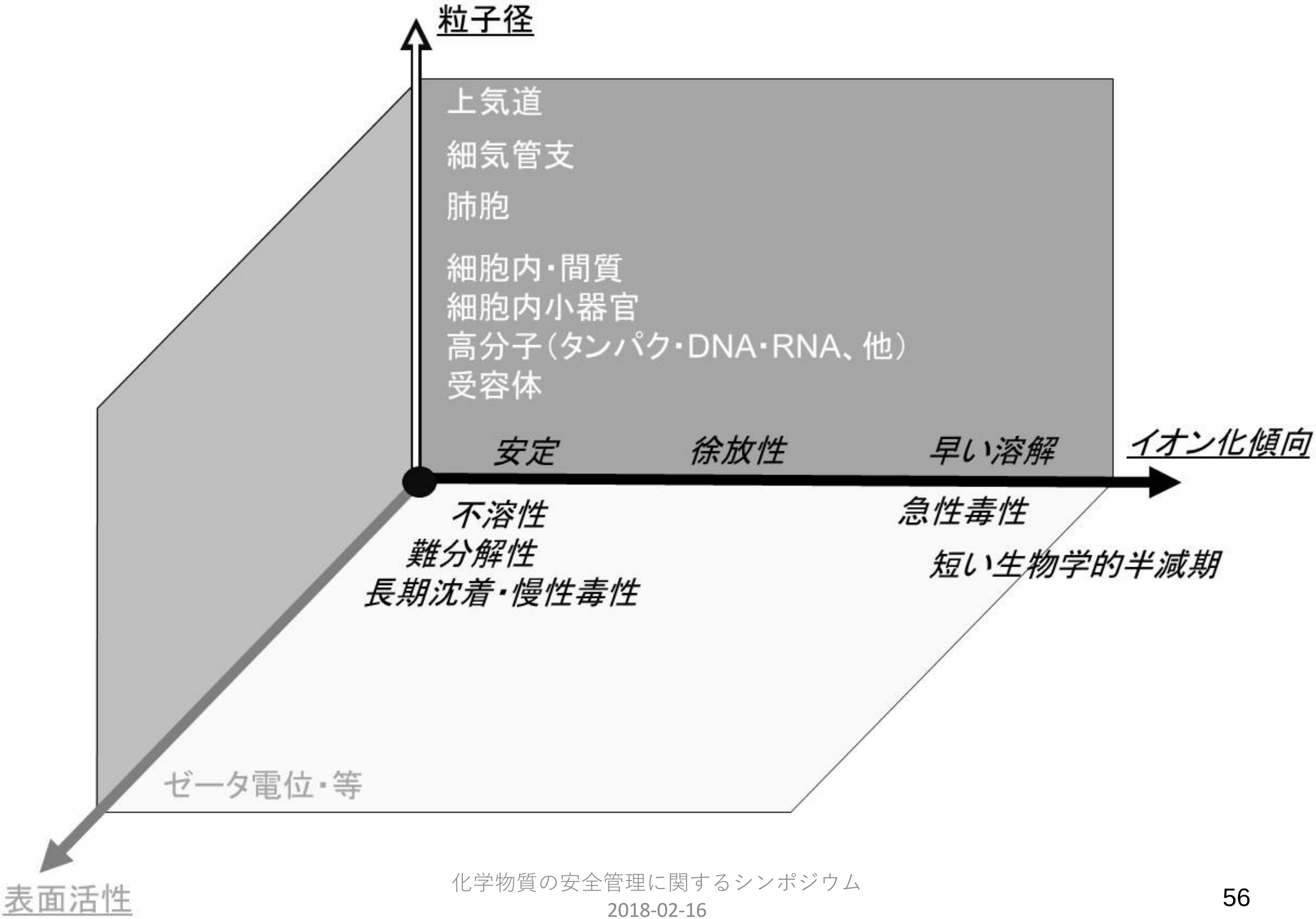




https://www.sumitomoseika.co.jp/upImage/product/1463446903_031576100.pdfより

【参考図２　高分子化合物の架橋構造（イメージ図）】




粒子径
上気道
細気管支
肺胞
細胞内・間質
細胞内小器官
高分子（タンパク・DNA・RNA、他）
受容体
安定
徐放性
早い溶解
イオン化傾向
不溶性
難分解性
長期沈着・慢性毒性
急性毒性
短い生物学的半減期
ゼータ電位・等
表面活性

今後の課題

- 粉体毒性学の推進⇒がん病変、および、非がん病変
  - 全身吸入曝露試験の推進。（水溶性のものは気管内投与困難）
  - 粉体（異物）による肉芽腫形成、瘢痕形成、肉芽腫形成に向かわないFrustrated Phagocytosisのメカニズム解析。
  - TLRを介した自然免疫系による反応（Macrophage）
  - 獲得免疫系の寄与の解明（T cell、B cell）
    - その他