

図168 解剖所見 (雌)

Table 16. Macroscopic findings of female rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days

Findings	Group	Com oil	Distilled water	C60	PVP-C60	SW-CNT	MW-CNT	PVP-K30
		(control 1)	(control 2)					
	Grade	- P	- P	- P	- P	- P	- P	- P
Kidney								
Pale colored area								
bilateral		5 0	5 0	5 0	5 0	4 1	5 0	5 0
Lymph node, submandibular								
Enlargement		5 0	4 1	5 0	5 0	4 1	5 0	5 0

Notes) - : No abnormal changes P: Non-graded change

Numerals represent the number of animals.

図169 病理組織学所見 (雄)

Table 17-1. Histopathological findings of male rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days [H.E. staining]

Findings	Group	Control 1					Control 2					0.50					1.00					5.00					10.00					50.00				
		n	m	+	±	-	n	m	+	±	-	n	m	+	±	-	n	m	+	±	-	n	m	+	±	-	n	m	+	±	-	n	m	+	±	-
Lymph node subcapsular																																				
Thymus																																				
Thymic body macrophage, cortex																																				
Lung																																				
Accumulation, foam cell, alveolus																																				
Cellular infiltration, macrophage, alveolus																																				
Emphysema																																				
Cellular infiltration, macrophage, blood vessel																																				
Hemorrhage, focal																																				
Metaplasia, ciliated, bronchus																																				
Mineralization, alveolus																																				
Esophagus																																				
Lymph node, subcapsular																																				
Heart																																				
Degeneration fibrous, myocardial, focal																																				
Liver																																				
Fatty change, hepatocyte, perportal																																				
Microgranuloma																																				
Necrosis, focal																																				
Spleen																																				
Hemorrhage, sinusoidal																																				

Notes: + No abnormal changes = Negligible - Slight ± Moderate ± Marked
 F Non-faded staining NE Not examined Pos Total of affected animals
 Numerals represent the number of animals

Table 17-2. Histopathological findings of male rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days [H.E. staining]

Findings	Group	Control 1					Control 2					0.50					1.00					5.00					10.00					50.00				
		n	m	+	±	-	n	m	+	±	-	n	m	+	±	-	n	m	+	±	-	n	m	+	±	-	n	m	+	±	-	n	m	+	±	-
Kidney																																				
Macrophage infiltration, cortex																																				
Cellular infiltration, lymphocyte, interstitial																																				
Cyst, medulla																																				
Fibrosis, focal, subcapsular																																				
Hyperplasia transitional cell, multi cellular infiltration																																				
Mineralization, medulla																																				
Adrenal gland																																				
Testis																																				
Atrophy, seminiferous tubule, focal																																				
Multinucleated giant cell, seminiferous tubule																																				
Epididymis																																				
Cell debris, lumen																																				
Cellular infiltration, lymphocyte, interstitial																																				
Skin																																				
Attachment crust, focal, epidermis																																				
Cell debris, hair follicle																																				
Cellular infiltration, lymphocyte, dermis, muscular layer																																				
Cellular infiltration, macrophage, dermis, muscular layer																																				
Edema, dermis																																				
Hyperplasia squamous cell, focal																																				

Notes: + No abnormal changes = Negligible - Slight ± Moderate ± Marked
 F Non-faded staining NE Not examined Pos Total of affected animals
 Numerals represent the number of animals

図170 病理組織学所見 (雌)

Table 18. Histopathological findings of female rats in the repeated dose toxicity study of nanomaterials by transcutaneous administration for 28 days [H.E. staining]

Group	Osm oil (control 1)						Distilled water (control 2)						O60						PVP-O60						SiVACNT						MVAQNT						PVP400					
	-	+	+	+	+	P. Pos.	-	+	+	+	+	P. Pos.	-	+	+	+	+	P. Pos.	-	+	+	+	+	P. Pos.	-	+	+	+	+	P. Pos.	-	+	+	+	+	P. Pos.	-	+	+	+	+	P. Pos.
Lymph node, submandibular																																										
Thymus																																										
Tingible body macrophage cortex																																										
Lung																																										
Accumulation, foam cell alveolus																																										
Cellular infiltration, eosinophil, perivascular																																										
Metaplasia, ciliated, focal																																										
Mineralization, interstitial																																										
Bronchus																																										
Lymph node, mesenteric																																										
Heart																																										
Degeneration fibrous myocardial, focal																																										
Liver																																										
Fatty change, hepatocyte, perivascular																																										
Microgranuloma																																										
Spleen																																										
Deposit, pigment, brown																																										
Hemorrhage, extramedullary																																										
Kidney																																										
Eosinophilic tubule, cortex																																										
Cellular infiltration, lymphocyte interstitial																																										
Mineralization, cortico-medullary junction																																										
Adrenal gland																																										
Ovary																																										
Decrease, corpus luteum, bilateral																																										
Uterus																																										
Vagina																																										
Skin																																										
Cell debris, hair follicle																																										

Notes) - : No abnormal changes + : Very slight ++ : Slight +++ : Moderate ++++ : Marked
 P : Non-graded change NE : Not examined Pos. : Total of positive grade
 Numerals represent the number of animals.

群	被験物質	濃度 (ppm)	投与量 (mL/kg)	動物数
対照群 (溶媒)	注射用水 (溶媒)	0	2	雄5 雌5
2	snPt ASP-WM500C 直径1nm以下	5000	2	雄5 雌5
3	nPt ASP-WM500C 直径20nm前後	5000	2	雄5 雌5

図 171 群構成

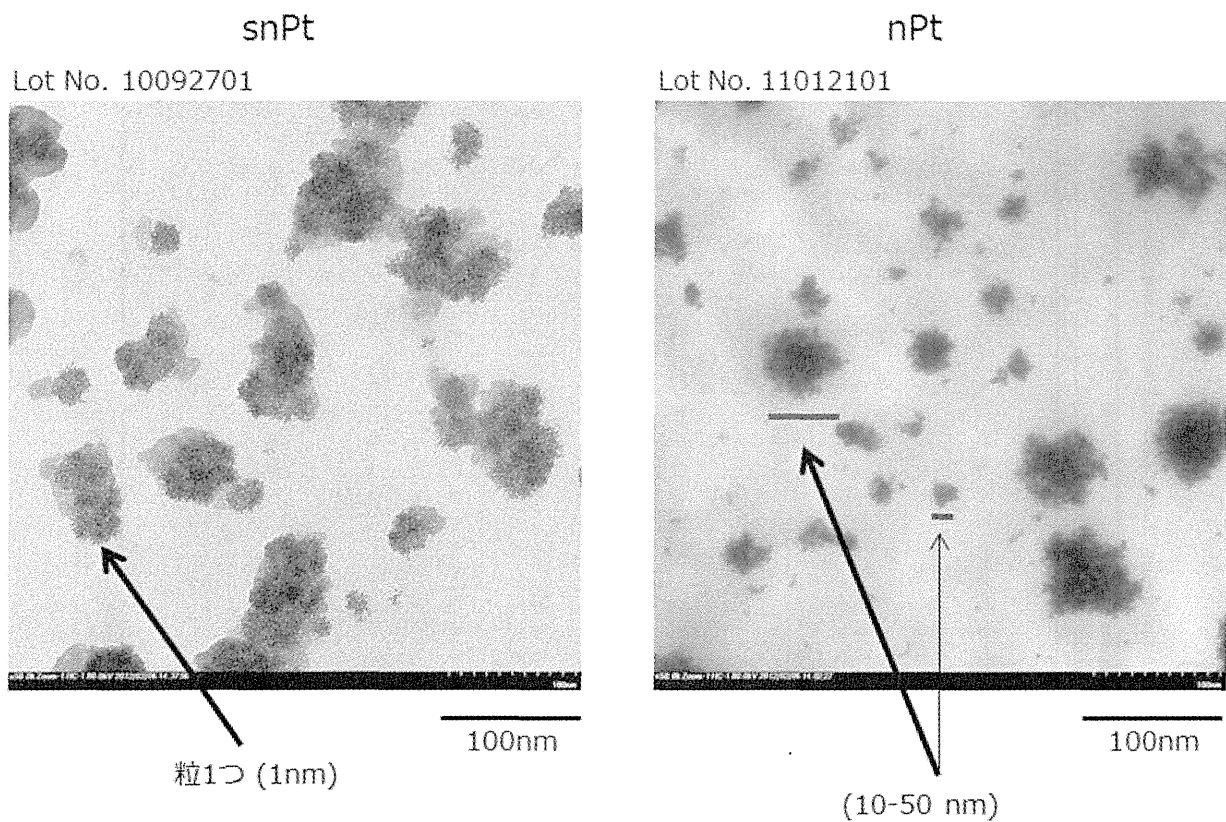
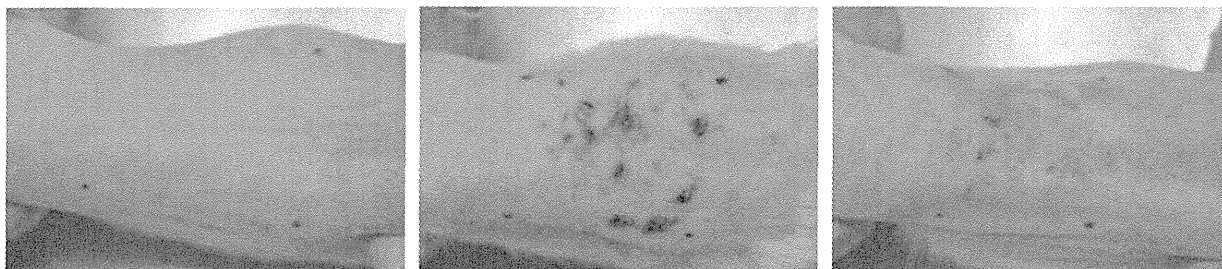


図 172 試験に使用した snPt および nPt (TEM)

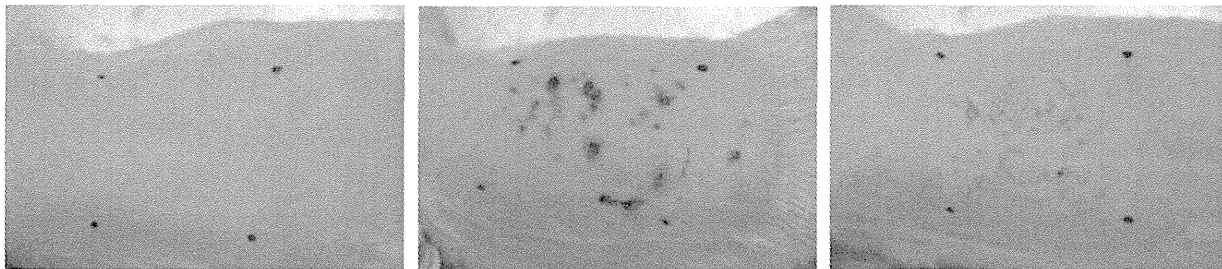
コロジオン膜貼付メッシュ上に被験物質を滴下し自然乾燥させて観察した。

提供元： Polytech & Net GmbH 社製

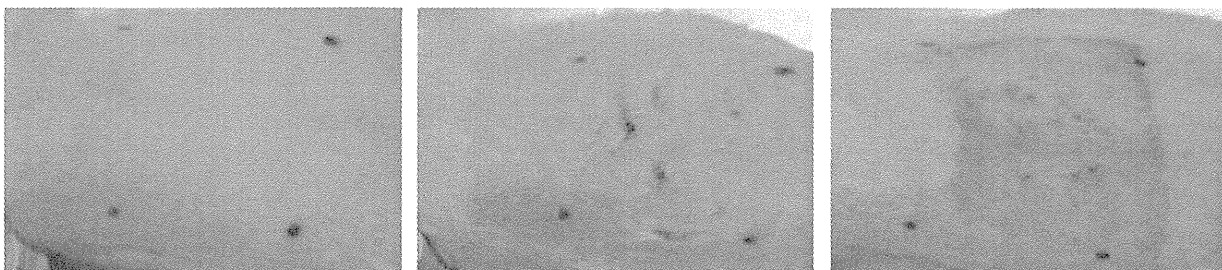
投与15日雄（11回貼付）



投与21日雄（15回貼付）



投与28日雄（20回貼付）



対照群（注射用水）

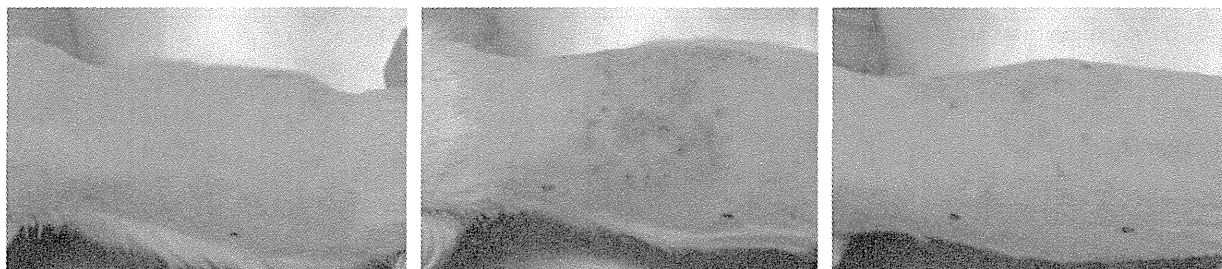
snPT群

nPT群

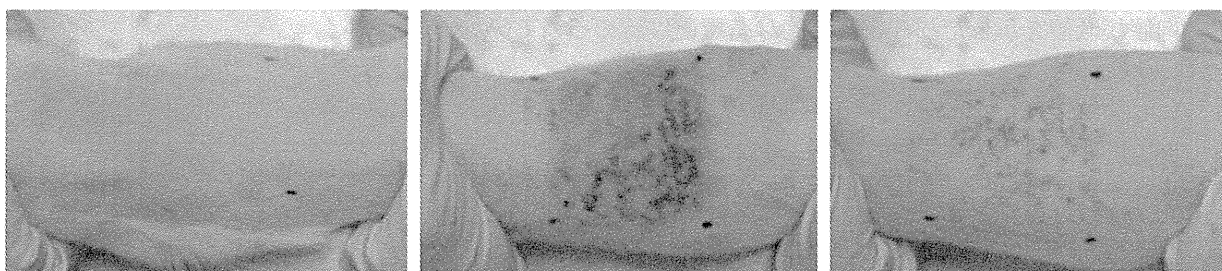
図 175 貼付部位皮膚の変化見(雄)

投与第 2 週から貼付部位に痂皮(一部潰瘍)が認められたが、投与終了時には回復傾向にあった。

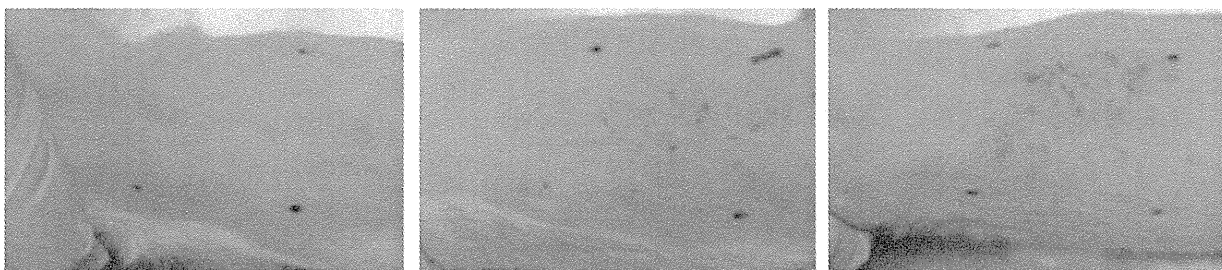
投与15日雌 (11回貼付)



投与21日雌 (15回貼付)



投与28日雌 (20回貼付)



対照群 (注射用水)

snPT群

nPT群

図 176 貼付部位皮膚の変化見(雌)

投与第 2 週から貼付部位に痂皮(一部潰瘍) が認められたが、投与終了時には回復傾向にあった。

Group	Control (Distilled water)		snPT	nPT
Number of males	5		5	5
Days of administration				
	1	236.6 = 3.5	236.6 = 3.9	237.9 = 4.7
	8	289.5 = 1.6	284.0 = 17.0	291.5 = 14.5
	15	338.6 = 4.4	321.8 = 27.5	341.8 = 17.6
	22	382.1 = 8.4	350.7 = 43.8	382.1 = 21.2
	28	408.4 = 13.9	375.0 = 47.7	407.0 = 22.1

Each value shows mean (g) = S.D.

図 177 体重(雄)

皮膚病変が重篤であった snPt 群の 2 例の体重推移がやや低値に推移したために、snPt 群の体重平均値が低値を示したが、統計学的な有意差は認められていない。

Group	Control (Distilled water)		snPT	nPT
Number of females	5		5	5
Days of administration				
	1	163.9 = 5.4	162.9 = 7.5	164.7 = 4.8
	8	180.9 = 7.9	179.9 = 2.8	178.3 = 3.4
	15	192.8 = 9.1	200.0 = 2.5	197.5 = 6.9
	22	209.5 = 14.1	217.2 = 6.0	212.6 = 6.7
	28	218.2 = 18.1	221.4 = 10.5	217.7 = 8.9

図 178 体重(雌)

snPt 群および nPt 群ともに対照群と同様に推移した。

Group	Control (Distilled water)		snPT	nPT
Number of males	5		5	5
Days of administration				
	1	25.3 = 2.3	25.4 = 2.9	24.9 = 1.5
	8	30.4 = 1.2	29.0 = 5.5	30.4 = 3.1
	15	32.2 = 1.8	27.1 = 6.5	29.8 = 2.8
	22	32.0 = 1.6	28.8 = 5.5	32.1 = 3.4

Each value shows mean (g) = S.D.

図 179 摂餌量(雄)

摂餌量には snPt あるいは nPt 投与による影響は見られなかった。

Group	Control (Distilled water)		snPT	nPT
Number of females	5		5	5
Days of administration				
	1	17.4 = 1.2	17.7 = 0.9	17.4 = 1.9
	8	18.6 = 3.9	18.7 = 2.3	17.6 = 1.5
	15	19.5 = 4.1	19.4 = 1.7	19.5 = 2.2
	22	19.4 = 1.7	20.3 = 1.8	22.3 = 1.3 *

Each value shows mean (g) = S.D.

Significantly different from the control group (*: P<0.03, **: P<0.01).

図 180 摂餌量(雌)

摂餌量には snPt あるいは nPt 投与による影響は見られなかった。

Group	Number of animals	RBC ($\times 10^4$ μ L)	Hemoglobin (g dL)	Hematocrit (%)	MCV (fL)	MCH (pg)	MCHC (g dL)	Platelet ($\times 10^4$ μ L)	PT (sec)	APTT (sec)
Distilled water	5	744 ±16	15.3 ±0.3	43.5 ±1.2	58.5 ±1.9	20.6 ±0.7	35.2 ±0.6	86.7 ±11.7	18.9 ±3.6	22.2 ±1.6
snPt	5	751 ±22	15.1 ±0.5	43.0 ±1.5	57.3 ±1.9	20.1 ±0.7	35.0 ±0.4	85.1 ±7.2	20.0 ±2.6	21.3 ±1.5
nPt	5	776 ±34	15.6 ±0.1	44.9 ±0.8	58.0 ±3.0	20.2 ±0.9	34.8 ±0.6	89.1 ±1.6	19.4 ±3.9	21.9 ±2.2

Group	Number of animals	WBC ($\times 100$ μ L)	Neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)	Reticulocyte (%)
Distilled water	5	105.4 ±15.8	10.8 ±4.0	1.0 ±0.4	0.0 ±0.0	2.6 ±0.8	85.6 ±4.5	3.46 ±0.82
snPt	5	65.4 *** ±16.5	15.2 ±5.6	1.2 ±0.3	0.0 ±0.0	3.6 ±1.5	80.0 ±6.3	3.22 ±0.29
nPt	5	67.0 * ±23.4	20.1 *** ±3.4	1.2 ±0.3	0.0 ±0.0	2.4 ±0.7	76.2 *** ±3.4	3.21 ±0.44

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

図 181 血液学検査(雄)

snPt 群、nPt 群ともに白血球数が減少した。白血球分類では snPt 群で好中球比率が増加し、リンパ球比率が減少した。この変化は雌には認められていない。

Group	Number of animals	RBC ($\times 10^4$ μ L)	Hemoglobin (g dL)	Hematocrit (%)	MCV (fL)	MCH (pg)	MCHC (g dL)	Platelet ($\times 10^4$ μ L)	PT (sec)	APTT (sec)
Distilled water	5	710 ±15	14.4 ±0.2	40.5 ±0.9	56.8 ±0.9	20.3 ±0.1	35.8 ±0.5	83.9 ±10.0	12.7 ±0.9	16.6 ±1.5
snPt	5	700 ±45	13.8 ±0.8	39.1 ±2.1	55.9 ±2.0	19.7 *** ±0.5	35.2 ±0.8	86.4 ±11.7	13.3 ±1.2	17.0 ±1.2
nPt	5	752 ** ±18	15.2 ** ±0.4	42.6 ** ±1.2	56.6 ±0.5	20.2 ±0.3	35.6 ±0.3	76.7 ±9.5	13.3 ±0.9	16.7 ±1.3

Group	Number of animals	WBC ($\times 100$ μ L)	Neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)	Reticulocyte (%)
Distilled water	5	66.3 ±16.7	12.5 ±3.5	1.1 ±0.4	0.0 ±0.1	1.7 ±0.7	83.7 ±3.6	3.0 ±0.7
snPt	5	88.2 ±13.1	16.7 ±3.7	2.0 ±0.9	0.0 ±0.0	3.1 ±0.9	78.3 ±3.8	3.2 ±0.5
nPt	5	65.1 ±17.4	14.7 ±3.4	2.0 ** ±0.4	0.0 ±0.0	1.5 ±0.7	80.8 ±5.9	2.4 ±0.2

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

図 182 血液学検査(雌)

赤血球数、ヘモグロビン値、ヘマトクリット値、MCH 値が統計学的に有意に高値を示したが、わずかな変化であることから、毒性とは判断しない。

snPt 群では白血球数が増加傾向を示した。この変化は皮膚病変に起因した変化と考えられた。白血球分類では snPt 群、nPt 群ともに好酸球が占める割合が高かった。

Group	Number of animals	Total protein (g dL)	Albumin (g dL)	Total cholesterol (mg dL)	Triglyceride (mg dL)	Phospholipid (mg dL)	Glucose (mg dL)	BUN (mg dL)	Creatinine (mg dL)	Total bilirubin (mg dL)	ALP (U/L)
Distilled water	5	5.7 ±0.2	3.8 ±0.1	47 ±16	32 ±5	75 ±14	143 ±10	16 ±1	0.5 ±0.1	0.05 ±0.01	572 ±100
snPt	5	5.4 ±0.3	3.6 ±0.2	42 ±8	26 ±6	70 ±10	136 ±8	16 ±1	0.5 ±0.1	0.05 ±0.01	567 ±92
nPt	5	5.5 ±0.3	3.8 ±0.2	36 ±7	21 * ±6	63 ±9	131 ±7	17 ±3	0.4 ±0.0	0.05 ±0.01	735 * ±50

Group	Number of animals	AST (U/L)	ALT (U/L)	γ-GTP (U/L)	LDH (U/L)	Ca (mg dL)	Inorganic phosphorus (mg dL)	A/G	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Distilled water	5	70 ±5	31 ±5	0 ±0	155 ±46	9.6 ±0.4	7.9 ±0.4	2.01 ±0.11	145.3 ±1.2	3.42 ±0.17	106.0 ±1.4
snPt	5	73 ±5	28 ±3	0 ±0	128 ±44	9.5 ±0.2	7.8 ±0.3	2.04 ±0.21	146.1 ±0.9	3.48 ±0.13	107.5 ±1.5
nPt	5	80 ±14	31 ±4	0 ±0	177 ±51	9.5 ±0.2	7.3 ±0.5	2.16 ±0.21	145.9 ±1.0	3.37 ±0.03	108.3 * ±0.8

Each value shows mean±SD
Significantly different from the control group (*: P<0.05, **: P<0.01).

図 183 血液生化学検査(雄)

snPt 群、nPt 群ともに栄養状態が良好ではない徴候がみられたが、体重値には影響がない程度であった。貼付ストレスに加え皮膚病変ストレスが一因と考えられる。同じ徴候は雌でも認められている。

Group	Number of animals	Total protein (g dL)	Albumin (g dL)	Total cholesterol (mg dL)	Triglyceride (mg dL)	Phospholipid (mg dL)	Glucose (mg dL)	BUN (mg dL)	Creatinine (mg dL)	Total bilirubin (mg dL)	ALP (U/L)
Distilled water	5	5.5 ±0.4	3.8 ±0.3	54 ±4	14 ±3	98 ±6	121 ±15	16 ±2	0.4 ±0.0	0.07 ±0.01	375 ±54
snPt	5	5.7 ±0.5	3.7 ±0.3	48 ±14	14 ±5	91 ±15	121 ±9	18 ±3	0.5 ±0.0	0.06 ±0.01	450 ±174
nPt	5	5.4 ±0.4	3.8 ±0.2	50 ±14	11 ±5	79 * ±13	113 ±13	20 * ±3	0.5 ±0.0	0.06 * ±0.01	357 ±72

Group	Number of animals	AST (U/L)	ALT (U/L)	γ-GTP (U/L)	LDH (U/L)	Ca (mg dL)	Inorganic phosphorus (mg dL)	A/G	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Distilled water	5	74 ±16	28 ±6	0 ±1	94 ±22	9.1 ±0.3	6.9 ±0.4	2.22 ±0.20	143.8 (4)a ±1.2	3.35 ±0.20	107.1 ±1.4
snPt	5	107 ±73	30 ±6	1 ±0	128 ±25	9.1 ±0.6	7.6 ±1.5	1.86 *** ±0.11	142.9 (4)a ±1.7	3.71 ±0.43	106.5 ±2.0
nPt	5	83 ±9	29 ±4	1 ±0	69 ±33	9.0 ±0.3	7.0 ±1.1	2.38 ±0.25	143.6 (4)a ±1.0	3.31 ±0.08	107.4 ±0.8

Each value shows mean±SD
1) One animal data was deleted because the animal was died during collecting a blood sample.
Significantly different from the control group (*: P<0.05, **): P<0.01).

図 184 血液生化学検査(雌)

snPt 群、nPt 群ともに白血球数が減少した。白血球分類では snPt 群で好中球比率が増加し、リンパ球比率が減少した。この変化は眼雌には認められていない。

Group	Number of animals	pH			protein			glucose		ketone body			Bilirubin	occult blood				urobilinogen		Urine volume (mL 6 hr)	Electrolyte gross volume (mEq 6 hr)		
		6.5	7.0	7.5	-	=	1+	-	1+	-	=	1+	-	-	1+	2+	=	1+	Na		K	Cl	
Distilled water	5	0	4	1	0	5	0	5	0	0	4	1	5	4	1	0	0	1	4	3.7 ±0.7	0.3 ±0.1	0.5 ±0.1	0.4 ±0.1
mPr	5	2	1	2	0	5	0	5	0	1	1	3	5	5	0	0	0	3	2	3.1 ±1.0	0.5 ±0.2	0.5 ±0.2	0.4 ±0.1
nPr	5	2	1	2	0	4	1	5	0	1	2	2	5	5	0	0	0	3	3	4.5 ±1.9	0.5 ±0.1	0.5 ±0.1	0.4 ±0.1

Each value shows mean±S.D.

图 185 尿検査(雄)

Group	Number of animals	pH				protein			glucose	ketone body			Bilirubin	occult blood			urobilinogen		Urine volume (mL 6 hr)	Electrolyte gross volume (mEq 6 hr)				
		6.0	6.5	7.0	7.5	-	=	1+	-	1+	-	=	1+	-	1+	2+	=	1+		2+	Na	K	Cl	
Distilled water	5	0	5	0	0	0	1	4	5	0	1	3	1	5	4	0	1	1	3	1	1.5 ±0.5	0.1 ±0.0	0.2 ±0.1	0.1 ±0.1
mPr	5	0	0	1	4	0	3	2	5	0	4	1	0	5	4	0	2	2	3	0	2.0 ±0.6	0.2 ±0.1	0.5 ±0.1	0.2 ±0.1
nPr	5	3	1	1	0	1	1	3	5	0	2	3	0	5	5	0	0	3	2	0	1.9 ±1.0	0.1 ±0.2	0.2 ±0.0	0.1 ±0.1

Each value shows mean±S.D.

图 186 尿検査(雌)

Group		Control (Distilled water)		snPT		nPT	
Number of males		5		5		5	
Body weight	(g)	371.5	= 13.7	340.2	= 43.9	374.0	= 20.2
Brain	(mg)	1943.7	= 101.5	1970.6	= 92.0	1961.5	= 93.7
	(mg/g)	5.240	= 0.375	5.846	= 0.541	5.248	= 0.144
Thymus	(mg)	530.0	= 61.1	423.1	= 126.3	454.9	= 112.8
	(mg/g)	1.429	= 0.178	1.229	= 0.247	1.215	= 0.293
Heart	(mg)	1317.5	= 99.5	1177.0	= 120.9	1333.9	= 70.8
	(mg/g)	3.545	= 0.191	3.472	= 0.189	3.573	= 0.247
Liver	(mg)	12078.5	= 804.3	10037.4	= 1593.1	10946.6	= 471.5 *
	(mg/g)	32.491	= 1.235	29.433	= 1.486 **	29.348	= 2.216 *
Kidney (R)	(mg)	1430.1	= 103.6	1342.4	= 181.8	1485.6	= 94.7
	(mg/g)	3.847	= 0.186	3.943	= 0.041	3.988	= 0.404
Kidney (L)	(mg)	1439.1	= 134.5	1314.8	= 156.9	1528.1	= 49.1
	(mg/g)	3.869	= 0.249	3.869	= 0.089	4.093	= 0.196
Spleen	(mg)	706.2	= 110.3	651.2	= 108.1	695.3	= 93.5
	(mg/g)	1.908	= 0.342	1.916	= 0.219	1.856	= 0.206
Testis (R)	(mg)	1553.1	= 102.5	1603.1	= 51.9	1655.2	= 68.3
	(mg/g)	4.180	= 0.221	4.767	= 0.550	4.438	= 0.331
Testis (L)	(mg)	1550.1	= 139.8	1579.7	= 68.9	1668.2	= 80.8
	(mg/g)	4.171	= 0.309	4.694	= 0.529	4.468	= 0.259
Epididymis (R)	(mg)	419.3	= 31.2	428.3	= 47.3	431.5	= 16.6
	(mg/g)	1.130	= 0.098	1.264	= 0.083	1.157	= 0.085
Epididymis (L)	(mg)	409.4	= 22.6	415.9	= 45.2	426.0	= 12.2
	(mg/g)	1.103	= 0.063	1.227	= 0.085	1.141	= 0.056
Adrenal gland (R)	(mg)	32.5	= 7.3	26.3	= 3.7	30.6	= 7.0
	(mg/g)	0.087	= 0.020	0.078	= 0.013	0.081	= 0.016
Adrenal gland (L)	(mg)	35.8	= 7.6	27.3	= 3.8	31.5	= 6.8
	(mg/g)	0.097	= 0.022	0.081	= 0.013	0.084	= 0.014

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

Significantly different from the control group (*: P<0.05, **: P<0.01).

図 187 器官重量(雄)

snPt 群、nPt 群ともに肝臓重量が対照群と比較して低値を示したが、病理組織学検査では異常は認められていない。

Group		Control (Distilled water)		snPt		nPt	
Number of females		5		5		5	
Body weight	(g)	199.0	= 18.0	201.0	= 6.8	201.7	= 6.0
Brain	(mg)	1784.0	= 71.6	1782.7	= 110.5	1794.5	= 25.2
	(mg/g)	9.044	= 1.131	8.870	= 0.478	8.902	= 0.219
Thymus	(mg)	390.3	= 107.0	360.1	= 73.2	417.1	= 62.9
	(mg/g)	1.950	= 0.480	1.794	= 0.380	2.074	= 0.353
Heart	(g)	0.7	= 0.1	0.8	= 0.0	0.8	= 0.0
	(g/g)	0.004	= 0.000	0.004	= 0.000	0.004	= 0.000
Liver	(mg)	6238.7	= 668.9	6612.4	= 1022.8	5959.0	= 826.6
	(mg/g)	31.343	= 1.554	32.828	= 4.215	29.478	= 3.229
Kidney (R)	(mg)	864.3	= 65.3	902.6	= 107.8	839.4	= 50.2
	(mg/g)	4.363	= 0.423	4.491	= 0.505	4.163	= 0.228
Kidney (L)	(mg)	857.6	= 70.6	894.4	= 89.7	832.6	= 46.4
	(mg/g)	4.322	= 0.340	4.450	= 0.412	4.128	= 0.181
Spleen	(mg)	445.6	= 92.9	485.4	= 74.7	470.4	= 52.4
	(mg/g)	2.234	= 0.378	2.414	= 0.350	2.336	= 0.292
Ovary (R)	(mg)	45.6	= 5.2	45.0	= 9.7	37.9	= 4.5
	(mg/g)	0.229	= 0.019	0.224	= 0.045	0.187	= 0.017
Ovary (L)	(mg)	42.2	= 7.5	42.9	= 13.6	34.6	= 3.6
	(mg/g)	0.214	= 0.046	0.214	= 0.067	0.171	= 0.015
Adrenal gland (R)	(mg)	31.6	= 4.2	30.8	= 2.6	30.1	= 3.2
	(mg/g)	0.160	= 0.026	0.153	= 0.011	0.149	= 0.015
Adrenal gland (L)	(mg)	32.5	= 3.7	33.3	= 3.1	32.2	= 3.4
	(mg/g)	0.164	= 0.023	0.166	= 0.016	0.160	= 0.014

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

Significantly different from the control group (*: P<0.03, **: P<0.01).

図 188 器官重量(雌)

snPtあるいはnPt投与による影響は認められていない。

Findings	Group	Control-1		snPt		nPt	
	Dose(mL/kg)	2		2		2	
	Grade	-	P	-	P	-	P
Kidney							
Cyst, right		5	0	5	0	4	1
Skin							
Crust, exposure area		5	0	0	5	2	3

Notes) -: No abnormal changes P: Non-graded change
Numerals represent the number of animals.

図 189 肉眼的所見(雄)

snPt 群、nPt 群ともに貼付部位に痂皮が認められた。

Findings	Group	Control-1		snPt		nPt	
	Dose(mL/kg)	2		2		2	
	Grade	-	P	-	P	-	P
Liver							
Whitish spot		5	0	4	1	5	0
Lymph node, submandibular							
Discoloration, reddish		5	0	5	0	4	1
Skin							
Crust, exposure area		5	0	0	5	3	2

Notes) -: No abnormal changes P: Non-graded change
Numerals represent the number of animals.

図 190 肉眼的所見(雌)

snPt 群、nPt 群ともに貼付部位に痂皮が認められた。

Findings	Group Dose(ml. kg) Grade	Control						snPt						nPt								
		2						2						2								
		-	=	-	2+	3+	P	Pos.	-	=	-	2+	3+	P	Pos.	-	=	-	2+	3+	P	Pos.
Lymph node, submandibular		5						5						5								
Thymus																						
Tingible body, macrophage, cortex		2	3	0	0	0	3	4	1	0	0	0	1	4	1	0	0	0				1
Lung																						
Accumulation, foam cell, alveolus		4	1	0	0	0	1	4	1	0	0	0	1	3	2	0	0	0				2
Cellular infiltration, eosinophil, periaarterial		2	3	0	0	0	3	3	2	0	0	0	2	2	3	0	0	0				3
Cellular infiltration, inflammatory, periaarterial		4	1	0	0	0	1	5	0	0	0	0	0	4	1	0	0	0				1
Metaplasia, osseous, focal		4	1	0	0	0	1	3	2	0	0	0	2	5	0	0	0	0				0
Bronchus		5						5						5								
Lymph node, mesenteric		5						5						5								
Heart																						
Degeneration fibrosis, myocardial, focal		4	1	0	0	0	1	5	0	0	0	0	0	5	0	0	0	0				0
Liver																						
Fatty change, hepatocyte, periportal		1	4	0	0	0	4	3	2	0	0	0	2	2	3	0	0	0				3
Fibrosis, subserosa		5	0	0	0	0	0	4	1	0	0	0	1	5	0	0	0	0				0
Microgranuloma		1	4	0	0	0	4	2	3	0	0	0	3	4	1	0	0	0				1
Necrosis, focal		4	1	0	0	0	1	4	1	0	0	0	1	5	0	0	0	0				0
Spleen																						
Hematopoiesis, extramedullary		0	1	4	0	0	5	0	3	2	0	0	5	0	1	4	0	0				5

Notes) -: No abnormal changes =: Very slight -: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined Pos.: Total of positive grade

Numerals represent the number of animals.

Not significantly different from control.

Findings	Group Dose(ml. kg) Grade	Control						snPt						nPt								
		2						2						2								
		-	=	-	2+	3+	P	Pos.	-	=	-	2+	3+	P	Pos.	-	=	-	2+	3+	P	Pos.
Kidney																						
Basophilic tubule, cortex		4	1	0	0	0	1	4	1	0	0	0	1	2	3	0	0	0				3
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0	1	4	1	0	0	0	1	3	2	0	0	0				2
Cyst, medulla		5	0	0	0	0	0	5	0	0	0	0	0	4	1	0	0	0				1
Mineralization, cortex		4	1	0	0	0	1	4	1	0	0	0	1	4	1	0	0	0				1
Adrenal gland		5						5						5								
Testis		5						5						5								
Epididymis		5						5						5								
Skin																						
Attachment, crust, focal, epidermis		5				0	0	1					4	4	2						3	3
Cellular infiltration, lymphocyte macrophage, dermis		5	0	0	0	0	0	0	5	0	0	0	5**=	2	3	0	0	0				3
Cellular infiltration, eosinophil, dermis		5	0	0	0	0	0	2	3	0	0	0	3	5	0	0	0	0				0
Edema, epidermis dermis		5	0	0	0	0	0	2	3	0	0	0	3	2	3	0	0	0				3
Erosion		5	0	0	0	0	0	2	3	0	0	0	3	3	2	0	0	0				2
Hemorrhage, focal		5	0	0	0	0	0	2	3	0	0	0	3	3	2	0	0	0				2
Hyperplasia, squamous cell		5	0	0	0	0	0	0	2	3	0	0	5**=	1	3	1	0	0				4
Proliferation, fibroblast		5	0	0	0	0	0	0	2	3	0	0	5**=	2	3	0	0	0				3

Notes) -: No abnormal changes =: Very slight -: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined Pos.: Total of positive grade

Numerals represent the number of animals.

**P<0.01: Significantly different from control by Mann-Whitney U test.

=P<0.05, **P<0.01: Significantly different from control by Fisher's exact test.

図 191 病理組織学所見(雄)

皮膚所見以外は、被験物質投与によると考えられた変化は認められなかった。

Findings	Group Dose(mL/kg) Grade	Control						snPt						nPt							
		2						2						2							
		-	=	+	2+	3+	Pos.	-	=	+	2+	3+	P	Pos.	-	=	+	2+	3+	P	Pos.
Lymph node, submandibular		5						5						5							
Thymus																					
Tingible body macrophage, cortex		3	2	0	0	0	2	4	1	0	0	0	1	3	2	0	0	0			2
Lung																					
Accumulation, foam cell, alveolus		3	2	0	0	0	2	1	4	0	0	0	4	3	2	0	0	0			2
Cellular infiltration, eosinophil, perivascular		2	3	0	0	0	3	3	2	0	0	0	2	3	2	0	0	0			2
Cellular infiltration, neutrophil, focal		4	1	0	0	0	1	4	1	0	0	0	1	5	0	0	0	0			0
Hemorrhage, focal		4	1	0	0	0	1	4	1	0	0	0	1	5	0	0	0	0			0
Metaplasia, osseous, focal		4	1	0	0	0	1	5	0	0	0	0	0	5	0	0	0	0			0
Mineralization, arterial wall		4	1	0	0	0	1	5	0	0	0	0	0	3	2	0	0	0			2
Bronchus		5						5						5							
Lymph node, mesenteric		5						5						5							
Heart		5						5						5							
Liver																					
Fatty change, hepatocyte, periportal		3	2	0	0	0	2	2	3	0	0	0	3	3	2	0	0	0			2
Microgranuloma		4	1	0	0	0	1	4	1	0	0	0	1	3	2	0	0	0			2
Necrosis, focal		4	0	1	0	0	1	4	1	0	0	0	1	4	1	0	0	0			1
Spleen																					
Deposit, pigment, brown		0	5	0	0	0	5	0	5	0	0	0	5	0	5	0	0	0			5
Hemato poiesis, extramedullary		0	2	3	0	0	5	0	4	1	0	0	5	0	3	2	0	0			5

Notes) -: No abnormal changes =: Very slight +: Slight 2=: Moderate 3=: Marked
P: Non-graded change NE: Not examined Pos.: Total of positive grade
Numerals represent the number of animals.
Not significantly different from control.

Findings	Group Dose(mL/kg) Grade	Control						snPt						nPt							
		2						2						2							
		-	=	+	2+	3+	Pos.	-	=	+	2+	3+	P	Pos.	-	=	+	2+	3+	P	Pos.
Kidney																					
Basophilic tubule, cortex		4	1	0	0	0	1	3	2	0	0	0	2	2	3	0	0	0			3
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0	1	5	0	0	0	0	0	5	0	0	0	0			0
Hyperplasia, transitional cell, with cellular infiltration, lymphocyte		5	0	0	0	0	0	5	0	0	0	0	0	4	1	0	0	0			1
Mineralization, cortico-medullary junction		3	2	0	0	0	2	2	3	0	0	0	3	4	1	0	0	0			1
Adrenal gland		5						5						5							
Ovary		5						5						5							
Uterus		5						5						5							
Vagina		5						5						5							
Skin																					
Attachment, crust, focal, epidermis		5				0	0	0					5	5 ^{**}	1					4	4 [#]
Cellular infiltration, lymphocyte macrophage, dermis		5	0	0	0	0	0	0	5	0	0	0	5 ^{**}	3	2	0	0	0			2
Cellular infiltration, eosinophil, dermis		5	0	0	0	0	0	1	4	0	0	0	4 [#]	5	0	0	0	0			0
Edema, epidermis dermis		5	0	0	0	0	0	1	4	0	0	0	4 [#]	2	3	0	0	0			3
Erosion		5	0	0	0	0	0	0	2	3	0	0	5 ^{**}	3	2	0	0	0			2
Hemorrhage, focal		5	0	0	0	0	0	1	4	0	0	0	4 [#]	4	1	0	0	0			1
Hyperplasia, squamous cell		5	0	0	0	0	0	0	2	3	0	0	5 ^{**}	1	3	1	0	0			4 [#]
Proliferation, fibroblast		5	0	0	0	0	0	0	2	3	0	0	5 ^{**}	3	2	0	0	0			2
Ulcer		5	0	0	0	0	0	4	0	1	0	0	1	5	0	0	0	0			0

Notes) -: No abnormal changes =: Very slight +: Slight 2=: Moderate 3=: Marked
P: Non-graded change NE: Not examined Pos.: Total of positive grade
Numerals represent the number of animals.
**P<0.01 : Significantly different from control by Mann-Whitney U test.
#P<0.05, ##P<0.01 : Significantly different from control by Fisher's exact test.

図 192 病理組織学所見(雌)

皮膚所見以外は、被験物質投与によると考えられた変化は認められなかった。

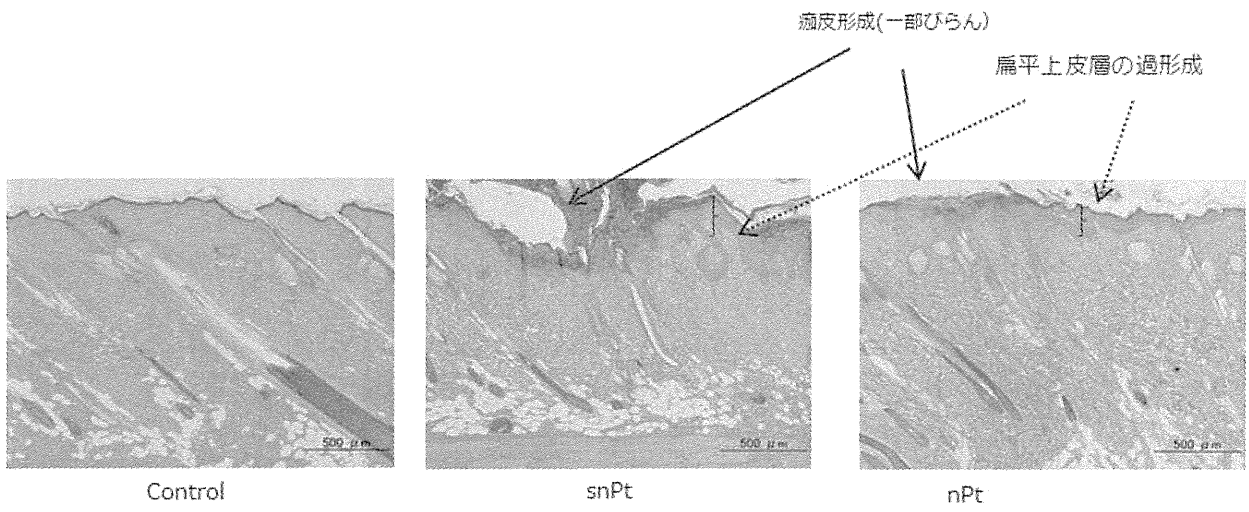


図 193 貼付部位皮膚の病理組織変化見(雄)

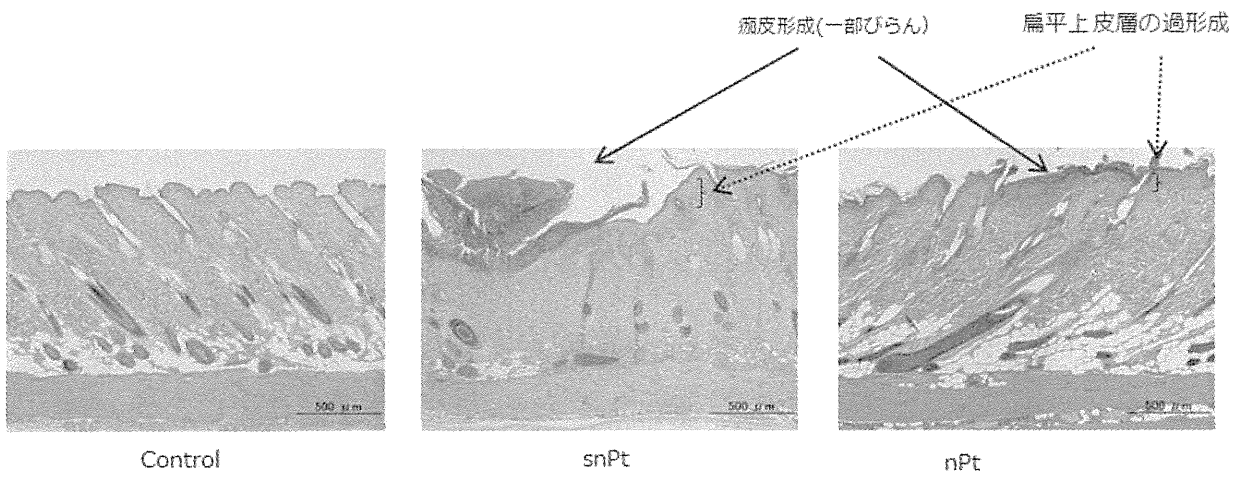


図 194 貼付部位皮膚の病理組織変化見(雌)

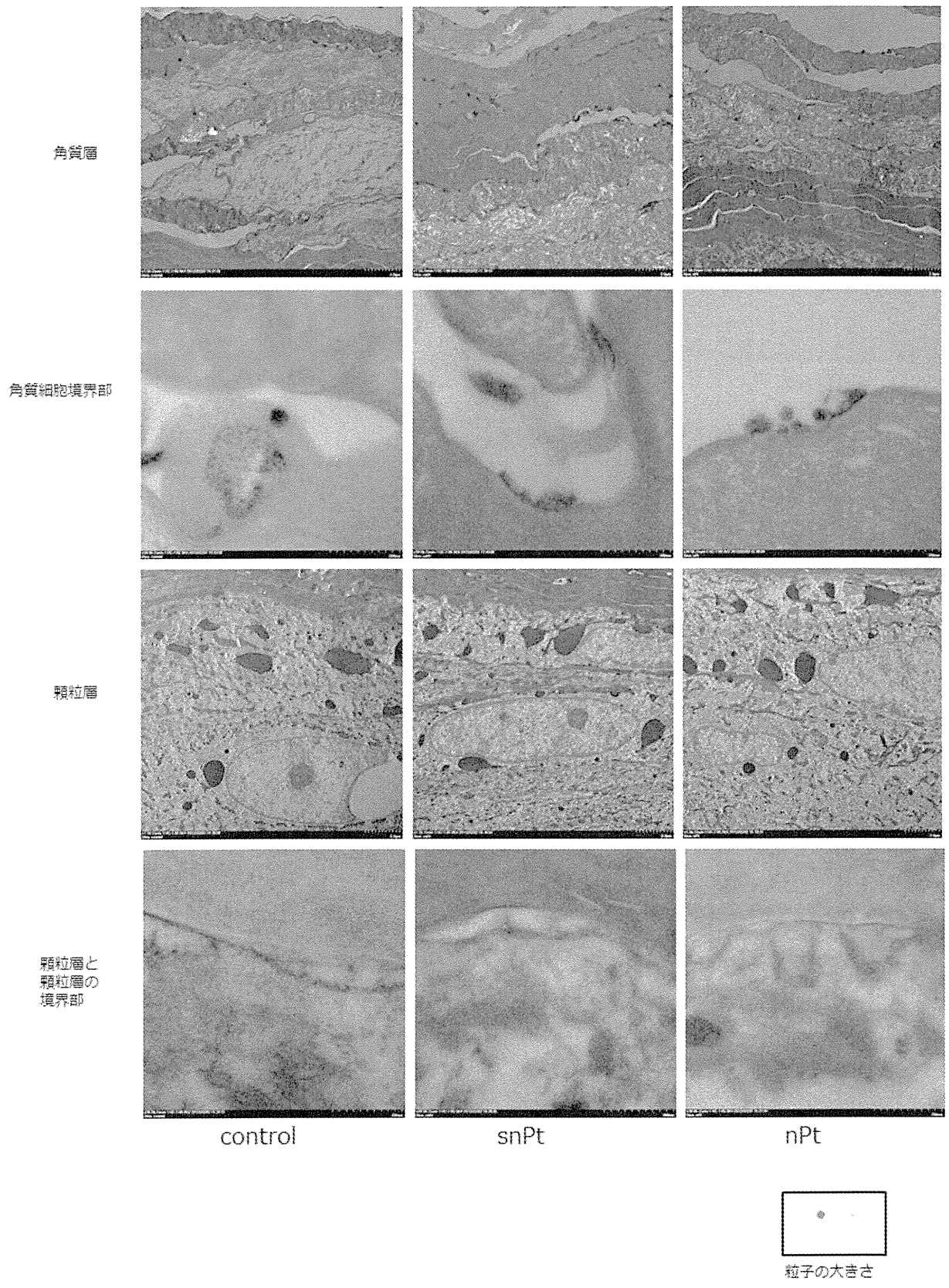


図 195 TEM 電顕像

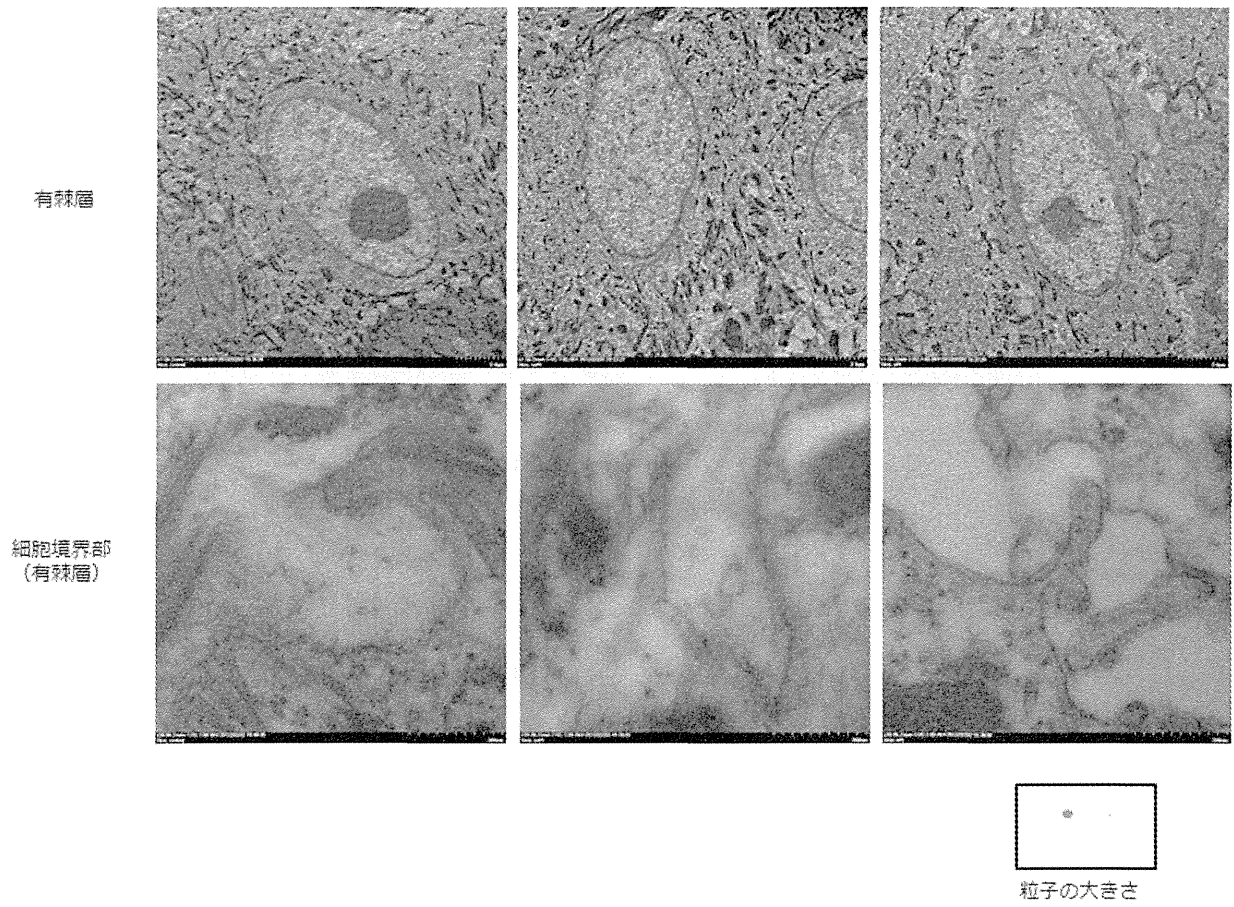
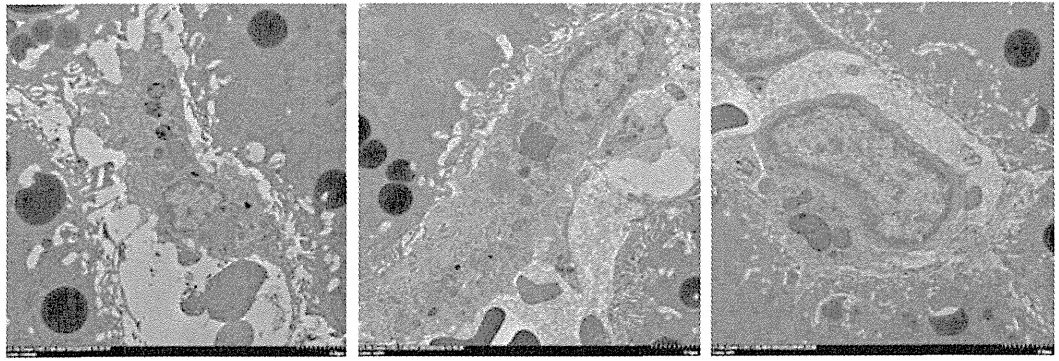


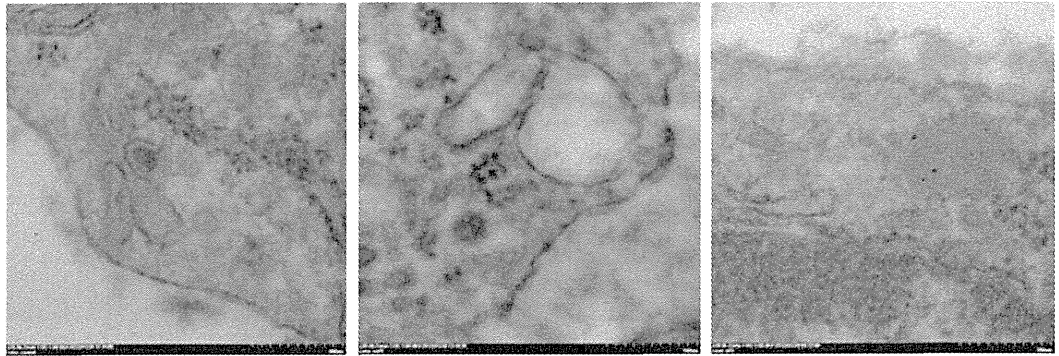
図 196 TEM 電顕像

肝臓

クッパー細胞

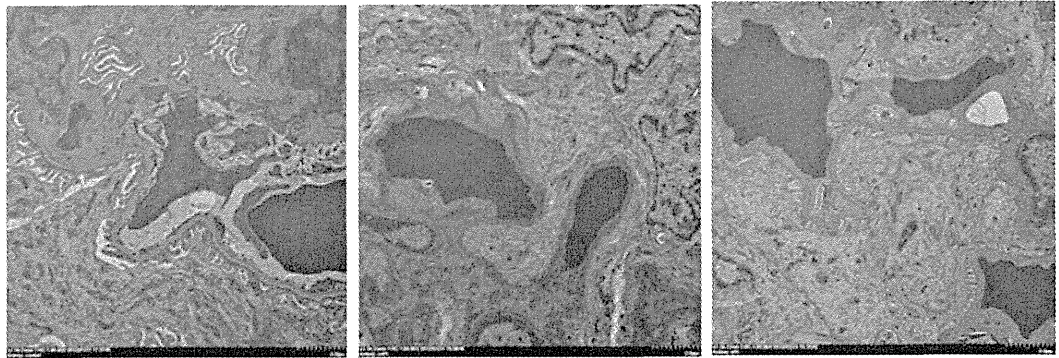


類洞面のクッパー細胞

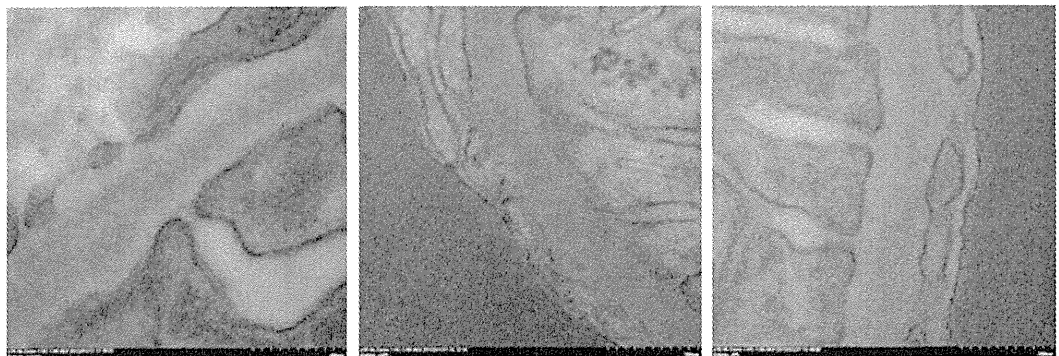


腎臓

糸球体



糸球体基底膜部



control

snPt

nPt



粒子の大きさ

図 197 TEM 電顕像

組織中のsnPtおよびnPtの分布 (ICP-MS分析、 $\mu\text{g/g}$)

Control													
Animal no.	下顎リンパ節	腸間膜リンパ節	胸腺	心臓	脾臓	皮膚	肝臓	肺	腎臓	副腎	精巣	精巣上体	
M01001	0	0	-	0	0	0	0	0	0	0	0	0	0
M01002	0	0	0	0	0	0	0	0	0	0	0	0	0
Ave	0	0	0	0	0	0	0	0	0	0	0	0	0
snPt													
M02002	2.1	0.81	0.34	0.44	2.8	89	1.5	0.86	11	1.1	0.43	0.46	
M02005	1.2	1.9	0.53	0.46	3	30	1.6	0.84	12	1.1	0.39	0.46	
Ave	1.65	1.355	0.435	0.45	2.9	59.5	1.55	0.85	11.5	1.1	0.41	0.46	
nPt													
M03002	0	0	0	0	0	1.3	0	0	0	0	0	0	0
M03003	0	0	0	0	0	1.1	0	0	0	0	0	0	0
Ave	0	0	0	0	0	1.2	0	0	0	0	0	0	0

図 198 雄の各組織中の snPt および nPt の分布 (ICP-MS 分析、 $\mu\text{g/g}$)

電頭を実施した動物で分析を行った(各群 N=2)。

snPt は皮膚以外に検査した組織に含まれていた。